From theoretical considerations one might have expected the first group to show a preponderance of strong responses with none at all in the latter. In fact, a strong response (205 μg. of oestrone per 24 hours) was given by a patient whose urinary total gonadotrophin excretion was 200 mouse uterine weight units per 24 hours. We believe these findings give firm support to Shearman's (1964) suggestion that the results of the gonadotrophin stimulation test would be more reliable than those of urinary gonadotrophin determination as usually employed for clinical diagnostic purposes.

Our observations lead us to suggest that a peak oestrone excretion after a single injection of 18,000 i.u. of P.M.S. of less than 15 μg./24 hours should be regarded as subnormal; that 15 to 80 μg./24 hours should be regarded as normal; and that responses in excess of 100 μg. imply ovarian hypersensitivity to P.M.S. We are not in a position to affirm that there would be similar responsiveness, or lack of it, to human gonadotrophin. However, at the upper and lower ends of the scale of response this certainly seems probable; in the intermediate range there might be room for doubt.

It is clear that there is a risk of producing ovarian hyperstimulation when a single injection of 18,000 i.u. of P.M.S. is given to a woman with polycystic ovaries. Our policy now, where the presence of such ovaries is thought possible, is to perform gynaecography before doing the gonadotrophin stimulation test and to withhold the latter if ovarian enlargement has been demonstrated.

Summary

After the injection of pregnant mares' serum gonadotrophin (P.M.S.) into women the urinary oestrone excretion reaches a peak most commonly on the sixth or seventh day. This is true if a total dose of 18,000 i.u. is given in a single injection or in two or three daily divided injections. On the basis of these observations a study has been made of a simple test of ovarian responsiveness to gonadotrophic stimulation involving a single injection of P.M.S. 18,000 i.u. and the determination of oestrone excretion on the seventh day after the injection (together with that in a baseline 24-hour urine specimen before treatment, shown not to be really necessary). The ovarian response so determined correlated well with ovarian size as estimated by gynaecography, while in contrast the urinary "total gonadotrophin" excretion was shown to be an unreliable guide to ovarian gonadotrophin responsiveness. It is suggested that a peak oestrone excretion after a single injection of 18,000 i.u. of P.M.S. of less than 15 μg./24 hours indicates a subnormal ovarian response; that 15–80 μg. covers the normal range; and that more than 100 μg. implies ovarian hypersensitivity, most probably indicative of polycystic ovaries.

Of 62 women investigated, none of whom had given a positive intradermal reaction, six complained of symptoms after the injection of P.M.S. In four these were minor, but two women developed more serious signs and symptoms of ovarian hyperstimulation, one being admitted as an abdominal surgical emergency. Both these last two women had polycystic ovaries, and use of the test is therefore not recommended in women *known* to have such ovaries.

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Comparison of Continuous and Intermittent Anorectic Therapy in Obesity

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Obese outpatients treated initially with diet and an anorexigenic drug usually lose more weight than those treated by diet alone. It is generally stated, however, that in most patients the anorectic loses its effect after two to four months of administration, and for this reason repeated short courses of drug treatment have been advocated (Silverstone, 1967). We report the results of a double-blind 36-week study undertaken to determine the efficacy of continuous and intermittent therapy with the anorexiant phentermine (Duromine).

Material and Methods

One hundred and eight women aged from 21 to 60 were included in the trial at the time of their first referral to the department. All were clinically obese and overweight by at least 20% of their standard (U.S.A. Medico-Actuarial Investigation, 1912). None had evidence of endocrine or cardiovascular disease, and patients who had previously experienced troublesome side-effects to amphetamine or its derivatives or who were thought to be psychologically unsuitable were excluded. No patient had knowingly taken an anorectic agent at any time during the previous two years, and though many stated that they were "dieting" none was on a prescribed dietary regimen.

Each patient was initially weighed, examined, had a dietary history taken, and was allocated to one of three comparable groups, each comprising 36 patients. Those in the first group were given four weeks' supply of dummy capsules, those in the second group were given capsules of identical appearance containing 30 mg. of phentermine, and patients in the third group were given alternate four-week supplies of the active and dummy capsules. They were told to take one capsule daily before breakfast, as phentermine is a drug-resinate complex which need be taken only once daily. Phentermine is also available as capsules containing 15 mg. of active drug. All patients were instructed in a diet based on the principles of simple carbohydrate restriction and designed to provide approximately 1,000 calories daily. No dietary advice was thereafter given.

Patients were asked to attend a special clinic every four weeks, wearing as nearly as possible the same clothing. Those who failed to report within a week of their appointment were withdrawn from the trial (Table I). At each visit the patient was weighed and was asked if any symptoms had occurred that she attributed to the capsules. She was then given a further four weeks' supply of capsules, the nature of which was not known

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to either the doctor or the patient. When the last patient had completed the 36-week period of study the pharmaceutical company supplying the capsules revealed which had been the active and which the inert ones.

TABLE I.—*Reasons for Patients Failing to Complete the Trial. Each Group Initially Comprised 36 Patients*

Treatment	Dummy	Phentermine	Alternate Phentermine and Dummy
Defaulted	7	7	6
Stopped capsules for more than 1 week	3	5	3
C.N.S. stimulation	—	3	4*
Left district	—	2	—
Intercurrent illness	1	—	1
Pregnancy	—	2	—

* One patient experienced symptoms while on dummy capsules.

Results

For various reasons 44 patients failed to complete the trial (Table I).

The relevant details of the 64 patients who completed the study are set out in Table II. The mean loss of weight in the 25 patients taking the dummy was 10.5 lb. (4.8 kg.), whereas in the 17 patients treated with phentermine and in the 22 with the alternate regimen the mean loss was 27.0 and 28.7 lb. (12.2 and 13.0 kg.) respectively (see Chart).

Five (20%) of the patients continuously taking the dummy and 12 (71%) of those taking phentermine felt less hungry, but only one in the latter group said that this persisted throughout the study. Of the 18 (82%) who felt less hungry with alternate therapy 10 did so only when taking phentermine, and of the other eight seven thought phentermine more effective,

TABLE II.—*Clinical Data and Weight Change in Three Groups of Patients. Last Line in Each Group Gives Means*

Age	Diet (cals.)	Standard Weight (lb.)	lb. Over Standard Weight	% Over Standard Weight	Weight Change per 4-Weekly Follow-up Visit (lb.) 1	2	3	4	5	6	7	8	9	Total Weight Change (lb.)
Continuous Treatment with Dummy Preparation														
55	1,780	153	47	31	−2	−2	−3	−10	−3	−3	−6	+3	+3	−23
31	2,150	141	43	31	−2	−4	−3	−6	−12	+8	−8	−4	−4	−35
55	1,810	145	36	25	−3	−2	+1	−4	−2	+1	−1	+2	0	−8
40	1,290	131	73	56	+2	+2	−5	+4	−9	−2	+1	+1	0	−6
24	2,310	124	82	66	−6	+2	+3	+2	+3	0	+2	+3	0	+9
54	1,950	147	46	31	+1	+4	0	−3	−2	+4	+1	−2	−1	+2
28	2,850	132	138	105	−13	−6	+1	+4	+8	−3	+4	−1	+4	−2
47	2,180	149	60	40	−10	−9	−5	−1	+1	+1	−5	0	+2	−26
28	1,440	130	81	62	−4	−2	+4	−6	+1	−1	−1	0	+1	−8
56	1,640	131	71	54	−10	+2	−5	0	+4	−4	+6	+2	+2	−3
41	2,930	148	62	42	−3	−3	−3	−4	+1	−2	+1	+2	+8	−3
52	1,060	131	59	45	−9	−5	−3	+2	0	+1	+1	0	+1	−12
57	1,560	138	54	39	−4	+1	−5	+3	0	−1	0	+2	0	−4
54	1,700	137	105	77	−1	−3	−1	+3	−5	−2	−1	+5	−2	−7
47	1,700	143	82	57	−12	−11	−3	0	−2	+1	−6	+2	+9	−22
54	2,460	153	46	30	−7	−2	−3	−2	+3	−3	+2	+2	−1	−11
25	2,000	142	87	61	−10	−6	+2	+2	+5	−1	+1	+4	−3	−6
48	890	137	75	55	+2	−2	−3	0	+4	+1	+2	+3	+2	+9
35	3,250	131	61	47	−7	−7	−2	−2	−4	+7	0	−1	−2	−18
26	1,350	120	99	83	−10	−2	0	−4	−5	+3	+3	−2	−3	−20
32	2,060	131	39	30	−3	−1	−1	−1	+2	+2	−2	−2	0	−6
36	1,950	155	57	37	−8	−6	−3	−2	+5	−9	−2	−3	0	−28
40	1,910	125	37	30	−1	0	−2	+1	−1	+2	−3	+2	+2	0
39	2,320	141	48	34	−9	−6	+3	0	−1	−4	0	0	−1	−18
55	1,530	131	34	26	−8	−3	−2	−3	−1	−2	+2	+1	−1	−17
42	1,880	138	65	48	−5·5	−2·8	−1·5	−1·1	−0·4	−0·2	−0·4	+0·8	+0·6	−10·5
Continuous Treatment with Phentermine														
50	3,190	138	150	109	−20	−9	−1	−4	−4	+5	+6	−1	−1	−29
28	2,100	149	57	38	−13	−8	−4	−5	0	−5	−3	+2	−3	−39
58	1,760	135	60	44	0	−14	+3	−4	+1	+3	−3	−4	+2	−16
35	1,870	126	121	96	−12	−11	−11	−6	−6	−4	−1	−2	−1	−54
46	1,310	142	65	46	−7	−10	−4	−2	−8	−1	−6	−6	−4	−48
22	1,710	130	68	52	−18	−9	−8	−3	−5	−5	−4	+3	−2	−51
27	1,440	120	90	75	−7	+1	−3	−4	−1	−4	−2	−1	−6	−27
38	1,710	152	83	55	−8	−4	−7	−1	+1	−1	+3	+9	−7	−15
21	1,560	130	154	119	−14	−12	0	−6	+2	−8	+9	+7	+4	−18
28	2,200	130	68	52	−11	−4	−3	−1	−1	0	+3	+2	+2	−13
24	1,110	121	43	36	−6	−5	−5	+2	−3	−3	+1	−3	−1	−23
50	3,730	142	87	61	−15	−4	−5	−8	+2	0	−5	+7	−6	−34
33	1,370	126	50	40	−12	−7	0	−3	0	−1	0	−3	+3	−23
35	1,750	121	32	26	−14	−4	−4	−2	+1	−3	+2	−1	0	−25
21	3,000	117	93	80	−16	−6	−4	−5	−3	−2	+1	−2	−5	−42
58	1,710	126	29	23	−1	+1	+1	+2	+1	+1	−2	+4	−1	+6
23	1,600	129	40	31	−4	−5	+1	+4	−7	−1	+4	−4	+5	−9
35	1,950	131	76	58	−10·5	−6·5	−3·2	−2·7	−1·8	−1·7	+0·2	+0·4	−1·4	−27·0
Alternating Treatment with Phentermine and Dummy														
36	1,300	134	107	80	−1	−13	−3	0	−7	−4	+4	+2	−2	−24
36	2,260	136	67	50	−14	−1	−6	−3	−7	+5	−4	+1	−2	−31
54	1,310	149	52	35	−6	+6	−9	0	−2	−2	+2	+6	−4	−9
47	1,920	140	49	35	−14	−2	−9	+2	−5	+4	−1	+2	−2	−25
44	950	142	58	41	−15	−3	−3	+5	−8	+8	−13	+3	+2	−24
21	1,700	129	76	59	−14	−1	−5	−1	−5	+7	−6	+2	−5	−28
28	3,470	154	142	92	−19	−12	−15	−5	−12	−3	−4	+13	−3	−60
48	2,100	129	41	31	−5	−1	0	0	−2	+1	−5	+6	0	−6
21	1,760	120	40	33	−6	0	−7	−6	−1	+4	+2	+1	−4	−17
37	1,750	126	79	60	−9	−2	−8	−6	−4	0	−5	−3	−1	−38
39	2,320	138	56	41	−12	−6	−9	−3	−4	−1	−3	−4	0	−42
50	2,570	158	86	54	−18	−1	−5	−1	−10	+2	−8	+6	−6	−41
27	1,640	123	82	67	−9	+3	−4	−1	−2	+2	−4	+2	−4	−17
35	2,000	158	94	60	−21	−9	−16	−9	−7	−6	−4	+2	−1	−71
42	3,000	152	125	82	−14	−5	0	+11	−5	+9	−11	+3	−10	−22
29	1,850	138	83	60	−13	−2	−7	−2	−5	−1	−5	−2	0	−37
54	1,790	134	40	30	−8	0	−2	+2	−2	+2	−1	+5	−1	−5
39	2,500	138	51	67	−16	+1	−5	+4	−3	0	+2	−1	+5	−13
36	2,000	142	71	50	−15	−3	−5	−1	−7	0	−6	+2	−1	−36
30	2,290	131	71	54	−17	−1	−6	0	+2	+1	+1	+4	−11	−27
48	1,120	143	101	71	−11	−3	−1	−2	+1	−1	0	+2	−1	−16
42	1,830	142	84	59	−16	−10	−8	−5	−2	−2	−2	+2	0	−43
38	1,930	139	75	55	−12·4	−3·0	−6·0	−1·0	−4·4	+1·1	−3·2	+2·5	−2·3	−28·7

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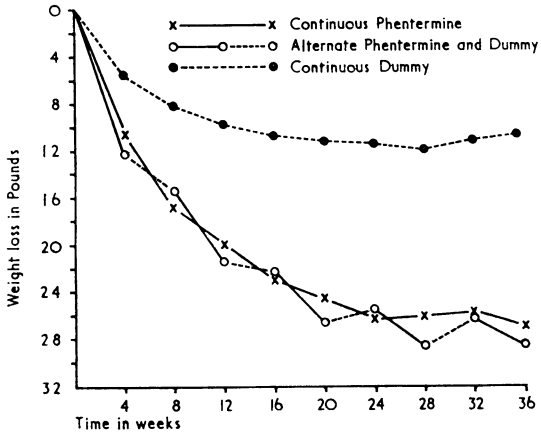
one noticing no difference between phentermine and the dummy. Nine of the patients in this group continued to report an anorectic effect with phentermine at the end of the study. Symptoms attributable to C.N.S. stimulation—insomnia, irritability, agitation, tension, and anxiety—were severe enough for discontinuance of treatment in seven patients, one of whom was



Mean weight loss in each group during the study.

TABLE III.—*Subjective Effects Reported During Treatment and Attributed by Patients to the Capsules*

Treatment	Dummy	Phentermine	Alternate Phentermine and Dummy
Total patients in group	25	17	22
Reduced appetite	5	12	18
C.N.S. stimulation	2	4	6
Depression	1	—	1
Constipation	2	1	—
Headaches	—	1	—
Dry mouth	—		4

receiving the dummy (Table I). Similar but transient symptoms were admitted by 12 patients who completed the study (Table III).

Discussion

Though only 64 (59%) of the patients completed the 36-week study, this is rather more than might have been expected in view of the duration of the trial (Silverstone and Solomon, 1965), and because obese patients are notorious defaulters (Seaton and Rose, 1965).

The present study confirms previous reports that phentermine reduces appetite (Freed and Hays, 1959; Le Riche, 1960; Seaton *et al.*, 1964a 1964b; Lorber, 1966). Like all anorectics its effectiveness varied considerably from patient to patient and was unrelated to the individual's degree of obesity, age, or previous dietary habits.

In earlier studies of patients who had "refractory obesity," administration of any one of several anorectics caused a maximum mean weight loss of from 2.6 to 9.3 lb. (1.2 to 4.2 kg.), this being achieved at the 8th to 12th week of treatment (Duncan *et al.*, 1960; Seaton *et al.*, 1961, 1964a, 1964b; Munro *et al.*, 1966). The present study shows that weight is lost more rapidly and over a longer period of time by newly referred obese patients treated with an anorectic. However, this is not entirely due to the latter patients being more sensitive to the appetite-reducing properties of the drug, since they were also given proper dietary advice for the first time, the effect of which is reflected by the response of those given the dummy (see Chart). The Chart also shows that alternating therapy with phentermine and placebo, each given for four weeks at a time, was just as effective as continued daily treatment with the anorectic.

It is difficult to determine for how long the appetite-reducing effect of the drug persisted. During the last four months there was no statistically significant difference between the mean weight change in all three groups of patients. Nevertheless, the Chart shows that the overall anorectic effect of phentermine when given intermittently persisted throughout the study but became less with each course of treatment, and that latterly weight was regained during the month the dummy was being taken. Also, 56% of patients treated intermittently or continuously with phentermine lost weight during the last 16 weeks of treatment, whereas only 28% of those given dummy capsules did so. However, this may merely reflect the greater mean weight loss of the phentermine-treated groups during the first 20 weeks, since, irrespective of treatment, those who lost most weight initially were those who continued to do so in the latter half of the study. Thus those gaining weight during the last 16 weeks had during the previous 20 weeks lost a mean of 9.5 lb. (4.3 kg.) if treated with the dummy and 15.4 lb. (7.0 kg.) if treated with phentermine, whereas those who continued to lose weight had lost 15.2 lb. and 29.7 lb. (6.9 and 12.6 kg.) respectively.

It may be that the weight loss achieved in this study can be improved (1) by extending the interval between courses of anorectic treatment from four to, say, eight weeks in an attempt to postpone the development of drug tolerance, (2) by altering the patient's dietary habits during the periods when an anorexiant is not being taken, or (3) by changing the anorectic agent from one course to another. These possibilities require further evaluation.

Summary

The appetite-reducing effect of phentermine administered continuously and intermittently was evaluated against an inert capsule during a 36-week double-blind trial in 108 women newly referred to hospital for dietary advice. Seven were withdrawn because of troublesome symptoms suggesting C.N.S. stimulation, though one was receiving the inert capsule.

Sixty-four patients completed the trial. The mean weight loss was 27.0 lb. and 28.7 lb. (12.2 and 13.0 kg.) for those who received phentermine continuously and intermittently, compared with 10.5 lb. (4.8 kg.) in the group treated with the dummy. The individual response to therapy was very variable, but irrespective of the method employed weight loss diminished with duration of treatment. There seems to be no advantage in taking an anorectic continuously, since intermittent treatment is as effective, is cheaper, and is possibly safer. Further clinical studies are still required to find out how anorectic drugs can best be used.

We wish to thank Riker Laboratories Ltd. for the supplies of phentermine (Duromine) and dummy capsules. We are grateful to the dietetic and nursing staff of the Diabetic and Dietetic Department.

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