A study of the thermic responses to a meal and to a sympathomimetic drug (ephedrine) in relation to energy balance in man

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1. Sixteen adult male volunteers were selected on the basis of body size and customary food intake: half could be described as 'lean' and habitually consuming large amounts of food (group mean ± SEM: 15·03 ± 1·13 MJ/d), the high-energy-intake group (HEI group), and half though 'lean' admitted to a weight problem and regularly consumed a lower than average food intake (group mean ± SEM: 6·90 ± 0·39 MJ/d), the low-energy-intake group (LEI group).

2. Energy expenditure was measured by open-circuit indirect calorimetry. Resting metabolic rate (RMR) was recorded. A meal (Complan, either 2·1 MJ or 4·2 MJ), ephedrine hydrochloride (0·25 mg and 0·50 mg/kg body-weight) or a water control were then administered and metabolic rate (MR) was measured for 4 h. Blood was collected before and 1 h after the meal or drug, and the serum analysed for various hormones and blood metabolites.

3. The size of the thermic response to feeding but not the time-course was related to meal size in both groups. MR increased by 21·6 and 28·6% in the HEI group and by 8·2 and 20·0% in the LEI group in response to the 2·1 and 4·2 MJ Complan meals respectively. Fasting insulin levels were similar in both groups but showed a significantly higher level in the LEI than HEI group after the Complan meals.

4. The mean RMR increased by 5·2 and 10·3% in the LEI in response to ephedrine and by 15·7 and 11·2% in the HEI groups after 0·25 mg and 0·50 mg ephedrine/kg respectively. The rise in serum-free fatty acids in response to ephedrine was significantly higher in the HEI group than in the LEI group.

5. These results suggest (1) the meal size required to promote a maximum thermic effect is smaller in energetically-inefficient individuals (2) the sensitivity to a sympathomimetic drug is also increased in energetically-inefficient individuals.

6. We conclude that in energetically-efficient individuals both the thermic response to a meal and the sympathetic-mediated thermogenesis are lower than in energetically-inefficient ones.

In recent years, there has been considerable interest in the mechanisms involved in maintaining energy balance. In particular, the possibility that the regulation of energy expenditure may be fundamental to the control of body-weight has been investigated in both animal and human studies. Thus, the ability to increase energy expenditure after prolonged overfeeding of carbohydrate in man (Sims *et al.* 1973) or of cafeteria diets in rats (Rothwell & Stock, 1979) has been well documented. This facultative thermogenesis involves an increase in the resting metabolic rate (RMR) and may be mediated through sympathetic stimulation of brown adipose tissue metabolism and other thermogenic pathways in much the same way as cold-mediated thermogenesis.

A second component of diet-related thermogenesis is the extra heat production associated with each individual meal, the thermic effect of feeding (TEF), which may lead to a 10–40% increase in RMR after feeding (Bray, 1970; Miller, 1976). Although reports are conflicting, a critical evaluation of the evidence (Garrow, 1978) has shown that the size of this thermic response to a meal is reduced in obese individuals. Indeed, the observation that anorectics who had previously been obese had a smaller TEF than anorectics with no previous history of obesity suggests that the TEF may have a genetic component and may make a significant contribution to the energy imbalance (Stordy *et al.* 1977).

It has recently been argued that the failure to regulate energy intake rather than energy expenditure is of paramount importance in maintaining a stable ideal body-weight (Garrow *et al.* 1980). However, it is more likely that weight gain may result from a whole spectrum of individual changes in energy intake or expenditure or both. For these reasons, we have chosen to study the thermic response to two sizes of meal in two groups of volunteers especially selected for their large differences in daily energy intake and for their ability to maintain a stable body-weight. In addition, we have investigated their thermogenic responses to two doses of the sympathomimetic drug ephedrine to investigate the possible relationship between TEF and sympathetic-induced thermogenesis.

METHODS AND MATERIALS

The study was divided into two trials. The first examined the effect of meal feeding on thermogenesis and the second the effect of a sympathomimetic drug ephedrine on the metabolic rate.

Subject selection

A questionnaire was devised and distributed among male postgraduate students and staff within the School of Biochemical and Physiological Sciences. Details of their weight history, present weight and height, smoking habits and usual physical activity, such as mode of transport to and from work, were obtained. In addition, present eating habits were assessed by the '24 h recall' system. Several subjects also provided a weighed food intake over a 7 d period. Energy and nutrient intakes were computed using a food composition table based on that of Paul & Southgate (1978).

From the information provided, volunteers were selected and divided into two groups: (1) eight 'lean' subjects, who appeared to maintain their weight without effort and who regularly consumed large amounts of food daily (group mean 15·03 MJ) constituted the high-energy-intake group (HEI), (2) eight 'lean' subjects who admitted to a weight problem or who had been overweight but had slimmed successfully and who consumed a lower than average amount of food (group mean 6·90 MJ) comprised the low-energy-intake group (LEI). Activity levels between the two groups were closely matched.

The subjects used in the ephedrine trial comprised six from the HEI and seven from the LEI group. An additional subject was incorporated into the HEI group who had not been in the previous trial.

Anthropometric measurements

At the outset of each trial, body-weight and height were measured and skinfold thickness at four sites were taken using skinfold calipers (Holtain Ltd, Crymych, Dyfed). Body fat was computed from the skinfold values according to the method of Durnin & Womersley (1974).

The measurement of energy expenditure

Metabolic rate (MR) was measured by open circuit indirect calorimetry. The subject sat in a comfortable arm chair and was allowed to read books and magazines throughout the experimental period. An anaesthetic face mask was attached to a two-way valve system and the volume of expired air recorded on a Wright Respiration Monitor (British Oxygen Co., London). A sample of air was passed through a calcium chloride trap and drawn through an infra-red carbon dioxide analyser (machine sensitivity $\pm 0{\cdot}15\%$ over the full range 0–15%) and a paramagnetic oxygen analyser (machine sensitivity $\pm 0{\cdot}75\%$ over the full range of 0–25%) (P. K. Morgan Ltd, Chatham, Kent). The flow monitor, O_2 and CO_2 analysers were connected to chart recorders to give a continuous recording of these factors. The area under each trace was calculated by planimetry using an Allbrit planimeter (W. F. Stanley Co. Ltd, London) and the results computed from these values using standard methods.

At each session room temperature was checked and maintained at between 23° and 25°.

The flow meter was calibrated at weekly intervals against a wet gas meter accurate to 1 ml (Alexander Wright & Co., London). The gas analysers were calibrated before each session against standard gas mixtures (British Oxygen Co., London).

Experimental protocol

Measurements of MR were carried out on each subject on five separate occasions. Many of the volunteers had previous experience in the measurement of MR and were therefore familiar with the type of apparatus. A similar protocol was adopted for each session, which lasted approximately 5 h and a period of at least 1 week elapsed between each session.

After an overnight fast, the subjects were transported to the laboratory where they sat in a comfortable arm chair for at least 30 min before measurement of respiratory rates were started.

RMR

RMR was measured over two 15 min periods separated by 15 min. The meal, drug or water control was then administered, after which MR was measured for alternate 15 min periods for up to 4 h. The time-schedule for the two trials varied slightly.

The Complan trial

After measurement of RMR, a meal of either 2·1 MJ or 4·2 MJ Complan (Glaxo Farley Ltd, Plymouth) was eaten within 15 min. On a third occasion, an equivalent volume of water was drunk. Complan contained (g/kg): 180 protein, 330 fat, 470 carbohydrate and had an energy value of 18·4 MJ/kg dry weight.

The ephedrine trial

Ephedrine was administered orally as ephedrine hydrochloride (BP) at either 0·25 or 0·50 mg/kg body-weight with 100 ml water.

Blood samples

Blood (20 ml) was collected by venepuncture before and 1 h after the Complan, water or ephedrine. The serum was stored at −20° before analysis for (1) insulin, by a radioimmunoassay technique described by Godbole & York (1978), using a human insulin standard (Wellcome Lab., Beckenham, Kent) (2) triiodothyronine, using a radioimmunoassay kit purchased from The Radiochemical Centre, Amersham, Bucks, (3) corticosterids based upon a globulin-binding assay system essentially as described by De Jong & van der Molen (1972), (4) triglycerides and cholesterol, by the autoanalytical method described by Rush *et al.* (1970), (5) glucose, by the procedure of Trinders (1976), (6) free fatty acids (FFA), by the method of Carruthers & Young (1973).

Statistical analysis

The results were analysed by analysis of variance (ANOVA) to give a test of interaction between meal size (or drug dose) and the HEI group or the LEI group, as well as making a comparison between groups. For the time-course data a two by two by six analysis of variance was performed.

Ethical Committee approval

The study was approved by the Hampshire Area Health Authority Ethical Subcommittee (submission nos. 67/79 and S46/79).

Table 1. *Physical characteristics of the adult male subjects in the high-energy-intake (HEI) and the low-energy-intake (LEI) groups*

(Mean values with their standard errors)

Trial...	Complan				Ephedrine			
Group...	HEI		LEI		HEI		LEI	
No. of subjects...	8		8		7		7	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age (years)	25·1	1·5	30·6	3·3	25·1	1·9	32·0	3·4
Body-wt* (kg)	71·2	2·8	81·4	2·7	72·3	3·2	81·1	3·0
Height (m)	1·83	0·02	1·76	0·03	1·84	0·02	1·78	0·03
Lean body mass† (kg)	62·2	2·0	63·1	2·4	63·0	2·5	63·4	2·4
Total body fat‡ (kg)	9·0	1·3	18·3	1·7	9·3	1·2	17·7	1·8
Daily energy intake (MJ/d)	15·0	1·1	6·9	0·4	15·1	1·1	6·9	0·4
Range	12·2–20·5		5·4–8·8		12·2–20·5		5·4–8·8	
RMR (kJ/kg per d)	84	7	84	5	93	7	92	3

RMR, resting metabolic rate.
* Light indoor clothing worn.
† Body-weight minus total body fat.
‡ Calculated by the method of Durnin & Womersley (1974).

RESULTS

The physical characteristics and calculated daily mean energy intake of the subjects are summarized in Table 1. Although the LEI group were heavier than the HEI group, their lean body masses (LBM) were similar. The differences in body-weight could be attributed to a mean of 10 kg more body fat in the LEI subjects.

There was at least a twofold difference in the daily energy intakes between the two groups. Two of the HEI group were consuming over 18·0 MJ daily but appeared to maintain their body-weight at approximately the same level as other subjects habitually consuming much less. However, the mean RMR was similar in both groups as shown in Table 1. The reason for the apparent increase in RMR between the Complan and ephedrine trials is unclear. There were some changes in the subjects within each group, as outlined in the Methods section, and the trials were performed at a 6-month time interval.

Thermic responses to meal feeding

The metabolic responses to Complan meals are shown in Fig. 1. Subjects in the HEI group showed a rapid increase in metabolic rate, which was maintained even after 4 h (Fig. 1). In the LEI group, there was only a small delayed and transient increase in MR after the 2·1 MJ Complan meal but the response after the 4·2 MJ meal was similar in time-course and size to that of the HEI group after the 2·1 MJ Complan meal. The effect of meal size was much more pronounced in the LEI group than in the HEI group where only a small increase in thermogenesis could be observed with increasing meal size. The increase in MR (calculated as an increase over RMR prior to the experimental period), which was still maintained 4 h after feeding, could not be attributed to a time-dependent increase in the RMR of the subjects as no such changes were observed in the water control experiments (Fig. 1).

The thermic responses of the subjects to Complan over the 4 h measurement period are summarized in Table 2. All results are expressed in terms of kJ/caput per d. Values were

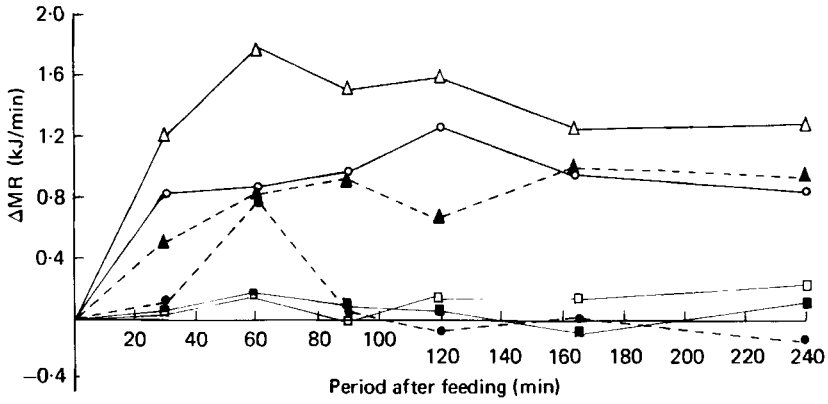

Fig. 1. Thermic effect of feeding (ΔMR; kJ/min) a meal containing either 4·18 MJ (△—△, ○—○) or 2·09 MJ (▲- -▲, ●- -●) of Complan to adult male subjects in the high-energy-intake group (△, ▲) and the low-energy-intake group (○, ●) over a 4 h period. □, ■ show values at each time for the water control experiments with HEI and LEI subjects. Points represent the mean values of eight subjects in each group. Details of methods are given on p. 22.

Table 2. *Changes in heat production in response to a meal by adult male subjects of the high-energy-intake (HEI) and low-energy-intake (LEI) groups*

(Mean values with their standard errors)

Group	No. of subjects	Meal size (MJ)	Total response (4 h) kJ/person Mean	SE	% increase over RMR Mean	SE	Test meal % mean
HEI	8	4·18	297	42	28·6	3·4	7·1
	8	2·09	211	40	21·6	4·4	10·0
LEI	8	4·18	227	31	20·0	2·8	5·4
	8	2·09	94	29	8·2	2·3	4·4
Analysis of variance							
Group (HEI or LEI)			$P < 0·05$		$P < 0·005$		
Meal size (4·18 or 2·09)			$P < 0·05$		$P < 0·025$		
Group/meal size			$P < 0·05$		$P < 0·025$		

also expressed in terms of kg/d, lean body mass, and metabolic weight (kg body-weight$^{0·75}$). However, the method of expressing the results did not alter the basic conclusion.

Total response (expressed in absolute terms and as a percentage over RMR) for the HEI group was significantly greater than for the LEI group. Furthermore, statistical analysis revealed a significant effect of meal size and a significant interaction between eater group and meal size. The effect of meal size was particularly pronounced in the LEI group but a smaller increase in thermic response with increasing meal size was evident in the HEI group. These differences were further illustrated by the fact that the HEI group expended a greater percentage of the energy consumed in the two Complan meals compared with that expended by the LEI group. ANOVA did not reveal any time-course differences of the response in the two groups (Table 3).

Table 3. *Statistical analysis (ANOVA) of the time-course responses to the thermic effect (ΔMR; kg/min) of a meal containing 4·18 and 2·09 MJ Complan and two doses of ephedrine hydrochloride (0·50 mg/kg and 0·25 mg/kg) administered to adult male subjects in the high-energy-intake group and low-energy-intake group over 4 h and 3 h periods respectively*

	Complan	Ephedrine hydrochloride
Group (HEI or LEI)	$P < 0·025$	NS
Time	$P < 0·002$	$P < 0·005$
Dose	$P < 0·05$	NS
Group/dose	$P < 0·05$	$P < 0·05$
Group/time	NS	NS
Dose/time	NS	$P < 0·05$
Group/time/dose	NS	NS

NS, not significant.

Serum metabolites and hormone concentrations

Fasting serum triglyceride levels were significantly higher in the LEI subjects than in the HEI subjects. Fasting insulin, triiodothyronine, corticosteroids, cholesterol, FFA and glucose levels were similar in both groups (Table 4). Although serum insulin increased after Complan in both groups, the response was greater in the LEI group than in the HEI group. FFA fell to similar levels in each group 1 h after the Complan meal. Complan feeding increased serum triglyceride and reduced serum FFA in a similar manner in both groups.

Complan acceptability. Subjects in the LEI group had difficulty in consuming the larger meal, some complaining of nausea and almost all of satiety approximately half-way through the meal. This phenomenon was not reported in the HEI group.

Thermic response to ephedrine

The time-course of the response to ephedrine is shown in Fig. 2. The ephedrine was administered on a weight basis as no differences were observed in the lean body masses of the two groups of volunteers.

ANOVA did not reveal any significant difference between the responses of HEI and LEI groups. However, it did show a significant interaction between group and drug dose. Thus, the LEI group with a small thermic response to the lower ephedrine dose showed a similar response to the HEI group after the higher (0·5 mg) ephedrine dose. The statistical analysis did not show any difference in the time-course of the response in the two groups. (Table 3).

The thermic responses to ephedrine over the 3 h measurement period are summarized in Table 5. When the results are expressed as % increase in MR, a significant effect of group is apparent. The interaction between group and drug dosage again revealed the enhanced response of the HEI group to the low ephedrine dose, increasing RMR by 15·7% as opposed to 5·2% in the LEI group.

Serum metabolite and hormone concentrations

Serum insulin was suppressed below 5 μU/ml in all subjects after ephedrine and precise values cannot be given as some fall below the sensitivity of the assay (Table 6). Because results from the Complan trial showed no changes for triiodothyronine and corticosteroids, no analyses were made on these hormones. No significant changes were observed for the cholesterol or glucose values. Fasting serum triglyceride levels were again higher in the LEI group than in the HEI group. Serum FFA were significantly reduced by ephedrine in both

Table 4. *Serum hormone and metabolite fasting levels and levels 1 h after a Complan meal in adult male subjects of the high-energy-intake (HEI) and low-energy-intake (LEI) groups*

(Mean values with their standard errors)

Group	No. of subjects	Meal size		Insulin (μU/ml) Mean	SE	Triiodothyronine (pmol/ml) Mean	SE	Corticosteroids (μmol/ml) Mean	SE	Triglycerides (mmol/l) Mean	SE	Cholesterol (mmol/l) Mean	SE	Free fatty acids (μmol/l) Mean	SE	Glucose (mmol/l) Mean	SE
HEI	8	4·18	Before	3·3	1·0	1·6	0·1	0·70	0·11	0·92	0·05	4·5	0·4	533	50	3·9	0·2
			After	22·5	4·9	1·6	0·1	0·59	0·08	0·90	0·05	4·2	0·3	326	22	3·8	0·3
HEI	8	2·09	Before	4·1	0·8	1·4	0·1	0·71	0·05	0·89	0·05	4·0	0·2	416	36	4·1	0·2
			After	13·9	2·2	1·4	0·1	0·72	0·06	0·93	0·06	4·2	0·2	302	43	3·4	0·3
LEI	8	4·18	Before	5·1	1·5	1·6	0·1	0·76	0·05	1·34	0·17	5·3	0·3	534	27	4·1	0·2
			After	33·4	9·9	1·6	0·1	0·67	0·09	1·38	0·16	5·1	0·3	330	27	4·3	0·5
LEI	8	2·09	Before	4·2	1·2	1·4	0·1	0·74	0·05	1·10	0·09	5·0	0·3	541	33	4·0	0·2
			After	20·4	3·2	1·2	0·1	0·58	0·08	1·23	0·12	5·4	0·4	341	46	4·3	0·3
Analysis of variance																	
Group (HEI or LEI)				NS		NS		NS		$P < 0·005$		NS		NS		NS	
Meal size (4·18 or 2·09)				$P < 0·005$		$P < 0·05$		NS		$P < 0·005$		NS		$P < 0·005$		$P < 0·05$	
Group/meal size				$P < 0·005$		NS		NS		NS		NS		$P < 0·05$		NS	

NS, not significant.

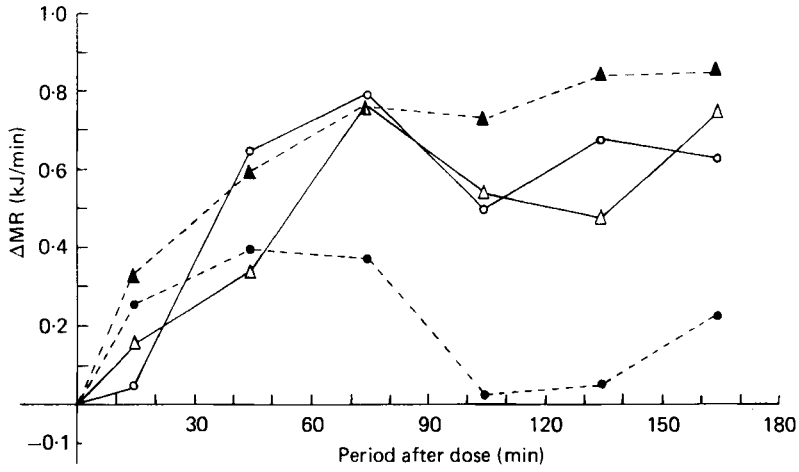

Fig. 2. Thermic effect of (ΔMR; kJ/min) two doses of ephedrine hydrochloride; 0·50 mg/kg (△−−△, ○−−○), 0·25 mg/kg (▲—▲, ●—●) administered orally to adult male subjects in the high-energy-intake group (△, ▲) and low-energy-intake group (○, ●) over a 3 h period. Points represent the mean values for seven subjects in each group. Details of methods are given on p. 22.

Table 5. *Changes in heat production in response to ephedrine hydrochloride by adult male subjects of the high-energy-intake (HEI) and low-energy-intake (LEI) groups*

(Mean values with their standard errors)

Group	No. of subjects	Ephedrine dose (mg/kg)	Total response (3 h) kJ/person Mean	SE	% increase over RMR Mean	SE
HEI	7	0·50	91	7	11·2	2·2
	7	0·25	120	9	15·7	3·0
LEI	7	0·50	97	11	10·3	2·7
	7	0·25	46	11	5·2	2·3
Analysis of variance						
Group (HEI or LEI)			NS		$P < 0·05$	
Dose (0·50 mg/kg or 0·25 mg/kg)			NS		NS	
Group/dose			$P < 0·05$		$P < 0·05$	

NS, not significant.

HEI and LEI groups. Furthermore, the very significant group–dose interaction was evidence of the greater response of the HEI group which was particularly marked after the 0·5 mg/kg ephedrine dose.

DISCUSSION

The two groups of subjects studied were similar in body-weight and in lean body mass but there was a very large difference between their mean energy intakes. The values of food intake were calculated from a '24 h recall' procedure in the majority of subjects. This method is inherently less reliable than weighing the food. In addition, it is recognized that

Table 6. *Serum metabolite fasting levels and levels 1 h after the administration of ephedrine hydrochloride in adult male subjects of the high-energy-intake (HEI) and low-energy-intake (LEI) groups*

(Mean values with their standard errors)

Group	No. of subjects	Ephedrine dose mg/kg		Triglycerides (mmol/l) Mean	SE	Cholesterol (mmol/l) Mean	SE	Free fatty acids (μmol/l) Mean	SE	Glucose (mmol/l) Mean	SE
HEI	7	0·50	Before	0·98	0·05	5·5	0·4	421	46	4·6	0·4
			After	0·98	0·04	5·9	0·6	1295	240	5·4	0·5
HEI	7	0·25	Before	1·08	0·06	6·4	0·8	434	87	4·6	0·4
			After	1·01	0·05	6·2	0·5	654	200	5·0	0·4
LEI	7	0·50	Before	1·28	0·14	6·6	0·7	499	21	5·2	0·4
			After	1·30	0·13	7·2	0·5	676	47	5·3	0·4
LEI	7	0·25	Before	1·17	0·13	5·6	0·4	459	38	4·6	0·3
			After	1·30	0·19	6·3	0·6	609	45	5·7	0·4
Analysis of variance											
Group (HEI or LEI)				$P < 0·05$		NS		NS		NS	
Dose (0·50 mg/kg or 0·25 mg/kg)				NS		NS		$P < 0·005$		NS	
Group/dose				NS		NS		$P < 0·005$		NS	

NS, not significant.

an individual's energy intake may vary widely from day-to-day (Dauncey, 1980) so that the values of energy intake assessed from a '24 h recall' may only be indicative of their general level of nutrient intake.

Although the LEI group was fatter than the HEI group, their mean energy intake was less than half that of the HEI subjects, an illustration of the great diversity of metabolic efficiency that can be observed in man which has been reported on many previous occasions (Widdowson, 1947; Rose & Williams, 1961; Garrow, 1974). This efficiency could not be related to a lower RMR in the LEI group. (In the present study the subjects were sitting rather than lying down so that the values obtained for RMR were probably 20–30% higher than the true values of RMR.) Rose & Williams (1961) were also unable to show any difference in the RMR between the large and small eaters in their study. However, it is clear that whereas the RMR comprises the major proportion of energy expenditure in the LEI group, it accounts for less than half the daily energy expenditure of the HEI group.

The possibility that the differences in energy requirement reflected differences in the daily levels in physical activity was considered. It is difficult to determine quantitatively the precise habitual differences in exercise levels. However, major differences appear to be unlikely since all subjects in both groups were involved in the similar occupations of teaching or research or both and a survey questionnaire revealed that a similar number of people in both groups regularly took part in sporting activities. It is possible, however, that the energy cost of exercise might differ in the two groups. A large variability in both the daily energy cost of a given exercise in the same individual and in the energy cost of a given exercise between individuals is known to exist although the underlying reasons for these differences are not understood (Passmore & Durnin, 1955; Apfelbaum, 1973; Garrow, 1974). However, it is unlikely that such differences could account for the observed differences in metabolic efficiency.

Thermic response to feeding

The TEF is dependent on meal size although the relationship is not linear (Miller, 1976). Our study, in confirming this effect, revealed differences in the relationship between meal size and TEF in the LEI and HEI groups. The HEI group exhibited a large thermic response to the small meal and showed only a small additional response when the meal size was doubled. This suggested that they had attained a response close to maximal after the small Complan meal. In contrast, the thermic response in the LEI group increased by more than twofold on doubling the meal size to a level similar to that in the HEI group. These results suggest that the meal size required to promote maximum thermogenesis is smaller in energetically-inefficient subjects (HEI group) but that the maximum thermogenic responses may be similar in all subjects irrespective of their efficiency.

These results contrast with those of Rose & Williams (1961) who were unable to observe any differences in the TEF in subjects with habitually low- and high-energy intakes. The reasons for the conflict in findings between the present study and that of Rose & Williams (1961) is unclear but could reflect a number of factors such as (1) only a single meal size of 3·39 MJ was used, a level at which any difference in response might be masked, (2) a difference in the composition and absorption rates of the commercial meal preparation used in this study and the 'English breakfast' used in the Rose & Williams (1961) study, (3) the effect of the previous exercise of the subjects in the study of Rose & Williams (1961). It has been suggested that TEF is potentiated by simultaneous exercise (Miller *et al.* 1967, Bray *et al.* 1973) but these studies have been criticized by Garrow (1978) who concludes that if it exists the potentiation is very small. A reduction in the size of the thermic response to an individual meal has been reported in obese subjects (Kaplan & Leveille, 1976; Pittet *et al.* 1976). That such a defect might contribute to the energy imbalance of obesity rather than be secondary to the obese state is suggested from the observation that the thermic response to feeding remains diminished in thin anorectics with a previous history of obesity (Stordy *et al.* 1977). By contrast, an exaggerated response to feeding (60% increase in RMR) has been reported in lipoatrophic individuals (Rossini *et al.* 1977). Such observations are consistent with the concept that differences in the TEF may be significant in the regulation of body energy stores.

The ability of man to adapt by increasing thermogenesis to a prolonged period of overfeeding is now well documented (Sims *et al.* 1973). Such adaptations, which are particularly pronounced on overfeeding high-carbohydrate diets, are accompanied by an increase in the RMR which may be mediated through the increased value for circulating triiodothyronine (T_3):reverse-triiodothyronine (r-T_3) (Danforth *et al.* 1979). In addition, work with overfeeding rats on 'cafeteria' diets suggests that the sympathetic stimulation of brown adipose tissue metabolism might be the basic mechanism for increasing thermogenesis (Rothwell & Stock, 1979) in a similar manner to cold-induced thermogenesis (Himms-Hagen, 1976). At present, the evidence that the sympathetic system is involved in such adaptive changes in man is very limited although Jung *et al.* (1979) have suggested that the thermogenic response to adrenaline may be impaired in obese subjects. In the studies reported in the present paper, it has been shown that the oral sympathomimetic drug ephedrine was less effective in stimulating thermogenesis (particularly at the 0·25 mg/kg dose) in the volunteers of the LEI group than in those of the HEI group. That this relationship becomes more significant when it is related to the RMR may reflect variations in absorption and metabolism of the orally administered drug.

These observations should not be interpreted as evidence that TEF is mediated through the sympathetic system in a similar manner to dietary-induced thermogenesis. It is generally assumed that the heat production associated with an individual meal represents the energy

required for the metabolic interconversions required in processing the dietary constituents into their storage forms and into new protein. However, since evidence is accumulating for the central regulatory role of the sympathetic nervous system in dietary-induced and cold-induced thermogenesis (Stirling & Stock, 1968; Himms-Hagen, 1976), its importance in TEF should be investigated. A recent report by Cawthorne & Arch (1980) tentatively concluded that both central and peripheral receptors were involved in the control system of TEF. Our results suggest that those individuals who have difficulty in maintaining a stable body-weight despite a relatively low energy intake (LEI group) may be characterized by a general reduction in the sensitivity of their thermogenic responses since in both the feeding and ephedrine studies the maximum responses attained were similar in the LEI and HEI groups but the responses to the smaller meal and smaller ephedrine dose were greatly attenuated in the LEI subjects. (It is possible that the attenuated thermogenic response to ephedrine in the LEI group could reflect a difference in the absorption of the drug or altered kinetics of its metabolism.) Although serum FFA were still increased 1 h after ephedrine in both LEI and HEI groups, the serum FFA of HEI subjects was significantly higher than that of LEI subjects, particularly after the higher dose of ephedrine. Although the time-course of the response of serum FFA to ephedrine was not investigated, these observations further suggest that the LEI subjects were less responsive to the sympathomimetic ephedrine.

The HEI subjects also differed from the LEI subjects in their insulin response to feeding. Although basal insulin values were similar in both groups, 1 h after feeding the serum insulin of LEI subjects was increased compared with the HEI subjects. This increase, at a single point of time, might reflect either a quantitative difference in the secretory response of the pancreas to the meal or a difference in the time-course of that response. Glucose-induced insulin secretion is enhanced in obese subjects (Rabinowitz, 1970). A further metabolic difference between the two groups was observed in their serum triglycerides which were consistently enhanced in the LEI group. Obesity is associated with an increase in serum triglycerides. It is possible that the increase in insulin secretion and in serum triglycerides may be related to the increased body fat of the LEI subjects. The experiments of Sims and his colleagues (Sims *et al.* 1973) demonstrated that increasing body fat as a result of over-feeding a mixed diet was accompanied by impaired glucose tolerance, enhanced insulin secretion and increased serum triglycerides. However, in such people the thermic effect of a standard meal and the RMR were increased (Goldman *et al.* 1976).

Relative contribution of TEF to difference in energy balance of HEI and LEI groups

Our study showed major differences in the thermic response to a meal between the HEI and LEI subjects. However, the difference still only amounted to 0·11 MJ (over a 4 h period) for the small meal, a very minor change in comparison to the 8·1 MJ difference in mean daily energy intake between the two groups. Clearly, the total daily increase in dietary-induced thermogenesis in the HEI group would vary with the number and size of individual meals, meal frequency and possibly exercise. Fabry *et al.* (1964) have suggested that there is an inverse relationship between body fatness and the number of meals taken daily, suggesting that TEF may be significant in the long-term regulation of body-weight. Calculations of 24 h energy expenditure from short-term measurements are prone to large errors (Webb, 1980) and the true significance of the thermic effect of feeding can only be ascertained by 24 h measurements. However, if one assumes that the daily energy intake is divided into four equal meals and that thermic effects were maintained for 4 h on each meal, i.e. 16 h/d, this would suggest that the RMR of the LEI group would be increased by approximately 8% and that of the HEI group by 29% (Table 2) during this 16 h period. Using these values, the difference in TEF would account for approximately 0·85 MJ/d. This is a small difference but maintained over a prolonged period could account for considerable accumulation of

body fat. The inability to account for the major proportion of the energy difference in the two groups suggests that the LEI subjects may be characterized not only by a reduction in the thermic effect of feeding but also a reduction in energy expenditure on exercise and in sympathetic-induced thermogenesis.

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