Original Communications

Chorionic Gonadotropin in the Treatment of Obese Women

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In 1954, Simeons reported that injection of 125 I.U. of chorionic gonadotropin daily enabled obese patients to adhere to a fat-free, 500 calorie diet for four to six weeks and to lose weight at a rate of 1 to 2 pounds daily during this period.[1,2] Without the hormone, the patients experienced discomfort and would either eat secretly or discontinue the diet. Simeons suggested that chorionic gonadotropin acted by mobilizing fat from adipose tissue, making it more readily available for metabolic use by the body and thereby replacing the caloric deficit resulting from the rigid dietary restriction. Subsequently, Sohar[3] treated a group of obese patients for forty days with Simeons' diet in combination with daily injections of either chorionic gonadotropin or saline solution. Both treated and control subjects showed a uniform average weight loss of 20 pounds. Sohar attributed the reduction in weight to diet rather than to the hormone. In a later study, Lebon[4] reported that the weight reductions obtained in surgical patients treated by diet and daily injections of chorionic gonadotropin appeared to confirm Simeons' results.

The present report describes further attempts to evaluate the use of chorionic gonadotropin in the treatment of chronic obesity. After two preliminary studies, a group of obese women were treated for a forty-day period with a modification of Simeons' diet and daily injections of either chorionic gonadotropin or a placebo solution. Administration of drug and placebo was carried out by the double-blind technic; the code was not broken until six months after the completion of the treatment period.

SUBJECTS AND PROCEDURE

The group consisted of twenty women with severe chronic obesity, dating in most instances from childhood. The women, who were chosen at random from patients in the Obesity Clinic, ranged from seventeen to sixty-three years in age. Most of them had been able to lose weight previously by means of diet and appetite depressants. All supportive measures were stopped during the forty-day treatment period, except for vitamins, thyroid medications and diuretic agents prescribed for other conditions which were continued at previously regulated doses. The women were instructed to follow a modification of Simeons' diet[2] (see Table 1), limiting them to 550 calories a day. They were urged to keep a daily record of basal body temperature and to note changes in well-being, fatigue and other subjective sensations during the study.

Each subject returned daily to the clinic for an injection of either 125 units of human chorionic gonadotropin* in 1 ml. of diluent or 1 ml. of diluent alone, given by the clinic nurse. Administration

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* Follutein,® the preparation used in this study, was supplied through the courtesy of E. R. Squibb & Sons.

TABLE I
Diet Used in Study

Basic Rules of Diet
(1) Calories limited to 550 per day
(2) Meals limited to two a day
(3) Unlimited intake of fluids but only water, tea or coffee (without sugar and with only 1 tablespoonful of milk in twenty-four hours) permitted; the juice of one lemon a day is permitted but no other beverages of any kind
(4) No changes may be made in the diet; no substitutions except from the list of vegetables

Daily Meal Pattern	
Morning	Evening
1 orange	100 gm. lean meat* or fish, all fat trimmed off
100 gm. lean meat* or fish, all fat trimmed off	1 cup of boiled carrots†
1 medium-sized baked potato†	1/2 rusk *or* 1/2 slice toast
1/2 rusk *or* 1/2 slice toast, no butter	1 apple
Black coffee	Tea or coffee, no sugar
	Not more than 1 tablespoon of milk

Saccharin, vinegar, salt and pepper may be used for flavoring.

* Start with a quarter of a pound of boneless meat.
† One of the following vegetables may be substituted: 1 cup beets, 2 small baked or boiled potatoes, 1 cup cauliflower, 10 to 12 ribs of celery, 1 cup string beans, 1 cup turnips, large lettuce salad (with no dressing other than vinegar or lemon juice if desired), 1 cup kohlrabi, 1 cup okra, 1 cup pumpkin or squash, 1 cup sauerkraut, 1 cup spinach (or greens) or 1 cup tomatoes (raw or cooked).

was by the double-blind technic. The women were weighed once a week. To show weight trends, the weight of each subject six months before the beginning of the study and six months after completion of the injections were recorded. Body measurements (circumference of waist, hips and axillary area) were taken before and after the course of injections.

Laboratory tests were carried out within three days of the beginning of the treatment period and within twenty-four hours of the last injection. Basal metabolic rate and fasting blood sugar levels (Somogyi) were determined by routine methods. Protein-bound iodine determinations were performed by the dry ash method of Salter and McKay[5] and serum cholesterol determinations (before treatment) by the Schoenheimer-Sperry method.[6] Serum lipid concentrations were determined by a modification of Natelson's microgravimetric method.*[7]

RESULTS

The double-blind code of drug administration was broken six months after the end of the treatment period. Eleven women had received chorionic gonadotropin, and nine had received the diluent only. One of the subjects was treated for only twenty-eight days; the remainder had completed the forty-day course of injections. The subjects' cooperation in tests and measurements was generally good, although body measurements, mood and basal temperature were not recorded consistently. In some cases, it was not possible to obtain data both before and after treatment. The available data on the twenty women and the results of treatment are summarized in Table II.

Weight Loss

All but one of the women lost weight during the treatment period. A weight gain of 2 pounds occurred in one woman who was treated with chorionic gonadotropin. The difference in loss of weight in the treated women and in the control subjects was insignificant. The average loss at the end of the treatment period was 6.5 pounds in the treated women and 8.8 pounds in the control subjects. Maximum loss in a treated subject was 23 pounds and in a control subject 17 pounds. The over-all loss of weight during the period beginning six months before and ending six months after treatment was 14.2 pounds in the treated women and 5.3 pounds in the control women. From the start of treatment until six months after its completion, the average loss was 10.7 pounds in the treated group and 10 pounds in the control group. The late effects of the injections, as estimated by changes in weight six months after cessation of treatment, did not vary significantly in the two groups, although weight gain seemed more common in the control subjects.

Body Measurements

Only fourteen women cooperated in allowing

* Performed in Dr. Waxler's laboratory.

TABLE II

Clinical and Laboratory Data on Twenty Obese Women Before and After a Forty-Day Period of Treatment with a 550-Calorie Diet and Daily Injections of Chorionic Gonadotropin or a Placebo Solution

Case No.	Age (yr.)	Height (in.)	Weight (lb.)				Basal Metabolic Rate (%)		Protein-Bound Iodine (μg./100 ml.)		Fasting Blood Sugar (mg./100 ml.)		Serum Lipids (mg./100 ml.)	
			6 mo. Before	Before	After	6 mo. After	Before	After	Before	After	Before	After	Before	After
Treated Women														
13	51	66.5	228.0	238.0	215.0	237.0	−13	+32	7.0	8.1	74	75	720	560
3	52	64.0	169.0	177.2	172.9	154.9	−20	+17	7.5	8.5	80	86	725	...
1	17	67.5	277.0	259.6	258.0	253.3	−15	+11	6.7	7.8	72	89	448	...
6	50	64.5	172.5	159.5	152.9	166.3	0	+36	...	6.6	79	78	580	...
5	58	65.25	184.5	188.0	190.0	183.7	− 2	+ 4	5.4	5.8	82	72	600	645
12	45	55.5	165.0	165.5	155.8	141.2	0	− 5	6.0	7.0	74	77	855	860
2	30	64.0	250.0	250.6	245.5	231.2	+ 4	+ 4	6.4	5.9	75	75	695	580
16	36	63.5	191.0	159.7	154.7	140.0	−14	−15	...	6.6	...	68	404	...
17	43	63.5	170.0	167.0	160.2	169.9	+ 7	−10	7.4	7.5	82	68	655	550
15	51	60.5	183.0	182.4	178.2	172.3	− 3	− 5	5.8	7.0	72	78	655	...
21*	33	60.5	240.0	246.7	241.1	225.0	− 9	...	6.5	...	74	...	390	390
Control Subjects														
9	50	65.0	200.2	218.0	211.0	222.2	+19	+27	4.9	6.1	87	86	815	715
8	33	64.5	202.0	237.2	220.0	200.0	− 9	− 9	5.6	5.9	...	73	600	690
20	46	65.5	233.0	242.0	234.5	219.0	− 5	−20	6.3	6.6	72	81	430	...
10	63	62.0	179.0	186.4	176.4	198.0	+19	−10	5.8	6.1	64	64	740	...
14	42	66.0	198.0	195.4	192.7	198.0	+28	+ 5	7.0	6.0	76	79	1,090	840
18	39	65.5	236.7	201.7	195.0	180.0	− 6	−11	6.4	6.0	76	72	418	490
19	43	67.0	337.0	344.5	337.0	323.0	+11	− 5	5.4	5.4	138	184	...	605
22	58	61.0	202.0	204.0	193.0	195.6	− 7	+ 1	7.2	6.0	65	...	590	...
11	58	61.0	219.0	221.0	210.5	224.0	− 1	...	...	7.5	...	119	560	...

* Completed only twenty-eight days of treatment.

body measurements to be taken before and after treatment. The circumference of waist, hips or axillary area of the treated women and of the control subjects did not vary significantly.

Basal Body Temperature

Only eight of the total group kept a daily record of basal body temperature.

Laboratory Determinations

The basal metabolic rate was determined before and after treatment in ten treated women and eight control subjects. The results showed no change in five treated subjects and in two control subjects. The basal metabolic rate was decreased 17 per cent in one treated subject and from 15 to 29 per cent in four control subjects. In four treated women the rate increased 26, 36, 37 and 45 per cent, respectively; in each of two control subjects it increased 8 per cent. Analysis by the t test[8] showed that the increase in basal metabolic rate after treatment was not significant at the 95 per cent level. At the 90 per cent level the significance in this small group was inconclusive.

Protein-bound iodine determinations were carried out before and after treatment in eight treated women and eight control subjects. The values obtained were within the normal range (4.0 to 8.0 μg. per 100 ml.). Variation

between the values obtained before and after treatment was less than 1.5 μg. per 100 ml. Individual variation was ±0.5 μg. per 100 ml. (technical error for this method, ±0.5 μg. per 100 ml.).

Fasting blood sugar levels, determined before and after treatment in nine treated women and six control subjects, showed no appreciable change, not even in one subject with mild diabetes.

Serum lipid determinations were carried out in six treated women and four control subjects. The levels before and after treatment were normal (normal range for this method, 450 to 750 mg. per 100 ml.) or only slightly elevated in all but one control subject (Case 14). In this subject the concentration of 1,090 mg. per 100 ml. before treatment decreased to 840 mg. per 100 ml. during the study.

Serum cholesterol levels were determined before and after treatment in eight treated women and ten control subjects. It is of interest that the values obtained before treatment were above the upper limits of normal in only two (327 and 402 mg. per 100 ml.; normal range for this method, 107 to 320 mg. per 100 ml.). Since determinations obtained after treatment were performed by three different technics, the results are not included; however, no increase in serum cholesterol was noted in those subjects in whom the same method was used for both determinations.

COMMENTS

The difficulties in carrying out a controlled investigation in any group of clinic patients are well known[9]; these problems are multiplied in studies on obese subjects due to the many variables, including the psychologic factors, involved. Our subjects' cooperation was not entirely adequate, and tests were not completed in all cases. For this reason and because of the heterogeneity and small size of the experimental group, only tentative conclusions can be drawn from our data.

The average loss of 6.5 pounds in our treated subjects and 8.8 pounds in the control subjects was considerably less than the average loss of 20 pounds or more reported in similar controlled studies by Sohar[3] and Carne.[10] Both investigators expressed doubts about the value of chorionic gonadotropin therapy. Sohar attributed the consistent weight loss in his subjects to certain advantages inherent in Simeons' dietary program, and both he and Carne stressed the necessity for rigid maintenance of the diet. The small losses of weight in our subjects, as well as the lack of uniformity, suggests varied adherence to the diet.[11] None of our subjects, however, showed a large gain in weight in the six-month period following treatment, not even those who had lost substantial weight during the experimental period. Maintenance of weight reduction after treatment also was reported by Carne.[10]

The significance of the increases in basal metabolic rate was inconclusive. In studies on metabolism in obese subjects, Kekwick and Pawan[12] reported that diet had no consistent effect on the basal metabolic rate. In our subjects, changes in metabolic rate could not be correlated with adherence to diet, with weight loss or gain or with protein-bound iodine levels. Possibly, the increased metabolic rate in the treated subjects resulted from an anabolic effect of chorionic gonadotropin.[13]

The similar loss of weight in the treated women and in the control subjects in our series appears to confirm the conclusion of others[3,13,14] that diet, rather than the action of chorionic gonadotropin, is the important factor in Simeons' program. In addition, the fact that all subjects were treated with a "drug" may have played a part, as pointed out by Loranger and associates[15] in their double-blind study on the effects of two placebos administered as active drugs. A somewhat similar conclusion was drawn by Carne[10] and Kalina[14] in their reports on the use of chorionic gonadotropin in obese subjects. Both investigators commented that a daily injection in itself, whether of placebo or drug, apparently provided a psychologic stimulus, making it easier for patients to adhere to a diet.

Our study provides an excellent example of the value of an injected placebo in a controlled evaluation of drug action. Orally administered placebos are usually easily discerned by their lack of effect, particularly by obese subjects who are accustomed to amphet-

amine-like appetite depressants which may have a perceptible taste and often produce a sense of increased well-being or some other psychic phenomenon.[16] Injection as the route of administration of a placebo has an advantage in that the subject does not expect an immediate discernible effect.

SUMMARY

No effect of chorionic gonadotropin therapy in producing weight loss was found in a study on a group of twenty obese clinic patients. The women were treated for a forty-day period with a 550 calorie diet and a daily injection of either chorionic gonadotropin or a placebo solution, administered by the double-blind technic. All but one subject lost weight, but the losses were small and not uniform, suggesting varied adherence to the diet. The basal metabolic rate was increased in four treated patients and two control subjects. These changes could not be correlated with weight loss, apparent adherence to diet or protein-bound iodine levels.

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REFERENCES

1. Simeons, A. T. W. The action of chorionic gonadotrophin in the obese. *Lancet*, 2: 946, 1954.
2. Simeons, A. T. W. Chorionic gonadotropin in geriatrics. *J. Am. Geriatrics Soc.*, 4: 36, 1956.
3. Sohar, E. A forty-day–550 calorie diet in the treatment of obese outpatients. *Am. J. Clin. Nutrition*, 7: 514, 1959.
4. Lebon, P. Action of chorionic gonadotrophin in the obese. *Lancet*, 2: 268, 1961.
5. Salter, W. T. and McKay, E. A. Iodine in blood and thyroid of man and small animals. *Endocrinology*, 35: 380, 1944.
6. American Association of Clinical Chemists, Standard Methods of Clinical Chemistry, vol. 1, p. 43. New York, 1953. Academic Press, Inc.
7. Natelson, S. Microtechniques of Clinical Chemistry for the Routine Laboratory. Springfield, Ill., 1957. Charles C Thomas.
8. Mood, A. M. Introduction to the Theory of Statistics. New York, 1950. McGraw-Hill Book Co., Inc.
9. Grenfell, R. F., Briggs, A. H. and Holland, W. C. A double-blind study of the treatment of hypertension. *J.A.M.A.*, 176: 124, 1961.
10. Carne, S. The action of chorionic gonadotrophin in the obese. *Lancet*, 2: 1282, 1961.
11. Hastrup, B., Nielsen, B. and Skouby, A. P. Chorionic gonadotropin and the treatment of obesity. *Acta med. scandinav.*, 168: 25, 1960.
12. Kekwick, A. and Pawan, G. L. Metabolic study in human obesity with isocaloric diets high in fat, protein or carbohydrate. *Metabolism*, 6: 447, 1957.
13. Landau, R. L., Knowlton, K., Lugibihl, K., Brandt, M. and Kenyon, A. T. The anabolic effects of chorionic gonadotropin in normal young men. *J. Clin. Invest.*, 29: 619, 1950.
14. Kalina, M. A. Chorionic gonadotrophin in the obese. *Lancet*, 2: 1307, 1961.
15. Loranger, A. W., Prout, C. T. and White, M. A. The placebo effect in psychiatric drug research. *J.A.M.A.*, 176: 920, 1961.
16. Modell, W. Status and prospect of drugs for overeating. *J.A.M.A.*, 173: 1131, 1960.