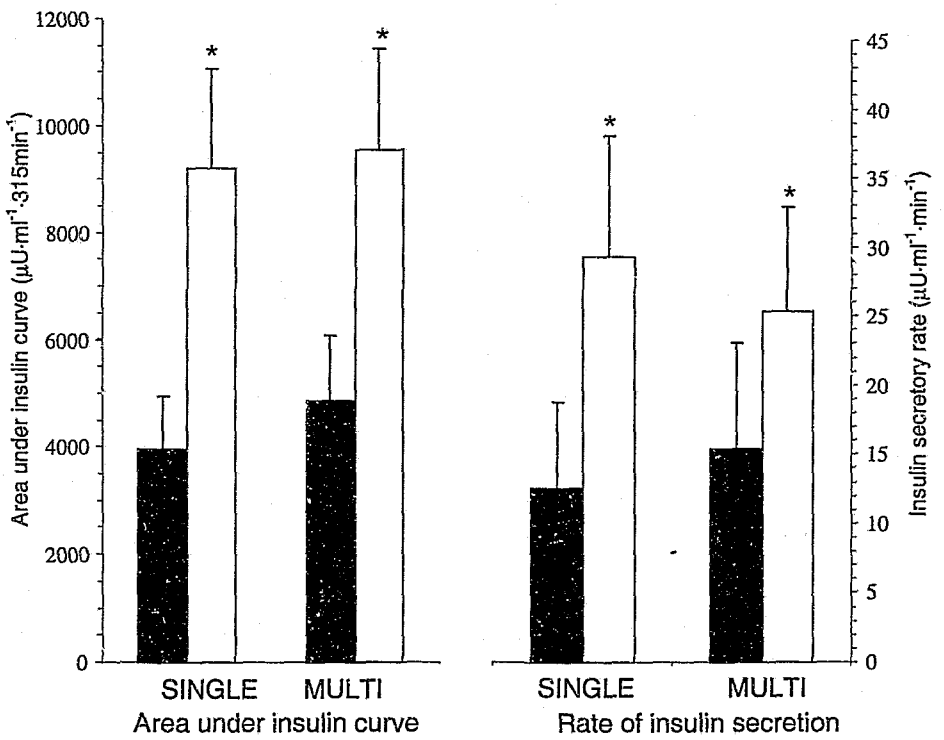
Despite this inter-treatment difference in insulin concentrations between the lean and obese groups, when the area under the insulin curves were compared, no differences ($P > 0{\cdot}05$) between the feeding treatments was observed (FIGURE 7·4). There was however, an inter-group difference where obese group secreted more than twice the amount of insulin [$F_{1,20} = 6{\cdot}1$, $P < 0{\cdot}05$] for the same amount of food intake over the 315-minute period.

FIGURE 7·4 *Calculated areas under the insulin curves (and their associated secretory rates)* between the lean (■) and obese (□) males in the pre-load period in the SINGLE and MULTI feeding treatments with restrictive energy density.



Where * $P <$ 0·05 between lean and obese groups within meal treatments

Visual Analogue Scales for subjective satiety

FIGURES 7·5; 7·6; and 7·7 depict the changes in VAS scores for the three sub-factors over the entire experimental period. These showed the lean group to have smaller fluctuations in subjective hunger ratings compared to those recorded by the obese group. There were differences however in all three sub-factors between the VAS ratings given in response to the different feeding patterns: the responses in the MULTI meal treatment were generally attenuated in subjective *hunger ratings* [$F_{6,120} = 3{\cdot}7$, $P < 0{\cdot}01$], the *amount that each subject felt that they could consume* [$F_{6,120} = 3{\cdot}3$, $P < 0{\cdot}01$], and the subjective urge to eat [$F_{6,120} = 3{\cdot}9$, $P < 0{\cdot}01$] over the 315-minute pre-load period. On average, the lean group reported greater subjective hunger ratings [$F_{1,20} = 2{\cdot}2$, $P < 0{\cdot}05$] compared to those reported by the obese group over the pre-load time period.

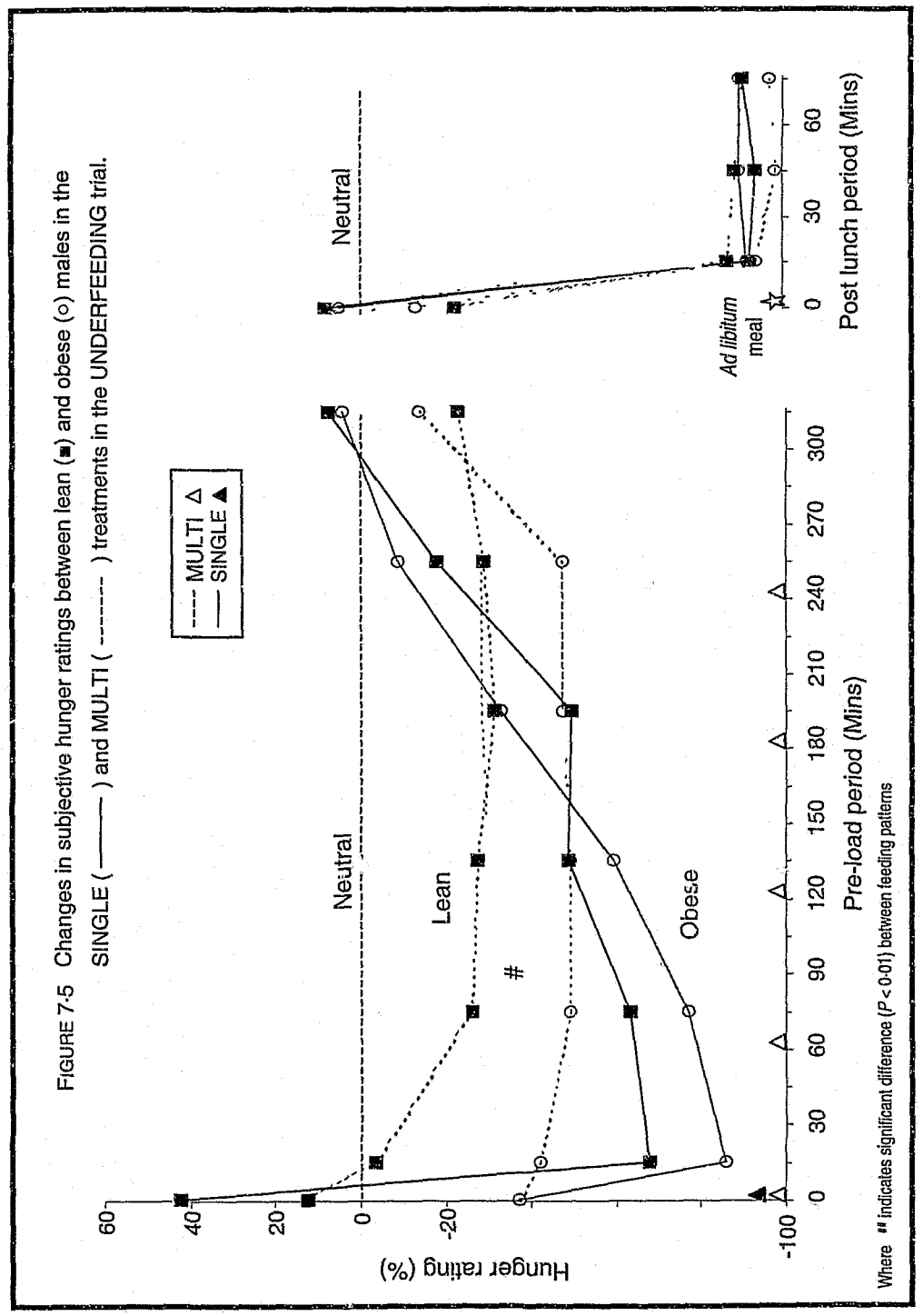


FIGURE 7·5 Changes in subjective hunger ratings between lean (■) and obese (○) males in the SINGLE (———) and MULTI (- - - - -) treatments in the UNDERFEEDING trial.

Where # indicates significant difference ($P < 0.01$) between feeding patterns

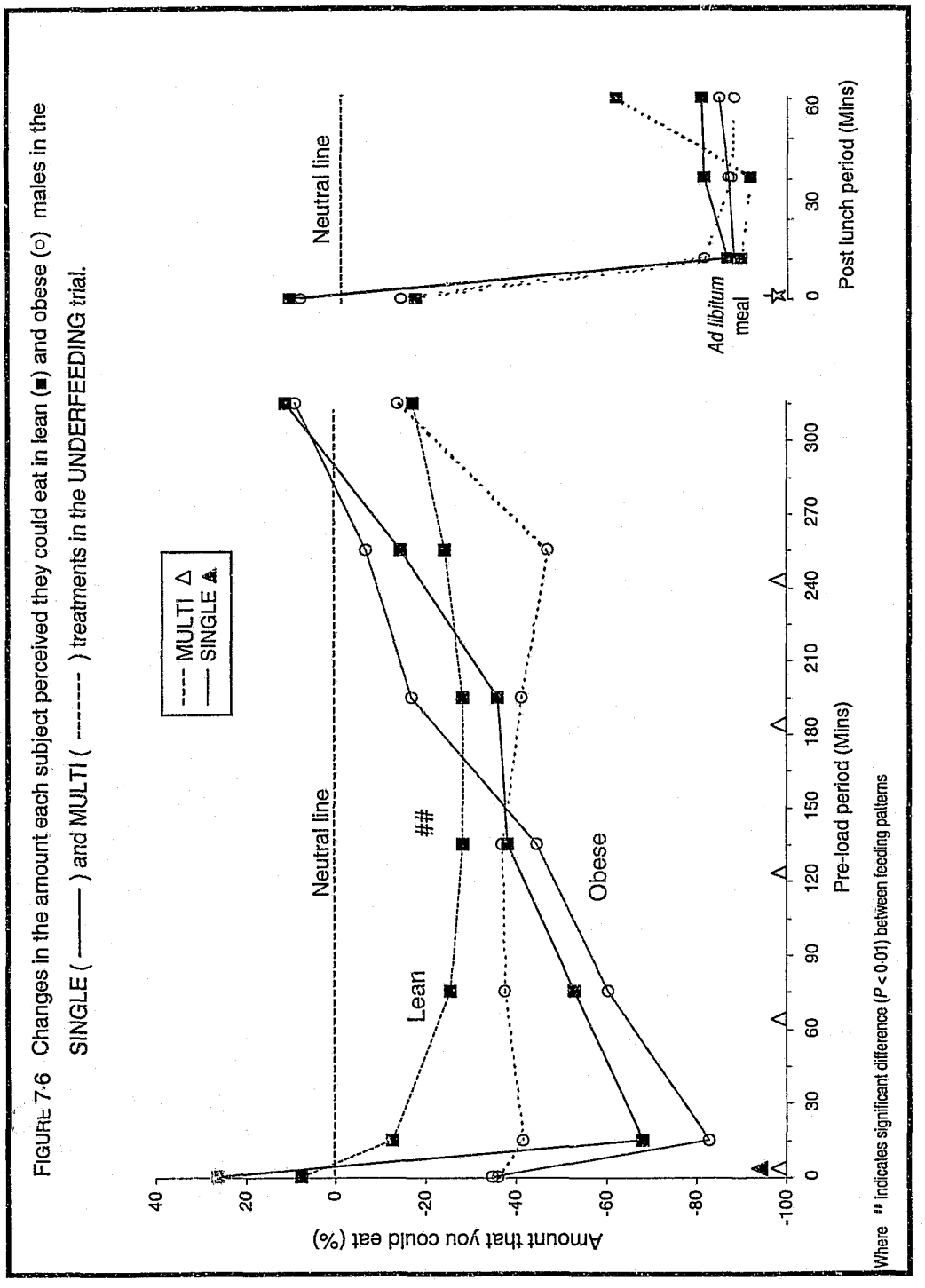


FIGURE 7·6 Changes in the amount each subject perceived they could eat in lean (■) and obese (○) males in the SINGLE (——) and MULTI (- - - - - -) treatments in the UNDERFEEDING trial.

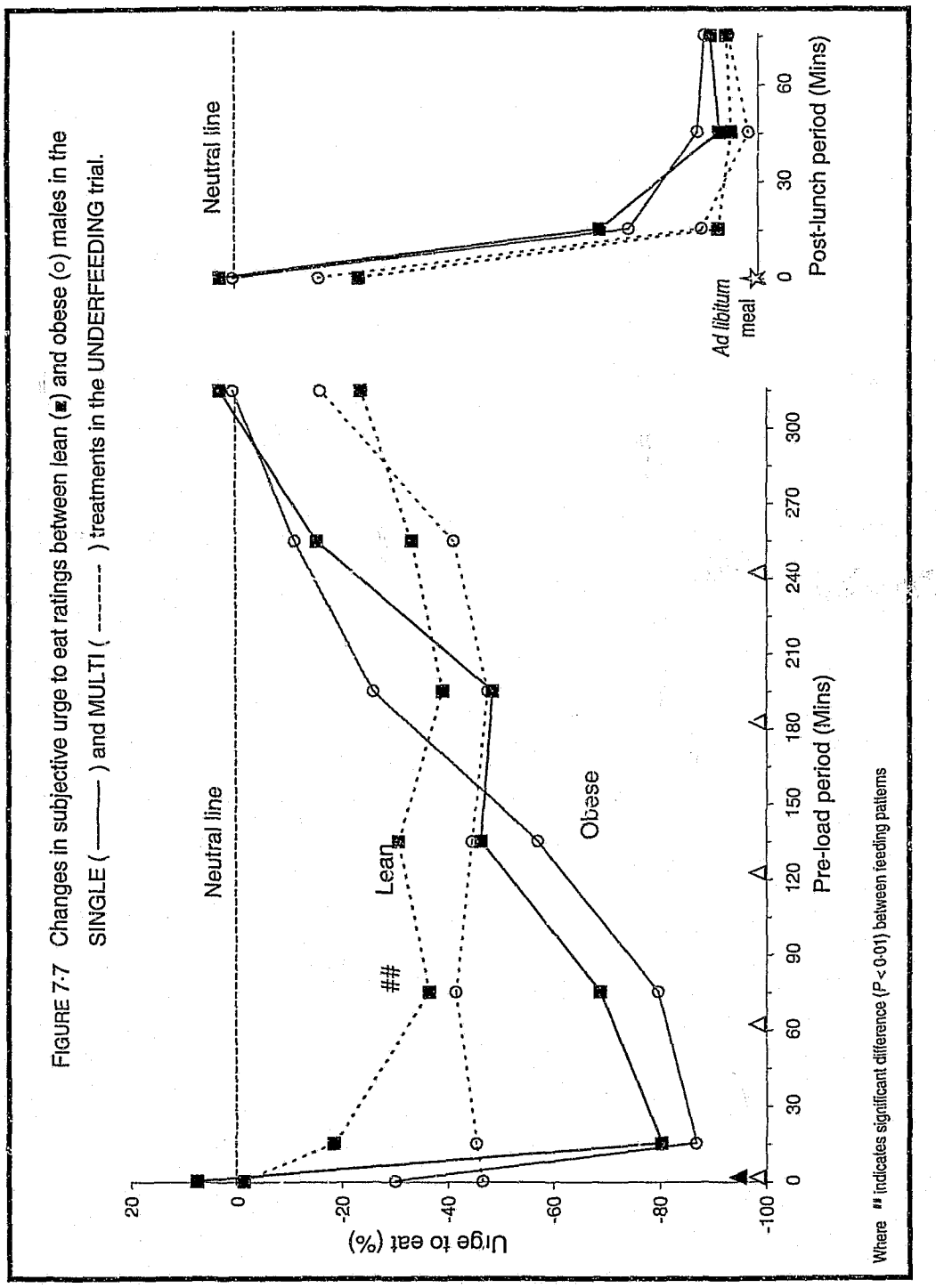


FIGURE 7·7 Changes in subjective urge to eat ratings between lean (■) and obese (○) males in the SINGLE (———) and MULTI (- - - - -) treatments in the UNDERFEEDING trial.

The post lunch period

Plasma glucose responses

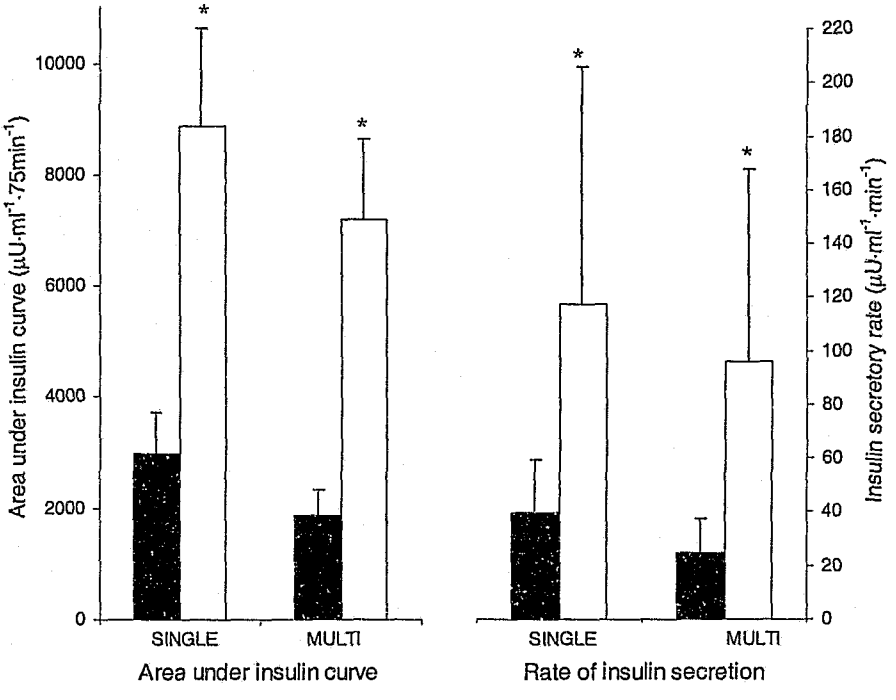
Immediately before the test meal was served, plasma glucose concentrations were similar between the lean and obese groups, and there were no differences in plasma glucose levels between feeding treatments. The change in plasma glucose with the test meal after the SINGLE treatment was almost double [$F_{1,20}$ = 4·60, P < 0·05] that following the smaller, but more frequent, MULTI meal treatment. Furthermore, the most pronounced change in glucose concentrations remained distinguished from that of the pre-load values for the full 75-minutes monitored after completion of the *ad libitum* test meal [$F_{3,60}$ = 8·47, P < 0·01] (FIGURE 7·2, *right*).

Serum insulin responses

Serum insulin concentrations in the obese group were higher (P < 0·01) than the lean group's immediately before the lunch was served. The effect of consuming the test meal caused the insulin level to rise over twice as high [$F_{1,20}$ = 9·57, P < 0·01] in the obese group compared to the increase in the lean group. Consequently, the insulin responses in the obese group were higher, and remained elevated for the full 75-minute post test meal period [$F_{3,60}$ = 3·87, P < 0·05] compared to those observed in the lean group (FIGURE 7·3, *right*).

Accordingly, the areas under the insulin curves in the post-lunch period were greater [$F_{1,20} = 6{\cdot}10$, $P < 0{\cdot}05$] in the obese responses (FIGURE 7·8) compared to the lean; but there were no differences in areas under the curves (and correspondingly insulin secretory rates) between the feeding treatments ($P > 0{\cdot}05$) for either the lean or obese group.

FIGURE 7·8 Calculated areas under the insulin curves (and their associated secretory rates) between the lean (■) and obese (□) males in the post-lunch period in the SINGLE and MULTI feeding treatments with restrictive energy density.



Where * $P < 0{\cdot}05$ between lean and obese groups within meal treatments

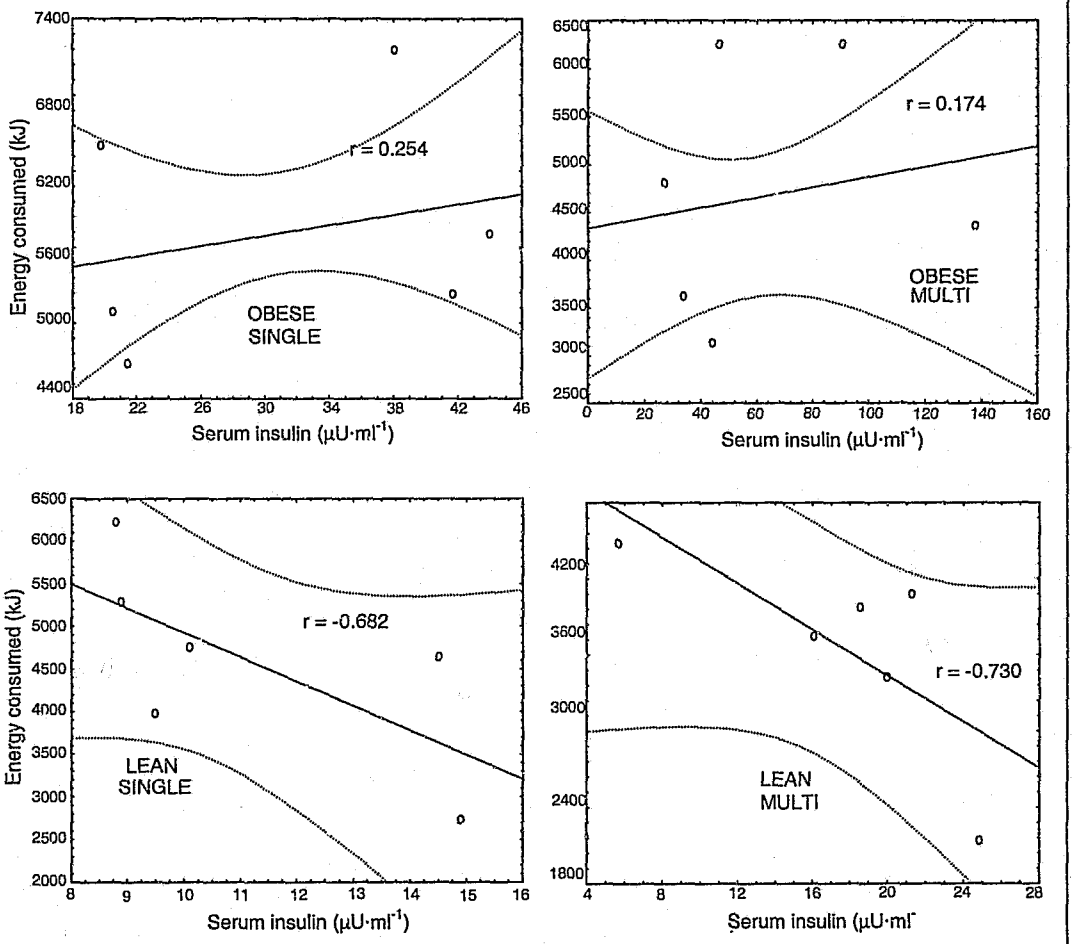
FIGURE 7·9 depicts the scatterplots relating serum insulin concentrations immediately before lunch and the amount of energy consumed at the *ad libitum* lunch meal in the two different eating treatments in the lean and obese groups. No significant relationships ($P > 0{\cdot}05$) were observed

between these variables. However the correlation between insulin and subsequent intake was strongly negatively correlated in the lean group fed the MULTI pattern (r = -0·730), but not correlated when fed in the SINGLE treatment (r = -0·682). There was no correlation in the obese group in either the SINGLE (r = 0·254) or the MULTI treatment (r = 0·174).

Visual Analogue Scales for subjective satiety

FIGURES 7·5; 7·6; 7·7 show no differences ($P > 0·05$) between any of the VAS scores for the three sub-factors after consuming the *ad libitum* lunch, except for the change in rating with time ($P > 0·01$).

FIGURE 7·9 Scatterplots depicting the relationship between serum insulin concentration immediately before lunch and the amount of energy consumed at the *ad libitum* lunch in the two different eating plans in lean and obese males following energetic restriction.



DISCUSSION

When obese males were fed isoenergetic meals more frequently, they consumed 17·0% less energy compared to when the pre-load was consumed as a SINGLE meal. This finding reinforces the postulate that increased frequency of feeding enhances appetite control in this group. Conversely, on the SINGLE treatment, the obese group consumed 24% more [$F_{1,20}$ = 14:39; $P < 0{\cdot}01$] energy at the test meal compared to that which the lean group consumed. Accordingly, there was a MULTI treatment-effect that enhanced appetite control in the obese group, which was absent in the lean group. Despite this difference, the obese group still consumed 16·4% more than the lean group at the test meal (following the MULTI treatment).

Changes in Blood Variables

The obese group had higher blood glucose and serum insulin levels than the lean group on both feeding treatments. These findings concur with published reports of a higher incidence of hyperinsulinaemia and insulin resistance in the obese population (Kolterman 1980; Faber *et al.*, 1981; Ferrannini *et al.*, 1991; Ferrannini *et al.*, 1999; Gould *et al.*, 1999). However, when consuming smaller, more frequent meals even the obese group showed less fluctuation in the plasma glucose response curve to feeding. The relatively smaller post-prandial hyperglycaemia observed in the 75-minutes after the test meal on the MULTI pre-load treatment was expected, since less energy was consumed at the test meal on that

treatment. However, the observed enhanced appetite control in response to increased frequency of eating occasions may be the result of insulin and glycaemic dynamics. Immediately before the test meal was served, plasma glucose concentrations observed in the lean and obese groups were similar. Furthermore, there were no differences in plasma glucose levels between feeding treatments either (FIGURE 7·2). On the MULTI meal treatment, the glucose concentration after the test meal was half that noted in the SINGLE treatment. This is a significant finding as it implies that it was not the digestion of the test meal that determined the amount of plasma glucose but rather, in this case, the preceding meals. Hamman & Hirschman (1919) first showed that the prior ingestion of glucose resulted in an increased tolerance to a subsequent glucose load. This phenomenon, referred to as the "Staub Effect", since Staub (1921) postulated that if a normal healthy person is given two glucose loads 30 minutes apart, the blood sugar level at 60 minutes should be no higher than that obtained at 30 minutes. Staub postulated that this was due to the "priming effects" of the initial sugar load. It would seem that this priming effect, and its influence on subsequent meals, may be the pivotal influence on the outcome effects exerted on appetite and satiety that occur with changes in meal frequency.

Although the insulin dynamics depicted in the post-lunch period show no inter-treatment differences, the inter-treatment (temporal) differences that were noted in insulin dynamics suggest that insulin contributed to the reduced energy intake in both groups at the *ad libitum* meal. As such data from the present study would support earlier findings both in humans and other mammals, that insulin exerts a direct effect on the regulation of appetite and the ingestion of energy (Ellis, 1934; Le Magnen, 1956; Hejda

& Fábry, 1964; Bray, 1972; Woods *et al.*, 1979; Vander Weele *et al.*, 1980; Woods *et al.*, 1984; Steffens *et al.*, 1988; Jenkins *et al.*, 1989; Vander Weele, 1994; Woods, 1997; Speechly & Buffenstein, 1999; Speechly *et al.*, 1999; Speechly & Buffenstein 2000). It is logical that the controller of both appetite and satiety should be regulated by stimuli linked to feeding.

Although the pre-load in the current study was only 20% of the measured ADER in both groups, the SINGLE pre-load effected a more-than-double response in serum insulin in the both lean and obese groups. This dramatic change in serum insulin corresponded with equivalent feelings of satiety in both groups. This attenuation in serum insulin on the MULTI treatment concurs with previous reports of the effects of increased feeding frequency in lean (Speechly & Buffenstein, 1999) and obese (Speechly *et al.*, 1999) males. The *priming effect* of insulin with increased frequency of feeding (Speechly & Buffenstein, 1999) was absent in the lean group maintained at this lower ADER. This led me to postulate that there may be a minimum energy load required to induce the accumulation of serum insulin. In the current study, 485kJ per pre-load "meal" in the MULTI feeding pattern may be too low to induce such an effect. This is an area which requires further research.

Despite the attenuation in the serum insulin concentrations observed in the obese group on the MULTI feeding programme, there were no differences between the areas under the curves between the two treatments (FIGURE 7·4). This finding reinforces the proposition that the effect of serum insulin on appetite is a function of temporal release rather than the absolute amount of insulin that is released. These results suggest the obese were regulating their intake in a similar fashion to the lean group, but at a higher

set-point and as such support the hypothesis proposed in this regard by Blundell *et al.*, (1994).

The strong negative correlation between serum insulin concentrations immediately before the test meal and subsequent energy intake (at that meal) observed in the lean group on both the SINGLE ($r = -0{\cdot}68$, $P < 0{\cdot}05$) and the MULTI ($r = -0{\cdot}73$, $P < 0{\cdot}05$) treatments was indicative of the potential feed-back effect that insulin may exert in the control over energy intake. The inverse nature of these relationships, while no relationship was observed in the obese group on either treatment, show that when fed a low-fat pre-load, irrespective of the pattern in which the pre-load was consumed, the lean males consumed less energy with higher serum insulin concentrations. This finding reinforces the notion that insulin regulates energy intake, and a dysfunction in insulin action may disrupt the appetite regulating system, which in turn exacerbates the problems of hyperphagia and passive overconsumption that is characteristic of the obese.

Visual Analogue Scales and Restraint

Throughout the pre-load period, the only differences that were note in appetite ratings were a function of the varied meal frequency. Given the differences detected in the Dutch Restrained Questionnaire profiles between the lean and obese groups (TABLE 7·1), this inter-group similarity was not the expected outcome (Westerterp-Plantenga & Ten Hoor, 1991; Federoff *et al.*, 1997). Dietary restraint is defined as the "the deliberate effort to combat t[illegible]ysiologically-based urge to eat in order to lose

weight, or maintain a reduced weight, through caloric restriction" (Federoff *et al.*, 1997). To maintain this dietary inhibition, restrained eaters must ignore internal cues of hunger in the desire to adhere to the externally-imposed demands of an energetically-restricted diet (Heatherton *et al.*, 1989; Herman & Polivy, 1993). This unresponsiveness to physiological hunger cues may impose on other internal cues, such as satiety. Previous studies have shown that restrained eaters are relatively insensitive to internal satiety scores (Polivy, 1976; Spencer & Fremouw, 1979).

When the energy intakes in this restrictive treatment were compared with a prudent energy intake (33% ADER), it was found that neither of the groups compensated for the reduction in energy served in the pre-load (TABLE 7·4). The obese group consumed 8-10% less in the restricted treatment compared to the prudent feeding pattern. Although the obese group appeared to be 40% less effective at controlling energy intake (than the lean group) (FIGURES 3·1, 4·1, and 7·1; TABLE 7·4), these data show that reduced energy intake, coupled to increased satiety sensations with more frequent smaller meals, are a useful finding for the management of obesity. Obese individuals wishing to lose weight through dietary restriction, would find it less challenging to consume a low-fat diet subdivided into smaller, but more frequent, meals. Furthermore, under hypoenergetic and low-fat conditions, the obese group exhibited appetite control similar to their lean counterparts. This may, in part, reflect the macronutrient composition on the low-fat diet. Foods containing carbohydrate have been shown to have a higher satiating efficiency compared to high-fat foods (Kissileff, 1984; Rolls *et al.*, 1995; Poppitt *et al.*, 1998).

The current findings of a positive relationship between low-fat food consumed more frequently and appetite control may provide an effective strategy in weight management. Clearly for this to be achieved the population as a whole, and the obese in particular, need to be educated about the significance of reducing dietary fat intake with concomitant regular frequent feeding episodes. Moreover, improved food science technology has brought with it more than 6,000 low-fat food items for enhanced choices for the end-consumer (Lichtenstein *et al.*, 1998; Nestle *et al.*, 1998; Albu *et al.*, 1997). These combined efforts of education and low-fat food availability are powerful drivers in the process required to reverse the increasing rates of obesity prevalence in the western world.

CONCLUSION

When obese males were fed 20% ADER in a MULTI meal pattern, their consequent intake at an *ad libitum* meal was reduced by 17% (compared to the SINGLE treatment). Increased meal frequency had a positive effect on appetite under these energetic restrictions. Greater appetite control with increased periodicity of eating on a low-fat diet has significant implications for the growing numbers of overweight and obese individuals who wish to reverse the condition.

Chapter Eight

Synopsis of Findings

Disruption to the appetite-satiety mechanism has been blamed for the excessive energy consumption that is characteristic of the obese. Findings obtained in this study support this premise, in that in all of the experiments I undertook, the obese consumed more than the lean group, with this being most pronounced when the energy preload was highest in fat content (55% ADER) and serum insulin concentration was maximal. It was hypothesised that increased meal frequency and varied macronutrient content influenced test meal intake, and that this response was correlated with serum insulin concentration. Regardless of the energy and macronutrient content of the preload, in both the lean and obese groups, increased meal frequency had a positive effect over appetite control and consequent energy intake. Furthermore, when the preload was divided into smaller, but more frequent meals, peak insulin concentrations were on average 2·5x lower than when a single meal was eaten. The significant negative correlation between serum insulin concentrations (immediately before the test meal) was evident in the lean group on the low-fat underfeeding trial. Indeed, when all the data from the three different trials are pooled together, the relationship between serum insulin concentration and subsequent food intake suggest that serum insulin is an important mediator in the control of ingestive behaviour. Moreover, this relationship appears to be weaker in the obese, implying that other factors may be overriding the mechanism, or that in this group, the mechanism itself is dysfunctional.

8.1 Meal Frequency and Appetite Control

The entire spectrum of responses to the effects of meal frequency on energy intake has been previously reported (Edelstein *et al.*, 1992; Basdevant *et al.*, 1993 Summerbell *et al.*, 1996; Drummond *et al.*, 1996; Drummond *et al.*, 1998; Metzner *et al.*, 1977). This, in part, reflects the manner in which data were obtained from subjective assessments and reports by free-living subjects rather than measurements in a controlled experimental setting. The hypothesis that meal frequency had no effect on appetite control was investigated in a controlled setting in lean (n = 8; BMI = 23·1 ± 2·8kg·m^{-2}) and obese (n = 7; BMI = 40·2 ± 10·9kg·m^{-2}) men, and was consequently rejected. Regardless of the energetic value and macronutrient content of the preload, when smaller and more frequent meals were consumed, the study participants subjectively reported that they were less hungry. Similarly, in covert studies these study participants voluntarily decreased food consumption at the test meal by 10 - 30% with increased feeding frequency (FIGURE 8·1). That is that the more frequently meals were consumed, the greater the control over appetite thereafter. This finding does not support the proposal that the increased incidence of obesity might be linked to an elevated "snacking" pattern (Booth, 1988; De Wit *et al.*, 2000). The literature contains a wide range of reports indicating the effects that altered feeding frequency exert on energy metabolism and weight regulation in humans. Most of the data contained in the literature however, have been based on dietary recall records, which should be interpreted with caution within the confines of *dietary under-reporting* (Bellisle *et al.*, 1997). Furthermore, no work has yet considered the effects that varied meal frequency may exert on appetite and energy

intake. This study has shown strong support for the positive effect that increased meal frequency exerts over appetite control in both lean and obese males.

The decline in food intake with more frequent smaller preloads was correlated with the energy content of the preload with the smallest decline in response to meal frequency evident when the preload was 20% of the ADER and the largest decline (30%) in the lean group when the preload represented 55% of the ADER (FIGURE 8·1). Both lean and obese showed similar responses to meal frequency when the preload followed a prudent diet (33% ADER: 60% carbohydrate; 25% fat, 15% protein).

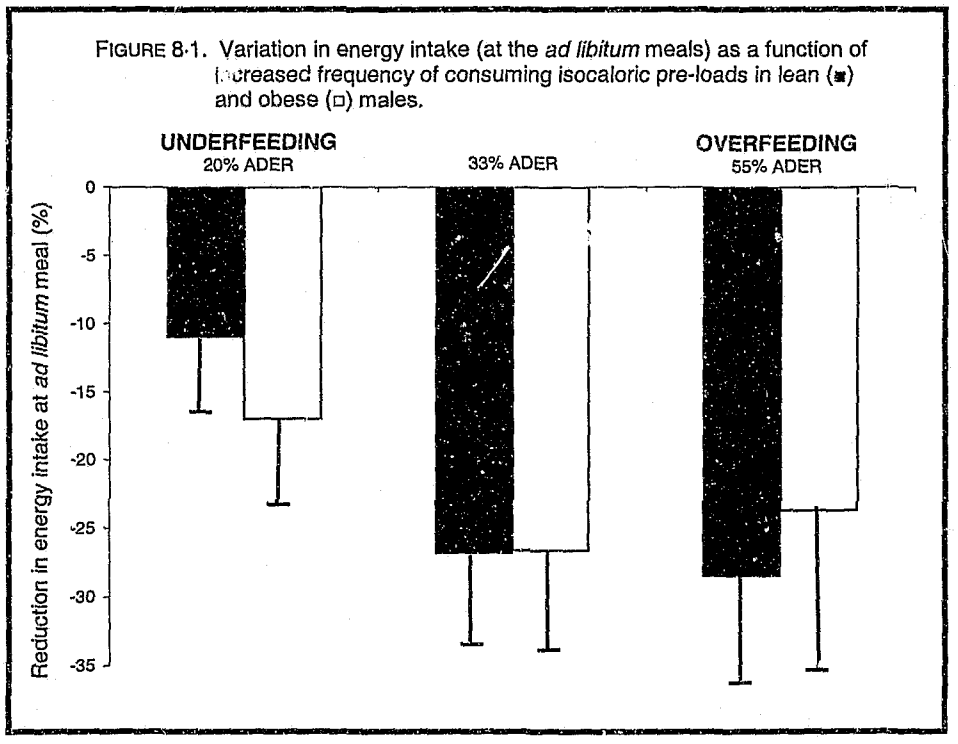


FIGURE 8·1. Variation in energy intake (at the *ad libitum* meals) as a function of increased frequency of consuming isocaloric pre-loads in lean (■) and obese (□) males.

However, when the preload was high-fat and energetically-dense (55% ADER: 35% carbohydrate; 43% fat; 22% protein), the obese men did not detect (nor compensate for) the energy overload and consequently

consumed 56·4% more [$F_{1,20}$ = 11·45; P < 0·01] energy at the *ad libitum* test meal than their lean counterparts did. This finding supported the notion of *passive overconsumption* with high-fat foods over-riding the intrinsic energy-regulating system. Since obese individuals reportedly prefer energetically-loaded foods, this may, among other factors, contribute to the aetiological dysfunction of appetite leading toward the obese state.

On an energy restricted preload, although the obese participants consumed substantially more than the lean group did, they nevertheless exhibited a pronounced drop in appetite with enhanced meal frequency, suggesting a therapeutic role for the consumption of smaller more frequent meals in dieting. Despite these differences in response to dietary and periodicity manipulations in lean and obese males, there were similarities in the relative energy regulation between the groups.

Of the studies that have investigated eating patterns and styles between lean and obese populations, most have found no differences between lean and obese groups (Kaplan, 1980; Rolls & Bell, 1999). The data presented in this study reinforce this postulate of similarities between lean and obese groups, which would imply that there is a well-regulated appetite-satiety mechanism present in both the lean and obese. However, it would seem that there is a different set point at which obese regulate their energy maintenance compared to lean individuals, and the obese appear more likely to experience a disruption to this appetite-satiety mechanism when confronted by a high-fat pre-load.

8.2 Insulin and Appetite

In 1956, Le Magnen showed that a reduced appetite for a flavoured test-diet was progressively induced in white rats when they were injected with insulin following each meal on that diet (Le Magnen, 1956). This long-term effect of post-prandial insulin on appetite might be interpreted as a consequence of its short-term action, which might augment the state of hunger and food consumption. The data presented in this study supports this hypothesis, and accordingly, it would seem that when isocaloric pre-loads are consumed more frequently, the positive effect over appetite control is exacerbated.

The experiments in the present study have shown that post-prandial insulin secretion may exert a strong negative feedback control in the regulation of subsequent energy intake. In the prudent pre-load experiment (33% ADER) both lean and obese groups exhibited smaller fluctuations in insulin and greater appetite control when fed multiple smaller meals and consumed ~27% less at the *ad libitum* meal. While there was a positive correlation ($r = 0{\cdot}87$, $P < 0{\cdot}05$) between insulin concentration before lunch and the amount of energy consumed at lunch in the obese group on the SINGLE trial, no such relationship was evident in the lean group. These elevated serum insulin levels in the obese may imply the relative reduction in insulin action, and reduced insulin clearance that may further contribute to the appetite dysfunction in the obese on the SINGLE treatment.

In both high-fat and low-fat trials, changes in insulin concentration in response to smaller, more frequent meals were attenuated ($P < 0{\cdot}05$)

compared to a single larger, but iscenergetic, meal. In addition, insulin concentrations following a single meal, were greater [$F_{1,20} = 43{\cdot}8$; $P < 0{\cdot}01$] following a high-fat meal when compared to a low-fat meal in both groups. Responses to the low-fat pre-load treatment were markedly different between the groups: there was a strong negative correlation between insulin and subsequent energy intake observed in the lean group on both the SINGLE ($r = -0{\cdot}68$, $P < 0{\cdot}05$) and the MULTI ($r = -0{\cdot}73$, $P < 0{\cdot}05$) treatments, while no relationship was observed in the obese group on either treatment. These data show that when fed a low-fat pre-load, irrespective of the pattern in which the pre-load was consumed, the lean males consumed less energy with concomitant elevated serum insulin concentrations. Moreover, this phenomenon was absent in a high-fat setting, suggesting a potential disruption to the regulatory system with high-fat foods. This gives further credence to the proposed hypothesis that insulin dysfunction disrupts the appetite regulating system, and exacerbates the problems of hyperphagia and passive overconsumption characteristic of the obese.

Insulin is an integral part of the absorptive process of feeding, and as such, may play an integral part in the feedback mechanism controlling ingestive behaviour (Woods, 1997). Whilst others have found this not to be true (Lavin & Read, 1995; Holt *et al.*, 1992; Holt & Brand-Miller, 1995), work performed in this laboratory supports the premise that insulin does play a part in appetite control (Speechly & Buffenstein, 1999; Speechly *et al.*, 1999; Speechly & Buffenstein, 2000). For appetite to be regulated by a stimulus linked to feeding, a regulatory signal from the gut to the central nervous system (CNS) would have to

meet three criteria. Firstly, it would have to exist in amounts proportional to body size and circulate in the blood; secondly, it would have to acquire access to the CNS and be able to interact with the brain; and finally, it would have to have predictable effects on behaviour and metabolism (Woods, 1997).

The first criterion is met by the general proposition that obese persons i. have higher fasting insulin concentrations; and ii. exhibit exaggerated insulin responses to feeding compared to their lean counterparts (Ferrannini *et al.*, 1991; Elahi *et al.*, 1982; Woods, 1997). This is reinforced by the preliminary observation that obese males had a relatively elevated fasting serum insulin concentration of ± 35 $\mu U \cdot ml^{-1}$. The second and third criteria for insulin to exert effects on food intake have been shown to be true using baboons (Woods *et al.*, 1979; Woods *et al.*, 1984) and rats (Steffens *et al.*, 1988). Thus, insulin meets the three criteria to act as a feedback signal from the gut to the CNS in the regulation of adiposity and weight. There is consensus at present that peripheral information provides crucial information to the central nervous system to control food intake (Campfield, 1997). The effect of chronic hyperinsulinaemia on appetite and metabolic concerns in the maintenance of obesity is yet to be tested.

The incidence of fasting hyperinsulinaemia, with concomitant euglycaemia in non-diabetic Caucasian South African adults, showed a strong correlation between fasting insulin and body mass index categories in both men ($r = 0{\cdot}645$; $P < 0{\cdot}05$) and women ($r = 0{\cdot}751$; $P < 0{\cdot}05$). The hyperinsulinaemia observed in obese may be a fundamental driving force in appetite dysfunction. This is reinforced by the numerous studies (Franssila-Kallunki

et al., 1991; Slabber *et al.*, 1994; Sjostrom *et al.*, 1999) that have found that hyperinsulinaemia (and other pathologies linked to obesity) is reversed with weight loss.

8.3 Future Studies

This study has attempted to investigate the putative mechanisms involved in ingestive behaviour in the short-term, and under controlled settings. It has revealed a number of areas for new research into appetite dysfunction leading to obesity. While this study only addressed acute responses to changes in meal frequency, and covert manipulations of energy density and macronutrient content, these studies need to be repeated over a prolonged period under free-living conditions. Although fraught with problems both in terms of experimental design and control, Leveille's (1970) proposal that a longer *adaptation period* to eating patterns should be incorporated into the testing procedure is recognised as a valid criticism of most studies of this nature and long term studies would enrich the results presented here.

Also, future studies should investigate the metabolic effects of fat adaptation linked to passive overconsumption on appetite and satiety. This too requires a long term commitment by study participants and inherently is fraught with potential problems, such as the ethical considerations involved with potential pathologies associated with hyperlipidaemia, and compliance of obese participants.

This extension of laboratory work to the free-living population studies would emphasise a more *normalised* setting. Additionally, there are cultural issues that need to be addressed in the context of meal patterns and the frequency of feeding. Potentially, these multi-cultural studies could incorporate differences from the perspective of feeding frequencies and macronutrient intakes, whilst concomitantly investigating epidemiological phenomena linked to obesity.

Finally, the prevalence of obesity in the western world is undoubtedly on the rise (FIGURES 1·1, 1·2, and 1·3). This may be the direct consequence of elevated fat intake (Prentice & Jebb, 1996; Drewnowski, 1997; Cooling & Blundell, 1998; Blundell & Macdiarmid, 1997, Jebb, 1999) and reduced levels of activity, or a combination of the two (Rogers, 1999). Based on the finding of *passive overconsumption* in obese males with high-fat energetically overloaded pre-loads, a consistently elevated fat intake will continue to exert deleterious effects on health profiles. Although every effort is being made to avoid excessive intakes of fat (Lichtenstein *et al.*, 1998; Nestle *et al.*, 1998), a high-fat diet (~35-40% of dietary intake) in the general population appears to be both convenient and more palatable. As such, this in all likelihood, will remain for the foreseeable future. Future studies that investigate regulatory mechanism(s) over appetite need to investigate and determine functional strategies that incorporate the putative aspects of appetite control with high-fat diets in free-living individuals.

8.4 Conclusion

This study has shown that increasing the frequency with which food is consumed, irrespective of its macronutrient value, enhances appetite control (in the short-term) in both lean and obese males. Furthermore, these data have shown a concomitant influence over insulin dynamics with meal frequency, which appears to enhance appetite control. Based on the assumption that appetite dysfunction contributes to the chronic positive energy balance that manifests in obesity, these findings suggest that part of the therapeutic management of obesity hinges on the increased periodicity of feeding. The functionality of this postulate was reinforced by the finding that obese males experience an enhanced control over appetite following the more frequent ingestion of a low-fat hypoenergetic pre-load.

Within the parameters of appetite dysfunction, I have shown that obese males are more prone to *passive overconsumption* when confronted with high-fat foods than are lean males). This phenomenon can be controlled, to a certain degree, by increasing the eating episodes. Finally, these data suggest that the therapeutic treatment of obesity may be more successful through the combination of low-fat diets and by increasing the number of eating episodes, which would optimise appetite regulation in the obese.

Appendix A: Assays used in the determination of plasma glucose, serum insulin, and serum non-esterified fatty acids.

1. Assay used for the determination of glucose

Hexokinase method
Enzymatic UV Test for clinical Chemistry Analysers
Cat.-No.:OSR6121

Test Principle

Glucose is phosphorylated in the presence of hexokinase and ATP. The glucose-6-phosphate produced reacts with the NAD^+ in the presence of glucose-6-phosphate dehydrogenase to form gluconate-6-phosphate and NADH. The increase in absorbance is proportional to the glucose concentration.

Reaction Principle

$$\text{Glucose} + \text{ATP} \xrightarrow{\text{HK}} \text{Glucose-6-phosphate} + \text{ADP}$$

$$\text{Glucose-6-Phosphate} + NAD^+ \xrightarrow{\text{G6P-DH}} \text{Gluconate-6-}P + \text{NADH} + H^+$$

Linearity

The test is linear within a concentration range of 10 – 800mg·dl^{-1} (0·6 - 45·0 mmol·l^{-1}) for serum and plasma

Normal range

Serum and plasma	75 - 115mg·dl^{-1} (4·2 - 6·4 mmol·l^{-1})

2. Assay used for the determination of insulin

Coat-A-Count® INSULIN is a solid phase ^{125}I radioimmunoassay designed for the quantificative measurement of insulin in serum.
Cat.No.: **TKIN2** *200 tubes*

Test Principle

^{125}I-labelled insulin competes with insulin in the patient sample for sites on insulin-specific antibody immobilised to the wall of the polypropylene tube. After incubation, isolation of the antibody-bound fraction is achieved simply by decanting the supernatant. The tube is then counted in a gamma counter, the counts being inversely related to the amount of insulin binding and iodination. Maximum binding is approximately 50%.

Specificity

The antiserum is highly specific for insulin, with very low cross-reactivity to other compounds that might be present in patient samples. Cross-reactivity with proinsulin at mid-curve is approximately 40%. The freedom from "matrix effects" is demonstrated by patient sample dilution experiments and by studies on the effect of bilirubin and lipaemia.

Sensitivity

The procedure can detect as little as $1{\cdot}2\mu U{\cdot}ml^{-1}$ using the overnight procedure, or $1{\cdot}5\mu U{\cdot}ml^{-1}$ using the same day procedure.

3. Assay used for the determination of non-esterified free fatty acids

Test Principle

Sample Preparation

1. 0·5 ml sample + 0·05ml 50% V/V orthophosphoric acid (Dilution factor: 1:1).
2. After 30 minutes, samples were centrifuged.
3. 0·25 ml sample + 0·025 internal standard (No dilution factor: STD treated in the same way).

Calculation

As calculated from the chromatograms attained by gas chromatography from the following equation:

$$\frac{\text{PA(FFA) SAMPLE} \cdot \text{STD concentration (Ac)} \cdot \text{dilution factor (mmol} \cdot 100\text{ml}^{-1})}{\text{PA (FFA)STD}}$$

Where PA: peak area on chromatogram
FFA Free fatty acid
STD Free fatty acid standard

Correct for injection error by multiplying value calculated by the correction factor determined as follows:

$$\text{Correction factor} = \frac{\text{PA of Internal STD in the STD solution}}{\text{PA of Internal STD in the sample solution}}$$

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