

## THE ANORECTIC EFFECT OF DEXAMPHETAMINE SULPHATE

BY

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*(Received February 29, 1968)*

The popularity of amphetamine, dexamphetamine and their analogues is a striking feature of relatively recent medical practice. In 1959 alone there were five and a half million prescriptions for amphetamine and phenmetrazine in the United Kingdom (Ministry of Health, 1961). Yet, in spite of such widespread use of these drugs, particularly in the treatment of obesity, there is little controlled observation to support the commonly accepted view that they consistently and effectively reduce hunger and appetite.

Bahnsen, Jacobsen & Theslepp (1938) were among the first to attempt a critical examination of the "subjective effects" of amphetamine, comparing a group of 100 normal subjects given amphetamine with a similar control group given placebo. Nineteen of the subjects in the amphetamine group noticed appetite reduction, compared with only one subject in the placebo group. Jacobsen & Wollstein (1939) also reported an anorectic effect in a minority of their healthy young male subjects given amphetamine over longer periods.

Harris, Ivy & Searle (1947) investigated the suggestion that the effectiveness of amphetamine and dexamphetamine in the treatment of obesity depended on a reduction in food intake. A group of seven obese patients lost more weight when taking dexamphetamine than when taking placebo; this difference in weight loss was closely paralleled by an equivalent difference in calorie intake. These authors did not, however, attempt to measure the effect of the drug on hunger. More controlled examination of the hunger-reducing action of dexamphetamine was undertaken by Bernstein & Grossman (1956), who administered 10 mg of dexamphetamine or normal saline to normal subjects through an intragastric tube 30 min before a 1,500 calorie meal. There was no significant reduction in calorie intake attributable to the drug. In a companion study, these authors could detect no hunger-reducing effect of dexamphetamine as assessed by a five-point hunger questionnaire. Kroger (1962) also illustrated the weakness of the anorectic effect of amphetamine by demonstrating that three placebo capsules were more effective in reducing hunger than one amphetamine capsule.

There would appear to be some inconsistency among the published reports concerning the efficacy of amphetamine and dexamphetamine as anorexigenic compounds when used in clinical dosage. Some authors have claimed that these drugs are potent suppressants

of hunger, while others have failed to find any such effect. The present study was undertaken in an attempt to resolve this controversy.

#### METHODS

The investigation was conducted in two phases. In the first phase, the anorectic activity of 10 mg of dexamphetamine and of placebo was determined in a group of American subjects at the University of Pennsylvania. In the second phase, the anorectic effect of 5 mg, 10 mg, 15 mg and 20 mg of dexamphetamine was examined in a group of British subjects at St. Bartholomew's Hospital, London.

The subjects participating in Phase 1 were eight male students attending the University of Pennsylvania, aged 19 to 25, in excellent health and of normal weight. The subjects in Phase 2 were eight male students attending City University, London, aged 18 to 21, who were also in good health and of normal weight.

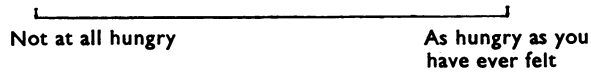


Fig. 1. Hunger rating scale.

The rating scale used to quantify reports of hunger is illustrated in Fig. 1. Similar scales have previously been used successfully in other studies involving the assessment of hunger (Spence & Ehrenberg, 1964; Jordan *et al.*, 1966), and the validity and reliability of this type of measure has been fully discussed by Stevens (1966). Subjects were instructed to mark the scale at the beginning of each experimental session, and at 15 min intervals thereafter, at a point which they considered appropriate to their subjective feelings of hunger at that particular time. For analysis of the results the scale was divided into thirteen points (0-12), the interval between each point being half an inch, and the ratings assigned an appropriate numerical value.

At 10.30 a.m. the subjects, all of whom arrived following an overnight fast, were instructed to swallow the contents of a coded packet of tablets. In the first series two tablets were taken each time, either two 5 mg dexamphetamine tablets or two placebo tablets, each subject participating in two experimental sessions. In the second series, four tablets were taken on each occasion, each subject taking part in five experimental sessions; the packets contained the following combination of tablets: (a) four placebo tablets; (b) three placebo tablets and one 5 mg dexamphetamine tablet; (c) two placebo and two 5 mg dexamphetamine tablets; (d) one placebo tablet and three 5 mg dexamphetamine tablets; (e) four 5 mg dexamphetamine tablets. In both series the order in which the subjects received the medication was random and strict double-blind procedure was maintained throughout. Not only was the trial double-blind; all the subjects were told that the drug under examination was an antacid preparation in order to avoid their ratings of hunger being influenced by preconceptions they might have had about anorexigenic drugs. Such preconceptions, termed "demand characteristics" (Orne, 1959), have previously been shown to influence significantly the results of an investigation into the action of an anorectic drug (Penick & Hinkle, 1964). To lend credence to this story, subjects were asked to complete a rating scale, similar to that for hunger, ostensibly concerned with gastric acidity.

At 12.30 p.m. each subject was given an individual luncheon packet containing a standard variety of sandwiches (each sandwich had the crust removed, and was divided into quarters), together with 8 ounces of milk. The sandwiches were prepared by the same person each time. The calorie content of each sandwich was estimated using standard food tables (Bowes & Church, 1956; McCance & Widdowson, 1960); the total calorie content of the meal given in Phase 1 was 1,606 and in Phase 2 was 1,535 (Table 1). At the end of the 30 min luncheon period all the sandwiches of each type remaining in each individual packet were counted, the number of quarter sandwiches of each type which had been consumed was noted, and the calorie intake calculated.

TABLE 1  
COMPOSITION OF STANDARD SANDWICH MEALS

	Contents	Number of Sandwiches	Calories per quarter	Total Calories
Phase 1	Tuna fish, onion, mayonnaise, lettuce	2	54	
	Peanut butter, jam	2	70	
	Egg, mayonnaise	1	47	
	Bologna sausage, American cheese, mayonnaise	1	75	
	+ 8 ounces of milk			1,606
Phase 2	Cheddar cheese, butter	1½	71	
	Ham, butter	1½	57	
	Tomato, butter	1½	42	
	Jam, butter	1½	60	
	+ 8 ounces of milk			1,534

From weighing sample sandwiches at random it was estimated that the maximum error due to variations in sandwich content was less than 10%.

To measure the occurrence of restlessness and dryness of the mouth, two commonly reported side-effects of amphetamine, subjects completed rating scales similar to those used to assess hunger.

To avoid all possible carry-over effect or the development of tolerance, experiments were conducted at weekly intervals on the same day of the week each time.

At the end of the investigation the subjects were asked what they had thought the purpose had been and were given a brief explanation of the study. No subject had ascertained the aim of the investigation or the nature of the drug under examination.

## RESULTS

### *Effect of dexamphetamine sulphate on hunger*

To determine the anorectic effect of dexamphetamine sulphate, the change in hunger rating following administration of the drug was estimated every 15 min for each subject. This was then compared with the change in hunger ratings occurring in the corresponding periods following placebo and the mean of these individual differences calculated.

*Phase 1.* There was considerable individual variation in response to 10 mg of dexamphetamine as compared with placebo; although five of the eight subjects had their hunger ratings reduced by dexamphetamine, the response of the whole group did not reach statistical significance (Table 2).

*Phase 2.* The group of British subjects seemed somewhat more sensitive to the anorectic effect of dexamphetamine. Although the effect of each dose individually failed to reach statistical significance, the anorectic effect of all four dosages taken together was statistically significant ( $P < 0.05$ ) 105 min and 120 min after administration (Table 3). Although no one dose was significantly more effective than any other, 10 mg and 15 mg did appear to be somewhat more potent than 5 mg (Fig. 2). The action of 20 mg did not begin until rather later.

As in Phase 1, there was marked individual variation in responsiveness to dexamphetamine, and the variance due to this was significant 2 hr after administration ( $P < 0.001$ ). Two subjects failed to show any anorectic response at all.

TABLE 2  
HUNGER RATINGS (PHASE 1)

Dose of dexamphetamine (mg)	Mean hunger rating ( $\pm$ s.e.)								Lunch		
	0	15	30	45	60	75	90	120			
0	4.0 ( $\pm 0.6$ )	3.8 ( $\pm 0.6$ )	4.0 ( $\pm 0.4$ )	4.1 ( $\pm 0.5$ )	4.6 ( $\pm 0.5$ )	4.4 ( $\pm 0.6$ )	4.8 ( $\pm 0.7$ )	4.5 ( $\pm 0.6$ )	4.9 ( $\pm 0.6$ )	135 1.7 ( $\pm 0.5$ )	150 1.1 ( $\pm 0.3$ )
10	3.9 ( $\pm 0.7$ )	3.9 ( $\pm 0.7$ )	3.8 ( $\pm 0.5$ )	3.8 ( $\pm 0.7$ )	4.1 ( $\pm 0.5$ )	4.3 ( $\pm 0.6$ )	4.5 ( $\pm 0.5$ )	4.6 ( $\pm 0.4$ )	4.8 ( $\pm 0.4$ )	1.6 ( $\pm 0.4$ )	0.8 ( $\pm 0.3$ )

TABLE 3  
HUNGER RATINGS (PHASE 2)

Dose of dexamphetamine (mg)	Mean hunger rating ( $\pm$ s.e.)								Lunch		
	0	15	30	45	60	75	90	120			
0	5.1 ( $\pm 1.2$ )	5.3 ( $\pm 1.3$ )	5.2 ( $\pm 1.1$ )	5.4 ( $\pm 0.8$ )	5.6 ( $\pm 0.9$ )	5.4 ( $\pm 0.8$ )	6.2 ( $\pm 0.9$ )	6.8 ( $\pm 0.7$ )	6.8 ( $\pm 0.9$ )	135 2.9 ( $\pm 0.5$ )	150 0.8 ( $\pm 0.2$ )
5	5.0 ( $\pm 0.8$ )	5.3 ( $\pm 1.1$ )	5.2 ( $\pm 0.9$ )	4.7 ( $\pm 0.9$ )	4.9 ( $\pm 1.0$ )	4.8 ( $\pm 1.1$ )	5.3 ( $\pm 1.4$ )	5.7 ( $\pm 1.2$ )	6.3 ( $\pm 1.0$ )	0.9 ( $\pm 0.3$ )	0.3 ( $\pm 0.1$ )
10	4.5 ( $\pm 1.1$ )	4.4 ( $\pm 1.0$ )	3.7 ( $\pm 0.7$ )	3.5 ( $\pm 0.9$ )	3.3 ( $\pm 0.8$ )	3.5 ( $\pm 0.7$ )	4.7 ( $\pm 0.6$ )	4.4 ( $\pm 0.8$ )	4.1 ( $\pm 0.8$ )	2.0 ( $\pm 0.6$ )	0.5 ( $\pm 0.3$ )
15	6.1 ( $\pm 1.2$ )	5.2 ( $\pm 1.0$ )	5.8 ( $\pm 0.8$ )	5.6 ( $\pm 0.8$ )	5.4 ( $\pm 0.7$ )	5.5 ( $\pm 0.8$ )	5.2 ( $\pm 0.5$ )	5.0 ( $\pm 0.5$ )	6.1 ( $\pm 0.6$ )	1.8 ( $\pm 0.5$ )	0.3 ( $\pm 0.1$ )
20	4.1 ( $\pm 1.0$ )	4.3 ( $\pm 0.9$ )	4.4 ( $\pm 0.9$ )	5.2 ( $\pm 1.0$ )	5.3 ( $\pm 1.1$ )	5.5 ( $\pm 1.0$ )	5.4 ( $\pm 0.9$ )	5.2 ( $\pm 0.6$ )	4.9 ( $\pm 0.8$ )	2.6 ( $\pm 0.5$ )	0.8 ( $\pm 0.5$ )

Analyses of variance

Subjects	(a) 105 min after administration			(b) 120 min after administration		
	d.f.	Mean square	F	d.f.	Mean square	F
Placebo vs. dexamphetamine	7	13.4071	4.48	7	15.5266	5.58
Doses of amphetamine	4	6.8578	2.29	4	10.1781	3.66
	1	20.1285	6.73	1	13.6597	4.91
	3	2.4343	<1	3	9.0176	3.24
			<0.01			<0.001
			n.s.			<0.05
			<0.05			<0.05
			n.s.			<0.05

Mean change in  
hunger rating

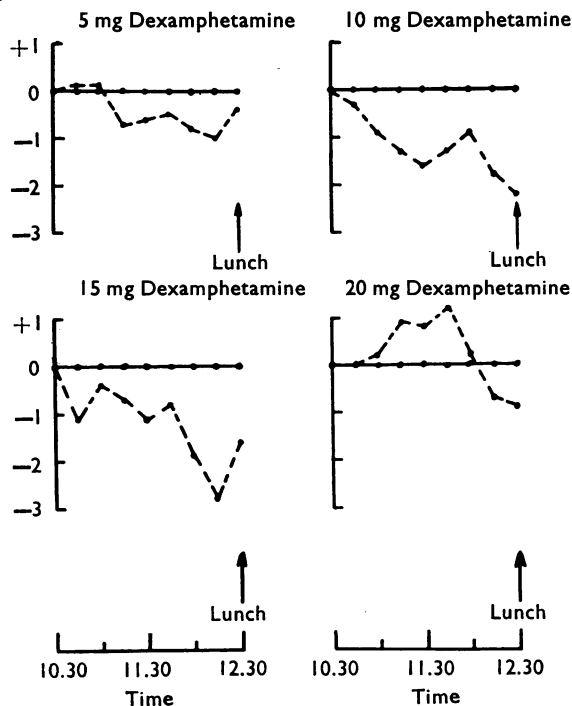


Fig. 2. Effect of 5 mg, 10 mg, 15 mg and 20 mg of dexamphetamine on hunger ratings (Phase 2).

Hunger ratings fell sharply during the standard lunch. In both series of experiments, dexamphetamine appeared to have no effect on this fall.

#### *Effect of dexamphetamine sulphate on food intake*

The calorie intake observed in each subject after dexamphetamine sulphate was compared with the calorie intake following placebo, and the mean of these individual differences were calculated.

*Phase 1.* There was no overall significant effect although there was considerable individual variation (Table 4). Three of the five subjects who had had their hunger ratings suppressed by dexamphetamine also had their food intake reduced.

TABLE 4  
CALORIE INTAKE (PHASE 1)

Subject	Placebo	10 mg of dexamphetamine
1	1,456	1,306
2	1,306	1,606
3	1,484	1,390
4	1,118	1,418
5	1,498	1,606
6	1,118	1,118
7	1,396	900
Mean	1,373	1,345

Difference  $28.5 \pm 96$  n.s.

TABLE 5  
CALORIE INTAKE (PHASE 2)

Subject	Placebo	Dexamphetamine			
		5 mg	10 mg	15 mg	20 mg
9	1,180	988	1,007	992	933
10	1,289	1,289	1,055	1,147	1,076
11	1,107	984	951	856	768
12	1,534	920	950	829	920
13	1,049	1,064	866	1,046	1,106
14	1,249	1,168	1,212	1,178	1,294
15	1,229	724	1,017	1,162	1,024
16	1,534	1,321	1,236	1,279	1,392
Mean	1,271	1,057	1,037	1,061	1,064
Diff. from placebo		214	235	210	207
S.E.		±81	±56	±78	±76

$P < 0.01$  for each dose dexamphetamine compared with placebo (Hartley's sequential  $t$ -test).

Analysis of variance

	d.f.	Mean square	$F$	$P$
Subjects	7	9.4581	6.24	$< 0.01$
Treatment	4	7.5957	5.01	$< 0.01$
Placebo vs. dexamphetamine	1	30.0155	19.81	$< 0.001$
Doses of dexamphetamine	3	1,224	$< 1$	n.s.

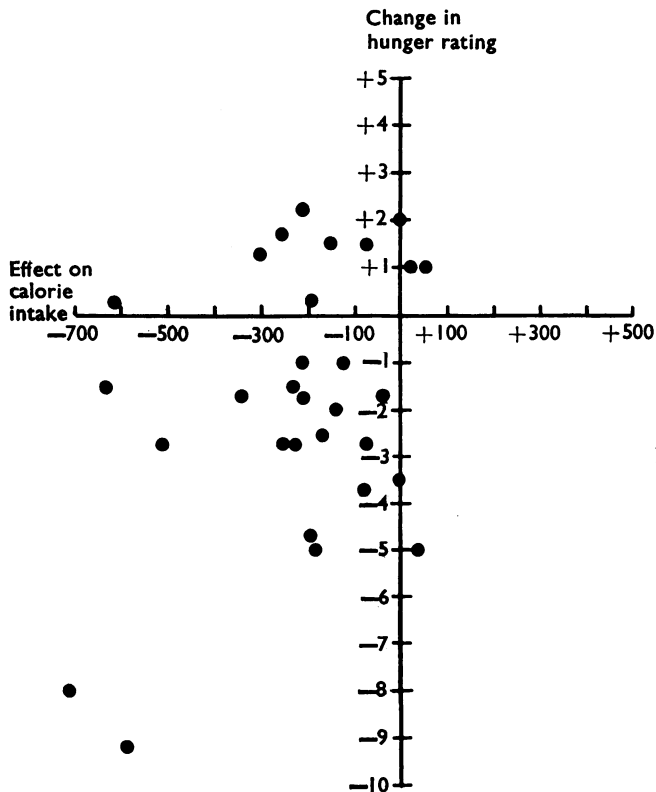


Fig. 3. Correlation between the effect of dexamphetamine on hunger and its effect on food intake.  $r = 0.38$ ;  $P < 0.05$ .

*Phase 2.* Dexamphetamine reduced calorie intake in most subjects and the overall effect of dexamphetamine as compared with placebo was statistically significant ( $P < 0.01$ ) (Table 5). As with the hunger ratings, none of the four doses was significantly more effective than the others (Hartley's sequential *t*-test, and analysis of variance).

*Relationship of the effect of dexamphetamine on hunger ratings to its effect on calorie intake*

In each of the eight subjects participating in Phase 2, the effect of each dose of dexamphetamine on hunger ratings at 12.30 p.m. was compared with its effect on the calories consumed between 12.30 and 1.00 p.m. (Fig. 3). There was a statistically significant positive correlation of 0.38 ( $P < 0.05$ ) between the effect of dexamphetamine on hunger and on food intake.

*Side effects*

*Restlessness.* Dexamphetamine did not seem to influence the subjective feeling of restlessness in any of the dose schedules used.

*Dryness of the mouth.* In Phase 1, dexamphetamine had little obvious effect on dryness of the mouth, whereas in Phase 2, dexamphetamine tended to reduce it if anything.

## DISCUSSION

*Techniques used in the investigation*

The assessment of subjective sensations such as hunger is greatly facilitated by quantitative estimations of the degree to which the sensation is experienced. In the present investigation, a linear rating scale was used to provide such a quantitative estimate of the change in hunger experience over a given time, and of the effect of dexamphetamine on this. The previous use of such scales has already been discussed.

The "face validity" of the rating scale employed in the present investigation is supported by two findings. First, after placebo administration, hunger rating scores rose as lunch-time approached, and fell sharply after food had been eaten. Secondly, the amount of food actually eaten under these conditions was found to be significantly related to the hunger scores obtained at the beginning of the meal (Silverstone, 1966).

The procedure developed to measure calorie intake permitted it to be determined simply and repeatedly without recourse to direct calorimetry.

*Effect of dexamphetamine on hunger*

Dexamphetamine sulphate in doses of 5–20 mg was found to reduce hunger ratings in the majority of subjects studied. There was, however, considerable individual variability in response, certain subjects appearing more sensitive than others to the anorectic action of the drug. It will be recalled that earlier investigations into the clinical pharmacology of amphetamine had revealed a similar individual variation (Bahnsen *et al.*, 1938; Jacobsen and Wollstein, 1939).

Within the range of doses studied, no one dose appeared to be strikingly more effective than the others, although 10 mg and 15 mg did appear to have a somewhat more potent

action than 5 mg. There was, however, no difference at all between 10 mg and 15 mg. Besser (1967) similarly detected no difference in effect between 10 mg and 15 mg of dexamphetamine on auditory flutter fusion threshold.

The anorectic effect of dexamphetamine was not maximal until approximately 2 hr after oral administration. This is in keeping with the finding that blood levels do not reach their peak until 2–3 hr after ingestion (Gallagher & Knight, 1958). Other pharmacological investigations (Smart & Turner, 1966; Besser, 1967) have also confirmed that the action of dexamphetamine on the central nervous system in man does not reach its maximum until at least 1.5 hr after administration. Such findings, taken in conjunction with our own, would suggest that if dexamphetamine is to be prescribed to reduce hunger it should be taken about 2 hr before meals (not 0.5–1 hr as is currently recommended).

#### *Effect of dexamphetamine on calorie intake*

The effect on calorie intake tended to parallel the effect on hunger; in the majority of subjects (twelve of the sixteen studied), calorie intake was reduced by dexamphetamine. As with hunger, there was considerable individual variation in response and there was little difference in effect between the dosages used.

Although the reduction in calorie intake produced by dexamphetamine among the British subjects was statistically significant, they still consumed on average more than 1,000 calories at a sitting even after 20 mg of dexamphetamine. Therefore dexamphetamine in clinical doses does not by any means suppress food intake completely and will consequently only be effective in the treatment of obesity when used in conjunction with a low calorie diet.

The degree of reduction in calorie intake following dexamphetamine was positively and significantly correlated with the degree of reduction of hunger rating scores obtained on the same occasion. Thus it appears likely that dexamphetamine does, in certain subjects at least, act by reducing hunger (“the desire to eat”), which in turn leads to a reduction in calorie intake. Although such an association between reduction of hunger and reduction of food intake following amphetamine was presumed by many earlier workers, it had not previously been verified experimentally.

Dexamphetamine did not appear to affect satiety; the fall in hunger ratings following the standard meal was in no way influenced by the drug.

#### *Side effects of dexamphetamine sulphate*

*Restlessness.* We obtained no evidence that dexamphetamine, given in doses of 5–20 mg under the conditions described, had any significance on the subjective feeling of restlessness. There was certainly no association between the reduction of hunger and restlessness. Modell (1960) had suggested that the anorectic action of amphetamine and related compounds “is the direct consequence of the central stimulant action common to all.” If a feeling of restlessness can be taken to reflect central nervous system stimulation, our findings would fail to support Modell’s hypothesis.

It is possible that subjects participating in previous investigations may have been influenced by their knowledge that amphetamine and dexamphetamine were widely known as “pep” pills; they would therefore expect to experience restlessness. Furthermore,



Bahnsen *et al.* (1938) and Smith & Beecher (1960) also reported that restlessness was experienced by a minority of subjects only. More recently Besser & Steinberg (1967) have shown that 5 mg of dexamphetamine had no significant effect on a whole range of subjective feelings including restlessness, although with 15 mg of ( $\pm$ )-amphetamine reports suggesting "jitteriness" are sometimes made (Legge & Steinberg, 1962).

*Dryness of the mouth.* Surprisingly, dexamphetamine sulphate, in the present investigation, tended to decrease rather than increase dryness of the mouth rating scores. In Phase 2, the mean fall in dryness of the mouth ratings following dexamphetamine paralleled the mean fall in hunger ratings.

In animal studies, it has been found that water intake, as well as food intake, was suppressed by dexamphetamine (Anderson & Larson, 1956; Epstein, 1959). If dexamphetamine in human subjects did have a "thirst reducing" activity as well as an anorectic action, the fall in dryness of the mouth ratings observed may reflect a fall in thirst sensations. Smith and Beecher (1960) found that more subjects felt less thirsty after dexamphetamine than felt more thirsty, but the difference did not reach statistical significance.

### Conclusions

Dexamphetamine sulphate in doses of 5–20 mg has a definite, but relatively small, hunger-reducing action in most subjects when administered in an acute experimental situation. Sensitivity to it varies considerably, however, and this individual variability may explain some of the discrepant results previously reported.

These results seem to lend support to the use of dexamphetamine sulphate in the treatment of obesity, but only as an adjunct to dietary restriction. While it is not known with any accuracy how long the anorectic action of this compound will last before tolerance develops, it would seem reasonable, because of the well known dangers of dependence, if it is to be used at all in the treatment of obesity, that it be prescribed intermittently for a few weeks at a time. Furthermore, it should be given about 2 hr before food so the time of maximum effectiveness will coincide with the meal.

### SUMMARY

1. Using a specially devised hunger rating scale and a simple measure of calorie intake, the anorectic activity of dexamphetamine sulphate, in doses from 5 mg to 20 mg, was estimated quantitatively under strict double-blind conditions in normal male subjects.
2. There was an overall tendency for dexamphetamine sulphate to reduce hunger ratings and calorie intake, but there was marked individual variation in sensitivity to the drug.
3. There was a significant positive correlation between the degree by which dexamphetamine reduced hunger rating scores and the degree by which calorie intake was reduced.
4. The maximum anorectic effect of dexamphetamine occurred at least 1.5 hr after administration.
5. Side effects, such as restlessness and dryness of the mouth, were never pronounced. In some subjects, dryness of the mouth was actually decreased rather than increased.

We should like to express our gratitude to Dr. Paul Turner, Reader in Clinical Pharmacology at the Medical College of St. Bartholomew's Hospital, for his considerable advice and help in the preparation of this paper and Miss C. Duncan for her assistance with the statistical analysis. We should also like to thank Miss V. Wang, Dietitian at the University of Pennsylvania, and Miss P. Humpherson, Chief Dietitian, St. Bartholomew's Hospital, for providing the standard calorie meals. We are grateful to Smith, Kline and French Laboratories, both in Philadelphia and Welwyn Garden City, for supplying the dexamphetamine sulphate and the placebo tablets used throughout.

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