Aliment Pharmacol Ther 2003; 17: 1007–1013. doi: 10.1046/j.0269-2813.2003.01530.x

Impact of carbohydrate and fat intake on weight-reducing efficacy of orlistat

A. ULLRICH*, J. ERDMANN†, J. MARGRAF‡ & V. SCHUSDZIARRA†
*Tiefenthal Hospital, Saarbrücken, Germany; †Department of Internal Medicine II, Technical University of Munich, Munich, Germany; ‡Department of Psychology, University of Basle, Basle, Switzerland

Accepted for publication 23 January 2003

SUMMARY

Background: Orlistat treatment of obesity results in a poor long-term weight loss (< 5%) in about 30% of patients.

Aim: Total energy and macronutrient intake were examined to assess the effect of a change in eating habits on weight loss.

Methods: Sixty-two patients consumed a hypocaloric diet, together with orlistat (3 × 120 mg/day), for 72 weeks, with a maximal fat allowance of 30% of the energy intake. At regular intervals, food diaries were recorded.

Results: Fifty-six patients completed the study and lost 8.5 ± 0.88 kg ($P < 0.001$). Energy intake was ≈ 1500 kcal/day during the entire study period. In three sub-groups established according to weight loss (1, < 5%; 2, > 5% and < 10%; 3, > 10%), fat intake was within the recommended range in all groups during the first 6 months, but thereafter only in group 3. All groups increased their carbohydrate consumption, with the greatest increase in group 1, which could account for the rapid regain of initially lost body weight in this group.

Conclusion: At the beginning of a weight management programme in conjunction with orlistat, a low fat intake is advised for an efficient reduction in body weight. Subsequently, in patients with poor long-term weight loss, dietary recommendations must also consider carbohydrate restriction to ensure an adequate hypocaloric diet.

INTRODUCTION

Obesity is a major global public health problem,[1] with an increasing prevalence virtually throughout the world.[2, 3] Excess body weight has a substantial impact on morbidity and mortality, mainly due to cardiovascular diseases and some forms of cancer.[1, 4] A modest weight loss of 5–10% has been shown to improve cardiovascular risk factors and co-existing disorders.[5–7]

Most weight loss programmes can produce acute weight loss, but the long-term maintenance of reduced body weight, even after very intensive treatment programmes, is much more difficult and is still a major challenge in medicine.[8, 9] Modern concepts of obesity treatment favour a multi-modal approach comprising a hypocaloric diet together with a change in eating behaviour, increased physical activity and support by specific drug treatment. Such combinations of therapeutic efforts have been shown to effectively induce weight loss during the initial 6–9 months of therapy, followed by a period of largely stable body weight.[10–12]

Modification of the eating behaviour aims to reduce dietary fat intake while increasing the amount of complex carbohydrates and fibres. The latter should provide the volume of a meal necessary for gastric distension and the activation of satiety signals.[13–16] Fat, on the other hand, provides a high energy intake with little or no satiety,[17] and tends to be

Correspondence to: Professor V. Schusdziarra, II. Med. Klinik — Klinikum rechts der Isar, Ismaninger Strasse 20–22, 81675 Muenchen, Germany. E-mail: Johannes.Erdmann@lrz.tum.de

over-consumed by obese subjects due to its greater palatability.[18]

As obese subjects can lose weight when focusing on dietary fat intake, without attempting to reduce total calories,[19–21] low fat *ad libitum* carbohydrate diets have been promoted as weight loss programmes,[22–24] in combination with moderate exercise and behaviour modification. On the other hand, it has been shown that the efficacy of such regimens is attenuated in part by carbohydrate over-consumption.[25]

Orlistat, an inhibitor of pancreatic lipase activity, reduces energy uptake by the impairment of intestinal fat digestion[26] and improves weight loss and co-existing co-morbidities, such as type 2 diabetes mellitus and hyperlipidaemia. In all studies, orlistat treatment has been shown to be superior to placebo, but nevertheless approximately 30% of orlistat-treated patients show a fairly poor response (i.e. less than 5% weight loss). [12, 27–32]

Accordingly, it was the aim of the present study to examine the effect of changes in the intake of total energy and macronutrients during an 18-month weight management programme in conjunction with orlistat (3 × 120 mg/day) on long-term weight loss.

METHODS

Patients

Obese women and men (body mass index, 30–40 kg/m^2), aged 18–70 years, were eligible for inclusion. Recruitment was by local advertising in three cities in Germany. Women of child-bearing potential were included if they were using adequate contraception.

Patients were excluded if they were pregnant, lactating or if they had any clinically relevant condition that might affect the outcome of the study, such as psychiatric disorders, gall-bladder or pancreatic disease, chronic gastrointestinal, cardiac or renal diseases, or uncontrolled hypertension.

Other exclusion criteria were weight loss of > 4 kg within 3 months before screening, surgery for weight reduction, a history of bulimia or laxative abuse, consumption of drugs that might affect body weight during the 4 weeks prior to study initiation and drug or alcohol abuse.

The study conformed with the Declaration of Helsinki. The ethics committees of all centres approved the study and all participants gave informed written consent.

Study design

This multi-centre open trial was conducted in three centres in Germany. At the beginning of the 4-week run-in period, patients were prescribed a hypocaloric diet based on 30% energy as fat. The energy content of the diet was calculated from the patient's estimated basal metabolic rate, multiplied by 1.3 to estimate the total daily energy expenditure.[33] From this value, 600 kcal/day was subtracted to obtain a mildly hypocaloric diet and 30% of this energy content was recommended as the maximal daily fat intake. The minimum energy content was 1200 kcal/day. Patients were told to control their fat intake, but carbohydrate and protein consumption was *ad libitum*.

At weeks 24, 36 and 48, the recommended fat intake was adjusted according to the weight loss-induced reduction of the resting metabolic rate.[34]

After the 4-week run-in period, during which patients received placebo three times a day with meals, orlistat (3 × 120 mg) was given with meals for the following 72 weeks.

All participants completed a 4-day food diary, including at least one weekend day, at weeks − 4, − 2, 0, 12, 24, 36, 48 and 64.

All dietary protocols were calculated at a fourth centre. The fat content of each protocol was passed to the respective physicians at the three treatment centres, but all other details of the protocols, such as total calories and protein and carbohydrate consumption, remained unknown to the patients and physicians for the duration of the study.

At the beginning of the study and in eight subsequent sessions at 4-week intervals, patients participated in a group weight management programme that emphasized previous individual problems, pathogenesis of obesity, modification of eating habits, augmentation of physical activity, psychological and social factors and prevention of relapse.

Data analysis

Data were analysed for those patients who completed the entire study, with sub-groups generated according to final weight loss. An intention-to-treat analysis of food protocols is rather meaningless. All data are expressed as the mean ± S.E.M.

Dietary protocols were calculated with the program PRODI 4.5 Expert (Kluthe, Freiburg, Germany).

Cumulative data on food intake were calculated from week 0 to week 72 as the difference from the baseline intake, which is the mean value of the protocols at weeks − 4 and − 2. The calculation is based on the assumption that the food intake recorded during the 4 days following the visit to the study centre reflects the eating habits until the next food diary. Accordingly, the cumulative food intake at week 12 was based on the food intake recorded after the visit at week 0, and so on.

For statistical evaluation, analysis of variance was employed for comparison between groups and *t*-test for paired data for comparison within groups. Values of $P < 0.05$ were considered to be significant.

RESULTS

Sixty-two patients entered the 4-week run-in period. Two patients dropped out during this initial period, so that 60 patients entered the orlistat treatment phase. Subsequently, two patients were excluded because of non-compliance and two patients dropped out due to adverse events.

The 56 patients who completed the study (Table 1) showed a reduction in body weight from a mean value of 100.8 ± 3.5 kg to 98 ± 3.6 kg during the 4-week run-in period.

After 6 months, the body weight reached a plateau which was maintained fairly stable during the remainder of the study period. The total weight loss was 8.5 ± 0.88 kg ($P < 0.001$) for all patients, which corresponded to a decrease of 8% of the initial body weight (Figure 1).

According to the food protocols following the initial dietary advice at the start of the run-in period at week − 4, energy intake was approximately 1520 kcal/day, with only small and non-significant perturbations at weeks − 2 and 24 (Figure 2).

Table 1. Characteristics of the patients who completed the study (mean ± S.E.M.)

Number	56
Sex (female/male)	39/17
Age (years)	43.9 ± 10.4
Weight (kg)	100.8 ± 3.5
Body mass index (kg/m^2)	35.5 ± 0.7

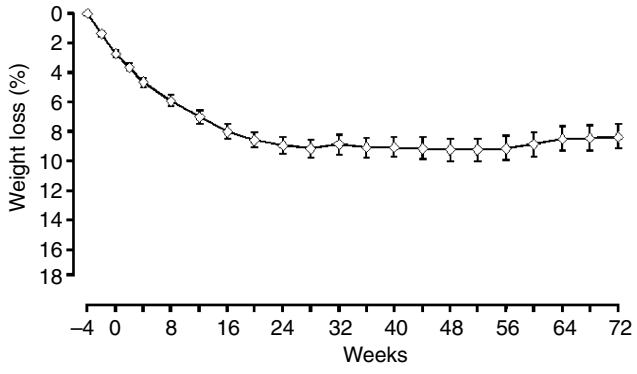

Figure 1. Mean percentage weight loss from the start of the run-in phase to the 72-week examination (mean ± S.E.M., $n = 56$).

Sub-group analysis

To obtain more detailed information about the patients' food intake in relation to the degree of weight loss, the study population was divided into three groups based on weight loss: group 1, < 5%; group 2, between 5 and 10%; group 3, > 10%. The demo-

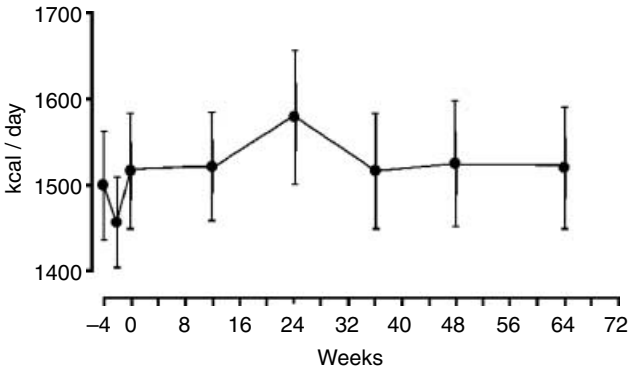

Figure 2. Daily food intake as calculated from the food protocols. Each point represents the mean value ± S.E.M. of four consecutive daily protocols in each of the 56 patients.

Table 2. Patient characteristics in the three sub-groups according to final weight loss (mean ± S.E.M.)

	Group 1 (< 5%)	Group 2 (> 5%, < 10%)	Group 3 (> 10%)
Number	21	15	20
Sex (female/male)	15/6	11/4	13/7
Age (years)	45.1 ± 9.2	42.8 ± 9.9	43.6 ± 11.2
Weight (kg)	98.4 ± 3.2	103.4 ± 3.8	101.6 ± 3.1
Body mass index (kg/m^2)	35.2 ± 0.6	35.9 ± 0.83	35.3 ± 0.59

graphic data of the three groups showed no substantial differences (Table 2).

Figure 3 illustrates the change in body weight in the three groups. In group 1, a weight loss of 6% occurred at week 28 and decreased steadily thereafter to 3% at week 72, which nevertheless was still significantly lower than the initial weight ($P < 0.001$). Group 2 lost approximately 6% at week 12 ($P < 0.02$ vs. group 1). The maximal weight loss of 8% was reached at week 24 and this plateau was maintained thereafter.

In group 3, the weight loss was more rapid during the run-in period. At week 0, there was a significantly greater effect compared with the other two groups (-3.5 ± 0.3 kg vs. -2.3 ± 0.4 kg in group 2 and -2.1 ± 0.4 kg in group 1; $P < 0.01$). These patients showed a progressively smaller but continuous decrease in body weight during the entire study period (Figure 3).

During the run-in period, the recommended fat intake was between 52 and 60 g/day in the three groups, decreasing further to a range of 44–51 g/day during the second half of the study according to weight reduction. Fat consumption in groups 1 and 2 was close to or within the recommended range until week 24. However, after the weight loss-induced adaptation of the hypocaloric diet, the fat intake was between 51 and 57 g/day which was more than the recommended amount. Only group 3 reduced the fat intake (36–45 g/day) below the recommended quantities during the entire study period.

Baseline carbohydrate intake was 172 g/day (group 1), 190 g/day (group 2) and 162 g/day (group 3). All groups increased their consumption. In group 1, the maximum was reached at week 48 with 208 g/day. In group 2, a plateau of between 195 and 200 g/day was maintained, whereas, in group 3, carbohydrate consumption was increased to 170–185 g/day.

Baseline protein intake was fairly constant in all three groups at between 64 and 66 g/day. In group 1, protein intake increased slightly to 67–70 g/day, group 2 showed a fairly constant intake around baseline levels, and group 3 decreased their protein intake to 56–60 g/day towards the end of the study period.

Cumulative carbohydrate intake increased in all three groups, being most pronounced in group 1 (Figure 4). The pattern of cumulative energy uptake paralleled the carbohydrate intake in groups 1 and 2, whilst the energy intake of group 3 remained at the level of the run-in period for the following 72 weeks (Figure 4). Figure 5 shows that groups 1 and 2 remained fairly stable with regard to fat and protein intake, whilst group 3 showed a substantial cumulative reduction of fat consumption in comparison with the initial run-in period.

The difference of 30 000 kcal of cumulative energy intake between groups 1 and 2 is mainly due to greater

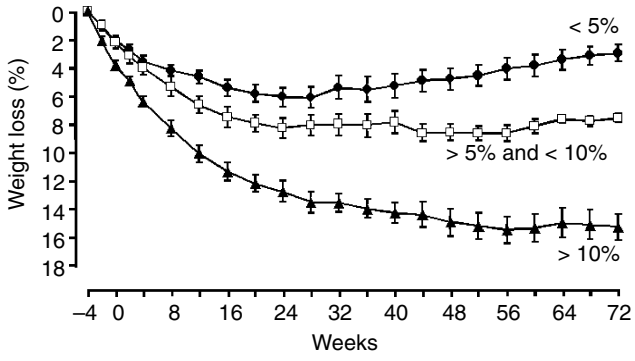

Figure 3. Mean percentage weight loss in the three sub-groups according to the final weight loss at week 72 (mean ± S.E.M.; group 1: < 5%, $n = 21$; group 2: > 5% and < 10%, $n = 15$; group 3: > 10%, $n = 20$).

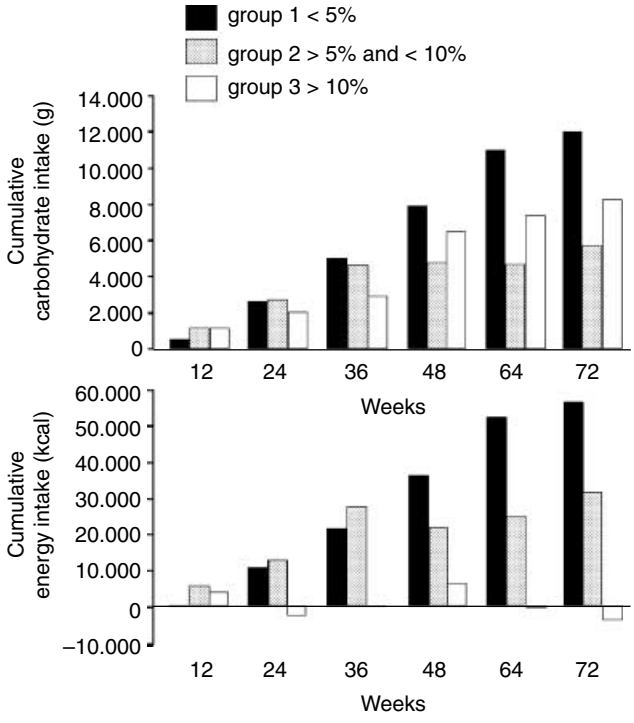

Figure 4. Mean cumulative intake of total energy and carbohydrates in the three groups of patients with different final weight losses. The data represent the difference from the mean value of the food protocols recorded at weeks − 4 and − 2, respectively.

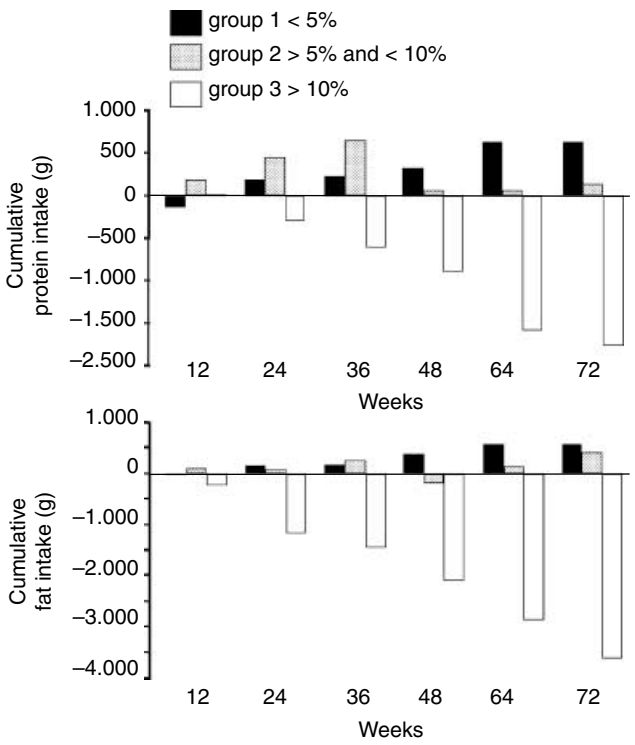

Figure 5. Mean cumulative intake of fat and protein in the three groups of patients with different final weight losses. The data represent the difference from the mean value of the food protocols recorded at weeks − 4 and − 2, respectively.

carbohydrate consumption, with only a minor contribution from fat intake. This amount of energy is equivalent to approximately 4 kg of body fat. It is noteworthy that this corresponds to the difference in weight loss at the end of the study period.

Patients in group 3 maintained their energy intake at the level of the run-in period. The substantial early reduction of energy intake below the calculated hypocaloric recommendation was carried forward, which largely explains the continuous weight loss in this group. The difference in body weight compared with group 1 is mainly due to the lower fat consumption (− 36 000 kcal), with a small contribution from the lower protein intake (− 8000 kcal) and a smaller degree of increased carbohydrate intake (+ 32 000 kcal vs. + 48 000 kcal).

DISCUSSION

The present study demonstrates that the weight loss of 8% in the entire study population is within the range previously reported in similar weight reduction trials.[10, 12, 27–32] In comparison with previously published data on orlistat-supported weight loss,[12] improvement in the maintenance of the initially reduced body weight was accomplished in the present study. This is most probably due to the adaptation of the caloric intake to the weight loss-induced reduction in the resting metabolic rate,[34] which has also been employed in two recently reported studies.[10, 30]

Following the initial dietary advice immediately prior to the start of the run-in period, the average energy intake of all patients was approximately 1500 kcal/day, which was sufficient to lose weight during the first 6 months. Thereafter, this energy content of consumed food permitted at least weight maintenance. Considering the reported fat intake, concomitant orlistat treatment can account for an energy deficit of 150–180 kcal/day via faecal fat excretion, which is equivalent to a cumulative deficit of 7–8 kg body fat per year. It should be noted, however, that such an 'energy balance' must be interpreted with caution, as no measured data on the basal metabolic rate are available, and it is based on a fairly constant energy expenditure, which was evaluated qualitatively in this study from reports of physical activity during the regular visits at the study centre.

The present analysis of food diaries suggests that the educational programme with a focus on low fat intake was successful, as all groups adhered to their fat allowance at least during the first 6 months.

However, after adaptation of the fat allowance as the result of the initial weight loss, only one-third of patients strictly adhered to these lower margins. Nevertheless, no group increased their fat consumption above the initial recommendation during the entire study period. This may have been reinforced by the concomitant orlistat treatment, as a substantial increase in fat intake would have been followed by steatorrhoea and related gastrointestinal side-effects.[36]

Similar to previous studies,[12, 27–32] one-third of the study population (group 1) was not capable of reducing their body weight consistently during the entire study period. Analysis of the dietary recordings demonstrates that the recommendation of '*ad libitum* carbohydrate' leads to an over-consumption that prevents the maintenance of reduced body weight (group 1). Only those patients who were capable of decreasing their fat intake substantially below the initially recommended quantities reduced and maintained their body weight

successfully, despite an increase in carbohydrate intake, as seen in group 3.

Although the training programme of eating behaviour, together with orlistat support, limits fat intake successfully, problems can arise from carbohydrate over-consumption. This does not mean that the focus on fat should be abandoned and a return to counting total calories will solve the problem. The present data clearly confirm that the initial focus on fat is successful and certainly facilitates the adherence to a hypocaloric diet. With ongoing treatment, and in patients with a small weight loss and/or a regain of body weight, carbohydrate intake may be a deleterious source of energy that shifts an initially sufficiently hypocaloric diet to a more or less eucaloric or even slightly hypercaloric state. Thus, the so-called 'bad or non-responders' of the previous studies could at least in part be due to a progressively increasing carbohydrate consumption up to an energetically relevant amount. In view of the overall low energy requirements during the maintenance phase of treatment, a positive energy balance of 100–200 kcal/day can easily be obtained even with fairly small quantities of complex carbohydrates having an energy density of 1.4–2.0 kcal/g (i.e. bread, pasta). Such a small but constant over-consumption, if not counterbalanced by increased energy expenditure, will account for several kilograms of weight gain per year.

Thus, education programmes on eating behaviour should not focus solely on fat intake when the loss of body weight has reached a plateau or weight gain returns. In these patients, limitations of carbohydrate intake may be necessary (especially when further reduction of fat intake is not compatible with their eating habits) for the therapeutically important long-term success of weight reduction.

ACKNOWLEDGEMENTS

This study was generously supported by Hoffmann-La Roche AG, Grenzach, Germany.

REFERENCES

1 World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO-Consultation on Obesity, Geneva, June 3–5, 1997. Geneva: WHO, 1998.
2 Hodge AM, Zimmer PZ. The epidemiology of obesity. Clin Endocrinol Metab 1994; 8: 577–99.
3 Seidel JC. The worldwide epidemic of obesity. 8th International Congress on Obesity In: Guy-Grand B, Ailhaud G, eds. Progress in Obesity Research, 8th edn. London: John Libbey, 1999: 661–8.
4 Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Health CW Jr. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med 1999; 341(15): 1097–104.
5 Goldstein DJ. Beneficial health effects of modest weight loss. Int J Obesity 1992; 6: 397–415.
6 Sjöström CD, Lissner L, Sjöström L. Relationships between changes in body composition and changes in cardiovascular risk factors: the SOS Intervention Study. Obesity Res 1997; 5: 519–30.
7 Williamsen DF, Paumuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight-loss and mortality in never-smoking overweight US white women aged 40–64 years. Am J Epidemiol 1995; 141: 1128–41.
8 Bray GA. Coherent preventive and management strategies for obesity. In: Chadwick DJ, Cardew G, eds. The Origins and Consequences of Obesity. London: John Wiley, 1996: 228–46.
9 Wadden TA, Frey DL. A multicenter evaluation of a proprietary weight loss program for the treatment of marked obesity: a five-year follow-up. Int J Eat Disord 1997; 22: 203–12.
10 James WPT, Astrup A, Finer N, *et al.* Effect of sibutramine on weight maintenance after weight loss: a randomised trial. The Lancet 2000; 356: 2119–25.
11 Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E. Long-term maintenance of weight-loss after a very-low-calorie diet: a randomised blinded trial of the efficacy and tolerability of sibutramine. Am J Med 1999; 106: 179–84.
12 Sjöström L, Rissanen A, Andersen T, *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. The Lancet 1998; 352: 160–61, 167–72.
13 Geliebter A. Gastric distension and gastric capacity in relation to food intake in humans. Physiol Behav 1988; 44: 665–8.
14 Schick RR, Schusdziarra V. Regulation of food intake. In: Ditschuneit H, Gries FA, Hauner H, Schusdziarra V, Wechsler JG, eds. Obesity in Europe 1993. London: John Libbey, 1994: 335–48.
15 Sichick RR, Schusdziarra V, Schröder B, Classen M. Effect of intraduodenal or intragastric nutrient infusion on food intake in man. Z Gastroenterol 1991; 29: 637–41.
16 Gonzalez MF, Deutsch JA. Vagotomy abolishes cues of satiety produced by gastric distention. Science 1981; 212: 1283–4.
17 Schick RR, Schusdziarra V. Appetit- und Sättigungsregulation. In: Wechsler JG, ed. Adipositas — Ursachen und Therapie. Berlin and Wien: Blackwell, 1998: 119–27.
18 Romieu I, Willett WC, Stampfer MJ, *et al.* Energy intake and other determinants of relative weight. Am J Clin Nutr 1988; 47: 406–12.
19 Lissner L, Levitsky DA, Strupp BJ, Kalkwart HJ, Roe DA. Dietary fat and the regulation of energy intake in human subjects. Am J Clin Nutr 1987; 46: 886–92.
20 Buzzard IM, Asp EH, Chlebowski RT, *et al.* Diet intervention methods to reduce fat intake: nutrient and food group com-

position of self-selected low-fat diets. J Am Diet Assoc 1990; 90(42–50): 53.
21 Brown GD, Whyte L, Gee MI, *et al.* Effects of two 'lipid lowering' diets on plasma lipid levels of patients with peripheral vascular disease. J Am Diet Assoc 1984; 84: 546–50.
22 Katahn MR. The T-Factor Diet. New York: Norton, 1989.
23 McCarthy MF. The unique merits of a low-fat diet for weight control. Med Hypotheses 1986; 20: 183–97.
24 Hammer RL, Barrier CA, Roundy ES, Bradford JM, Fisher AG. Calorie restricted low-fat diet and exercise in obese women. Am J Clin Nutr 1989; 49: 77–85.
25 Schlundt DG, Hill JO, Pope-Cordle J, Arnold D, Wirths KL, Katahn M. Randomized evaluation of a low fat ad libitum carbohydrate diet for weight reduction. Int J Obesity 1993; 17: 623–9.
26 Zhi J, Melia AT, Guerciolini R, *et al.* Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther 1994; 56: 82–85.
27 Heymsfield StB, Segal KR, Hauptman J, *et al.* Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. Arch Intern Med 2000; 160: 1321–6.
28 Hollander PA, Elbein StC, Hirsch IB, *et al.* Role of orlistat in the treatment of obese patients with type 2 diabetes — a 1-year randomized double-blind study. Diabetes Care 1998; 21: 1288–94.
29 Davidson MH, Hauptman J, DiGirolamo M, *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat — a randomized controlled trial. J Am Med Assoc 1999; 281: 235–42.
30 Finer N, James WPT, Kopelman PG, Lean MEJ, Williams G. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. Int J Obesity 2000; 24: 306–13.
31 Hauptman J, Lucas Ch, Boldrin MS, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. Arch Fam Med 2000; 9: 160–7.
32 Hill JO, Hauptman J, Anderson JW, *et al.* Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. Am J Clin Nutr 1999; 69: 1108–16.
33 James WPT, Schofield EC. Human Energy Requirement: A Manual for Planners and Nutritionalists (published by arrangement with the Food and Agriculture Organization of the United Nations). Oxford: Oxford University Press, 1990.
34 Prentice AM, Goldberg S, Jebb SA. Physiological response to slimming. Proc Nutrition Soc 1991; 50: 441–58.
35 Zhi J, Melia AT, Guerciolini R, *et al.* Retrospective population-based analysis of the dose–response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther 1994; 56: 82–5.