CHLORPHENTERMINE
A NEW “APPETITE SUPPRESSANT”
A CROSS-OVER DOUBLE-BLIND TRIAL

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CHLORPHENTERMINE (“Lucofen”) is 1-(p-chlorophenyl)-2-methyl-2-aminopropane hydrochloride. It is a synthetic amphetamine derivate claimed to have none of the excitatory effects of the parent substance. The chemical relationship to amphetamine may be seen by a comparison of their formulae:

\[
\text{Chlorphentermine: } \text{C}_1\text{H}_2\text{N} - \text{C}(\text{CH}_3)_2 \text{NH}_2\text{HCl.}
\]

\[
\text{Amphetamine: } \text{C}_2\text{H}_2\text{N} - \text{CH(CH}_3)\text{NH}_2.
\]

Initial trials suggested that it was an effective appetite suppressant both in animals and man (Holm et al., 1960; Munc et al., 1960; Erlandsson et al., 1960; Nordlander, 1961). In this paper we report a double-blind cross-over trial of chlorphentermine in ambulant obese patients on a restricted diet.

METHODS.

A double-blind cross-over technique was used. The procedure followed was the same as that previously used in a similar trial (Hadden and Lucey, 1961). Patients were given a standard 1,100 calorie diet, containing 100 gm. of carbohydrate, or told to continue with their existing diet if this was of a lower calorie value. They were divided into two groups according to a sequence obtained from a table of random numbers. Patients were instructed to take one tablet three times daily before meals (either chlorphentermine 25 mgm. or placebo). After four weeks on one type each patient received the alternative tablets for the second four-week period. They were reviewed by one of us after four and eight weeks. No direct enquiries were made about the patients' subjective impressions of the drug or possible side effects. Only spontaneous complaints were noted. Neither the patients, doctors, dietitians, nor the nursing staff knew which tablets contained the active preparation.

THE PATIENTS.

The criteria for admission to the trial were as previously reported, all patients being more than 15 per cent. above their standard weight. Eighteen completed the trial out of the thirty-two who were initially accepted. The remainder (44 per cent.) failed to attend on one or more occasions and therefore could not be included. The two groups are compared in Table 1. There is no significant difference between Group A and Group B as regards age, height, initial weight or percentage overweight. The two groups are therefore statistically comparable.
TABLE 1.
COMPARISON OF THE TWO GROUPS.

|                          | Group A       | Group B       | t          | p                |
|--------------------------|---------------|---------------|------------|------------------|
| Number                   | 9             | 9             |            |                  |
| Age (years)              | 35.7 ± 22.4   | 32.1 ± 9.8    | t=0.449    | 0.7>p>0.6        |
|                          | (13–75)       | (19–46)       |            |                  |
| Height (inches)          | 63 ± 3.1      | 63 ± 3.8      | t=0.120    | p>0.9            |
|                          | (59–69)       | (60–72)       |            |                  |
| Initial weight (in lbs.) | 196.4 ± 30.8  | 199.2 ± 24.0  | t=0.052    | p>0.9            |
|                          | (158–261)     | (169–241)     |            |                  |
| *Standard weight (in lbs.)| 139.8 ± 17.5 | 144 ± 17      | t=0.516    | p>0.9            |
|                          | (104–154)     | (132–182)     |            |                  |
| Overweight (percentage)  | 41.3 ± 24.0   | 39.9 ± 14.6   | t=0.150    | p>0.8            |
|                          | (17–47.9)     | (16.1–61.8)   |            |                  |
| Obesity of over 10 years' duration | 5       | 6             |            |                  |
| Previously in similar trial | 8         | 6             |            |                  |
| Males                    | 1             | 2             |            |                  |

Values in columns 1 and 2 are means, standard deviations, and ranges. Column 3 applies the "t" test of significance to the difference of the means.

*Tables of the Life Extension Institute of New York.

Eight patients of Group A and six of Group B had taken part in a double-blind trial of diethylpropion immediately preceding the present trial. Of these eight Group A patients, five lost weight, two gained, and one remained unchanged. Five of the six patients in Group B had lost weight and one had remained unchanged. Five patients in Group A and six in Group B had a history of obesity exceeding ten years' duration.

Two patients in each group had mild diabetes mellitus, being managed by dietary carbohydrate restriction alone. Two patients had had myocardial infarction in the past and another had angina of effort. Four of the fifteen women had oligomenorrhea. Two female patients had a troublesome degree of hirsutism with a male type of body hair distribution, and two others were partners of infertile marriages. On the other hand, the heaviest patient in the series, a woman of 18 st. 9 lb., had a family of eleven.

RESULTS.

The results are recorded in Table 2. It will be seen that the mean weight change for the two groups together while on chlorphentermine (-4.8 lb.), exceeds the mean weight change of the two groups while on placebo (-0.08 lb.). The difference between these two means is significant (0.02>P>0.01). Chlorphentermine is therefore an effective aid to weight loss; the results are significant in spite of the small numbers taking part in the trial. Taking each
TABLE 2.
RESULTS.

| No. of Patients | Mean Weight Changes in Lbs. |
|-----------------|-----------------------------|
|                 | First month Placebo | Second month Chlorphentermine | First and second months combined |
| Group A         | ... | +0.44 | ... | -2.83 | ... | -2.38 |
| Group B         | ... | -6.77 | ... | -0.61 | ... | -7.38 |

The best individual result was achieved in a 19-year-old male who lost 15 lb. in four weeks while on chlorphentermine. Only one out of the total series failed to lose weight during the period on chlorphentermine. Eleven gained weight while on the placebo. There was no correlation between loss of weight and age, height, sex, initial weight or the percentage by which the standard weight was exceeded. The patients placed little emphasis on the effects of the drug on their appetite but six volunteered that they felt less hungry while taking chlorphentermine. Three of these were amongst those who had originally complained of excessive appetite.

SIDE EFFECTS.

Only spontaneous statements by the patients were recorded. There were no complaints of insomnia. On the contrary, one patient felt more sleepy while on chlorphentermine. There were no complaints of restlessness or irritability and there was no evidence of the development of psychotic symptoms. There was no instance of any tendency to addiction during the period on chlorphentermine and no patient experienced withdrawal symptoms. Three patients complained of individual symptoms of nausea, heartburn, and lack of energy respectively. Neither the patients with ischemic heart disease nor those with diabetes mellitus showed any deterioration.

DISCUSSION.

To lose weight one must eat less food than the body requires for energy expenditure. Dietary restriction alone is often adequate, but there remains a residue of cases who for one reason or another fail to lose weight while on an allegedly low calorie intake. It is these cases of "refractory obesity" (Seaton et al., 1961) who present the main challenge. Initial enthusiasm in the use of amphetamine as an appetite suppressant was lessened when it was found that a
very high proportion of patients developed unpleasant and even dangerous side
effects. Insomnia and irritability were common while many cases became addicted
and developed a clinical picture indistinguishable from paranoid schizophrenia.
Connell (1958) found withdrawal symptoms in twelve out of forty-two cases of
amphetamine psychosis. He stressed the danger of psychotic effects when using
amphetamine derivatives for weight reduction. No significant side effects in
eighteen patients were found during one month's treatment with chlorphentermine
in the present trial.

These results show that chlorphentermine is an effective aid in the treatment
of obesity when combined with moderate dietary restriction. The mean weight
loss for the eighteen patients over four weeks was 4.8 lb. The results might have
been better were it not for the fact that fourteen of our patients had taken part
in a similar trial of diethylpropion in the three months preceding the present
trial, as the four who were not in the previous trial showed a mean weight loss
of 7.8 lb. Chlorphentermine appears to be less effective when given after four
weeks placebo therapy than when given at the commencement of the trial;
although the difference is not statistically significant. A similar phenomenon in
an earlier trial, using diethylpropion, was more marked. This is in keeping with
the findings of Seaton et al., using diethylpropion and is a frequent finding in
similar trials of appetite suppressant agents, irrespective of the drug used. Our
results compare favourably with the early reports on chlorphentermine (Erlend-
sson, V. and F., 1960, mean weight loss over four weeks 3.5 lb.; Mune et al.,
1960, mean weight loss over four weeks 4.8 lb.; General Practitioner Clinical
Trial, 1961, mean loss over four weeks, 4.5 lb.).

The retail cost of one month's treatment with chlorphentermine is 9s. 8d.

SUMMARY.

A double-blind cross-over trial using chlorphentermine in conjunction with
dietary restriction is described. Chlorphentermine is shown to be an effective
aid in the treatment of obesity. All patients with one exception lost weight while
on the drug. There was no evidence of central nervous system stimulation and
no serious side effects developed during a four-week period on chlorphentermine.

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