DIETHYLPROPION IN THE TREATMENT OF "REFRACTORY" OBESITY

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Diethylpropion ("tenuate") is a recently introduced anorectic agent which reduces the food intake of experimental animals without causing undesirable stimulation of the central nervous system (Martin, 1959). Its efficacy as an adjuvant to the dietary treatment of obese persons is, however, unproved, as the few clinical observations reported were uncontrolled and inadequate (Ravetz, 1959; Spielman, 1959; Wilson and Long, 1960). We report the results of a controlled double-blind trial of diethylpropion in obese persons who had failed to respond to dietetic instruction during the previous year and whose obesity we have defined as being "refractory" (Duncan *et al.*, 1960).

Methods

Selection of Patients

All the 48 patients selected were women. Each patient (1) had reported regularly to the dietetic department throughout the previous year for supervision of the treatment of her obesity with a suitable diet of 1,000 to 1,400 calories; (2) had lost little or no weight during this time or in the three months before starting the trial; (3) was visibly obese and overweight by at least 25% of her standard weight; and (4) was not known to have heart disease and had no detectable oedema. Two patients in each group had very mild diabetes but showed minimal glycosuria and were not taking insulin or a sulphonylurea.

These patients were divided into two deliberately matched groups (Table I). Four in each group had to be withdrawn during the trial—two failed to report, one left the district, and one became ill with cholecystitis—and four were admitted to hospital on account of carcinoma, varicose ulceration, myocardial infarction, or increasing incapacity due to obesity. The last patient, who was in group B, weighed 350 lb. (158.8 kg.) at the beginning of the study and had been matched with the patient of group A who weighed 337 lb. (152.9 kg.); the retention of the latter accounts for the difference in the standard deviations in the mean absolute weights of the two groups. These patients who were withdrawn did not differ in terms of their change in weight during the study from the others receiving the same tablets. The essential facts about the 40 patients who completed the trial are set out in Table I. Many of them had taken part in a previous trial of phenmetrazine ("preludin") and methylcellulose (Duncan *et al.*, 1960), but no patient had taken any anorectic drugs during the previous year.

TABLE I.—*Data Concerning the Two Groups of Patients*

	Group A		Group B	
No. of patients	20		20	
Age (years) ..	56·3 (43–71)		54·4 (34–67)	
*Body weight:	lb.	kg.	lb.	kg.
1 year before trial	195·4±40·2 (157–340)	88·6±18·23 (71·2–154·2)	195·8±25·7 (162–257)	88·8±11·66 (73·5–116·6)
3 months before trial	195·9±38·2 (165–336)	88·9±17·37 (74·8–152·4)	195·2±22·2 (161–255)	88·5±10·07 (73·0–115·7)
Change in 3 months preceding trial	+3·9±3·6 (−2–+11)	+1·77±1·63 (−0·91–+4·99)	+2·1±2·9 (−1–+10)	0·95±1·32 (−0·45–+4·54)
At start of trial	199·8±37·7 (169–337)	90·6±17·10 (76·6–152·9)	197·3±23·1 (163–265)	89·5±10·43 (73·9–120·2)
†"Standard weight"	140·5±8·4 (126–164)	63·7±3·81 (57·2–74·4)	138·9±7·3 (129–151)	63·0±3·31 (58·5–68·5)
Excess weight at start of trial	59·4±32·3 (35–173)	26·9±14·65 (15·9–78·5)	58·4±22·5 (34–126)	26·5±10·21 (15·4–57·2)
Excess weight at start of trial as % of standard weight	41·9±19·6 (25–106)		41·7±15·6 (26–90)	

* Values are means, standard deviations, and ranges.
† Standard weight for each patient was derived from tables of the U.S.A. Medico-Actuarial Investigation, New York, 1912.

Initial Procedure

One month before starting the trial all the patients were seen both collectively and individually, and the purpose of the study was explained. They were told, (1) that they would receive two types of tablets whose identity would be unknown to them and to those concerned with the study; (2) that these tablets might or might not help them to eat less and thus to lose weight; (3) that they were to continue to try to adhere to the dietary regime which they were supposed to have been following during the previous year; (4) that they would not be told their weight and were not to weigh themselves; (5) that they should wear, as nearly as possible, the same indoor clothes at each visit. At this visit each patient was weighed and then allocated to one group. Thereafter each reported to a special clinic at fortnightly intervals.

Tablets Administered

The diethylpropion tablets each contained 25 mg. of the drug and did not differ in appearance, texture, or taste from the dummy tablets; the latter contained 0.25 g. of mannitol, 70 mg. of starch, and a small quantity of magnesium stearate. They were supplied by the manufacturers in bottles containing 56 tablets and labelled "O" or "X"; this identification was removed and the tablets were dispensed in bottles bearing only the patient's name. The nature of the tablets was made known to us only after completion of the trial and analysis of the results. The patients took four tablets daily, one half an hour before each of the three main meals and one in the late evening.

Further Conduct of Trial

Each patient reported fortnightly for 24 weeks. She was weighed in indoor clothing on a regularly standardized lever-type balance and her weight was made known to A. M. S. only. The patient was then seen by D. A. S., L. J. P. D., or K. R.; any subjective effects spontaneously attributed to the tablets were noted, but direct inquiry regarding specific effects was avoided. The patient was then given a bottle containing 56 tablets. A datum sheet was kept for each patient. These were held by A. M. S., who recorded on them the patients' weights and comments; none of these data was divulged to the medical or dietetic staff until completion of the study.

Results

Changes in Weight.—Table II shows that the administration of diethylpropion for 12 weeks resulted in a fall in the mean weight of both groups of patients and

that the taking of dummy tablets resulted in an increase. It can be seen from Table III, however, that the reduction in mean weight occurred only in the first eight or so weeks of the diethylpropion treatment and that an increase followed thereafter. This is illustrated in the Chart. Nevertheless, the progressive rise in the mean weight of the patients when receiving dummy tablets was sufficient to make the difference between their responses to the two preparations statistically highly significant at all times ($P<0.001$). The impression that diethylpropion loses its efficacy in most patients after six to eight weeks of its daily administration is supported by the data set out in Table IV.

Subjective Effects.—The change from one type of tablet to the other was not noticed by any patient.

TABLE II.—*Influence of Administration of the Two Preparations on Body-weight of the Two Groups of Patients*

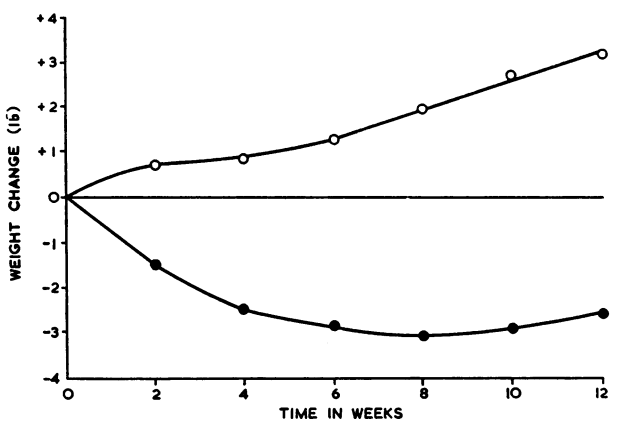
Period			Group A	Group B
	Initial weight*	lb.	199·8±37·7 (169–337)	197·3±23·1 (163–265)
		kg.	90·6±17·10 (76·6–152·9)	89·5±10·48 (73·9–120·2)
	After 12 weeks administration of:		Diethylpropion tablets	Dummy tablets
1	Weight	lb.	198·5±37·8 (165–336)	199·7±26·7 (159–268)
		kg.	90·0±17·14 (74·8–152·4)	90·6±12·11 (72·1–121·6)
	Change in weight	lb.	−1·33±5·07 (−10–+8)	+2·33±4·82 (−10–+11)
		kg.	−0·60±2·30 (−4·54–+3·63)	+1·06±2·19 (−4·54–+4·99)
	After 12 weeks administration of:		Dummy tablets	Diethylpropion tablets
2	Weight	lb.	202·3±38·5 (168–339)	195·9±27·3 (153–258)
		kg.	91·8±17·46 (76·2–153·8)	88·9±12·38 (69·4–117)
	Change in weight	lb.	+3·78±3·95 (−5–+9)	−3·78±4·34 (−10–+9)
		kg.	+1·71±1·79 (−2·27–+4·08)	−1·71±1·97 (−4·54–+4·08)

* Values are means, standard deviations, and ranges.

TABLE III.—*Mean Cumulative Weight Change of Groups A and B Combined during their Treatment With the Two Preparations*

Duration of Treatment (Weeks)	Weight Change			
	Dummy Tablets		Diethylpropion	
	lb.	g.	lb.	g.
2	+0·67 (±1·9)	+304 (±862)	−1·47 (±2·3)	−667 (±1,043)
4	+0·75 (±2·2)	+340 (±998)	−2·58 (±3·7)	−1,170 (±1,678)
6	+1·19 (±2·8)	+540 (±1,270)	−2·81 (±3·8)	−1,275 (±1,724)
8	+1·94 (±3·3)	+880 (±1,497)	−3·11 (±4·1)	−1,411 (±1,860)
10	+2·75 (±4·2)	+1,247 (±1,905)	−2·89 (±4·2)	−1,311 (±1,905)
12	+3·06 (±4·4)	+1,388 (±1,996)	−2·56 (±4·9)	−1,161 (±2,223)

Values are means and standard deviations.



Mean cumulative weight change of both groups combined when receiving the dummy tablets (○——○) and diethylpropion (●——●).

Indeed, many thought that the two types of tablets were being alternated every fortnight and others thought that each bottle contained both types of tablets; one of the latter remarked that every second tablet had a bitter taste. Table V lists the effects attributed by patients to the tablets. Of the 10 patients who felt less hungry when taking diethylpropion, eight were losing, one gaining, and one was not changing in weight.

TABLE IV.—*Pattern of Weight Change of the 40 Patients when Receiving the Two Preparations*

Type of Change in Weight	Diethylpropion	Dummy Tablets
Steady increase throughout the 12 weeks	5	19
,, ,, for 4 to 8 weeks and no change thereafter	0	8
No change during the 12 weeks	3	6
Steady loss throughout the 12 weeks	7	3
,, ,, for 4 to 8 weeks and no change thereafter	11	4
Steady loss for 6 to 10 weeks and gain thereafter	14	0

TABLE V.—*Subjective Effects Reported During Administration of the Two Preparations*

Side-effect Reported	Diethylpropion	Dummy Tablets
Increased appetite	0	5
Decreased ,,	10	2
Dry mouth	8	0
Difficulty in sleeping	2	2
More excitable	1	0
Depressed	1	0
More energy	3	2
Less ,,	4	1
Nausea	1	1
No changes	18	30

Discussion

Patients who for the first time seek medical treatment for their obesity usually adhere to the prescribed diet for some months and lose weight during this time; many continue to lose weight and achieve the desired standard. Although anorectic drugs may well accelerate initial loss of weight their use is neither required nor justified for these patients; they are therefore unsuitable subjects for the clinical evaluation of such agents. Nevertheless, many obese persons fail after a time to control their appetite, cease to lose weight, and may indeed put it on again. We have, as in a previous study (Duncan *et al.*, 1960), deliberately selected such patients for the clinical trial of diethylpropion as they are the only persons for whom an anorectic agent might be advantageous.

When subjected to this practical test diethylpropion caused a mean loss of weight which was significantly different from the mean gain in weight which occurred when the same patients were taking dummy tablets. The anorectic properties of the drug were therefore demonstrated, and it is possible to assess its mean efficacy in this respect. The caloric value of 1 g. of adipose tissue is 6 calories (Keys and Brožek, 1953), and the difference in mean weight of the 40 patients after 12 weeks of treatment with each preparation was 5.6 lb. (2,540 g.) (Table II). From these data we calculate that the caloric value of the daily diet eaten by the patients when taking diethylpropion was about 190 calories less than when they were receiving the dummy tablets. This represents about 2⅓ oz. (66 g.) of bread, ½ pint (280 ml.) of milk, or ¾ oz. (21 g.) of butter.

Nevertheless, the absolute loss of weight caused by the diethylpropion was very small; 20% of the patients did not lose weight and 80% of those who lost weight did so only during the first 6 to 10 weeks of treatment

and thereafter remained at that weight or gained weight. This latter type of response agrees with the generally accepted view that anorectic agents lose their efficacy in most patients within a relatively short time and that their long-term administration is valueless (Adlersberg and Mayer, 1949).

Diethylpropion did not cause any serious side-effects. In particular there was no evidence of undue central nervous stimulation or insomnia; a few patients noticed dryness of the mouth.

Consideration of the results of this study together with those of similarly conducted trials of the amphetamines and phenmetrazine (Edwards and Swyer, 1950; Duncan *et al.*, 1960; Hampson *et al.*, 1960), shows that there is little difference between the weight-reducing influence of the three drugs. Although the amphetamines and phenmetrazine are apt to cause central nervous system stimulation and may lead to addiction, it is justifiable to compare the costs of the drugs. The cost to the National Health Service of one month's treatment with each preparation when the tablets are prescribed in quantities of 100 on form E.C.10 and dispensed in Scotland is as follows:

	s.	d.
Diethylpropion (tenuate) tabs. 25 mg. q.i.d.	28	7
Phenmetrazine (preludin) tabs. 25 mg. t.i.d. ..	16	5
"Benzedrine" tabs. 5 mg. t.i.d.	5	10
"Dexedrine" tabs. 5 mg. t.i.d.	5	1
Tab. amphetamine sulphate *B.P.* or *B.N.F.* 5 mg. t.i.d.	3	6
Tab. dexamphetamine sulphate *B.P.* or *B.N.F.* 5 mg. t.i.d.	2	7

Finally, it is appropriate to consider the response to strict dieting of the very obese patient in group B, who was withdrawn from the trial because of increasing depression and physical incapacity due to her vast size. When admitted to hospital she weighed 355 lb. (161 kg.), and had no physical evidence of excessive fluid retention. For 10 weeks she was given a 600-calorie diet; during the first four to six weeks her activities were limited, but thereafter her daily caloric expenditure was increased by about 600 calories by walking. Over these 10 weeks a steady weight loss of 34 lb. (15.4 kg.) occurred, which is almost exactly that expected from the calculated mean daily deficit of 1,300 calories. During this time she did not experience hunger and was satisfied with her diet. This response is frequently seen in such patients dieted in hospital; it emphasizes that gross and persistent overeating is often due to psychological disturbances or habit, and therefore may well be refractory to the influence of the most effective of anorectic agents. It also refutes any suggestion that the obesity was due to irreversible abnormalities of appetite or metabolism and could not, therefore, be corrected by suitable reduction of food intake.

Summary and Conclusions

A double-blind trial of diethylpropion tenuate was carried out on 40 obese out-patients who had proved refractory to dietetic advice alone.

The difference between their mean gain in weight when given dummy tablets and their mean loss of weight when taking diethylpropion was statistically highly significant at all times during the 12 weeks' administration of each preparation. The absolute weight loss was, however, disappointingly small and similar to that previously recorded with the amphetamines and phenmetrazine (preludin). No important side-effects occurred.

Like other anorectic agents, diethylpropion lost much of its effect in most patients after 6 to 10 weeks of treatment. Apart from its expense, diethylpropion seems to be a suitable drug for use as a short-term adjunct to the dietary treatment of obesity.

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Medical Memoranda

A Case of Genital Prolapse in a Newborn Baby

Genital prolapse in the newborn is a rare condition usually associated with spina bifida. The following record is of a baby who showed no evidence of an associated lesion and who has made an apparently complete recovery after replacement of the prolapsed uterus. Some features of the mother's pregnancy and labour suggested that her abnormal uterine action was the important aetiological factor.

Case Report

A married woman aged 23 was referred to the antenatal clinic at 35 weeks with a breech presentation. One year previously she had an abortion at 11 weeks, but her medical history contained no significant feature.

During her present pregnancy there had been very slight vaginal bleeding at 5 and 13 weeks. A breech presentation, corrected at 34 weeks by external cephalic version, had recurred.

On her first visit to the clinic a midline fundal "dimpling" was noted and a provisional diagnosis of a degree of uterine duplication was made. Attempted version was again unsuccessful. At 37 weeks the impression of a fundal depression was confirmed, but exact palpation was difficult and the breadth of the uterus aroused a suspicion of twins. A flat abdominal film showed a single foetus presenting by the breech with both legs extended. Erect lateral pelvimetry demonstrated a true conjugate of 4.35 in. (11 cm.) and a pubo-sacral diameter of 4.25 in. (10.8 cm.). The pelvic shape appeared normal.

On later examinations the uterus felt normal and the foetal parts were much more readily palpable. The baby seemed small, and it was decided to await the spontaneous onset of labour in anticipation of a normal vaginal delivery, with the proviso that caesarean section be performed should progress not be satisfactory.

The patient was admitted to hospital three days before term. The membranes had ruptured spontaneously and clear liquor was draining. No contractions had been felt, the breech was free, and the foetal heart was satisfactory. Vaginal examination excluded cord prolapse.