

Guest Editorial**Chorionic Gonadotropin and Obesity?**

GUSMAN, in a paper appearing in this issue (1), writes convincingly about the chorionic gonadotropin treatment of obesity. The treatment first described by Simeons (2) is evidently in widespread use in this country and has attracted the attention of the lay press. Yet the scientific literature on this subject is scant. Dr. Gusman's plea for a second look must be considered in the frame of reference of known facts.

The subject resolves itself into three main parts and each of these will be discussed briefly. The first is whether this treatment helps to bring about acute weight loss. The second concerns the usefulness in long-range (life-long) treatment of obesity. The final topic is the possible mechanism of action of chorionic gonadotropin in obesity.

Acute Weight Loss

Many regimens, dietary and otherwise, have been claimed enthusiastically as good treatments for obesity. Yet, there is no uniformity in the method of reporting results, and results are often reported in such a way that comparison with results of others is impossible, as pointed out by Feinstein (3).

Simeons' program calls for a strictly prescribed diet of 500 kcal a day in two meals, for deep intramuscular injection of 125 units of human chorionic gonadotropin (HCG) six days a week, and daily conferences with the physician during which the previous day's diet is carefully reviewed (2). While Gusman clearly shows

that his patients lost weight, he shows no quantitative comparison with other studies.

In addition to the various appetite-suppressing drugs, numerous diets have been advocated from time to time. These include the usual low calorie diet, the low carbohydrate diet (4), and the low protein diet (5). More recently, total starvation has been found to be extremely effective in promoting acute weight loss and is remarkably well tolerated with few adverse symptoms although there are some untoward side effects (6). The literature is rampant with short-term good results of many different therapies. While no one can question that Dr. Gusman and Dr. Simeons achieve weight loss in their patients, it is proper to ask whether the weight loss is more comfortably or efficaciously brought about than by many other forms of treatment.

Long-Term Results

The chief issue in the treatment of obesity is really not how to bring about weight loss—this is relatively easily accomplished. It is how to prevent the relentless regain in weight, the main issue in the treatment of obesity. Very few studies give 5-year follow-up results, and those that do, show uniformly depressing results. One report showed that within 5 years 85% of the lost weight had been regained (7). Patients who had lost weight with starvation therapy were later found to have gained it back (8). Gusman states that it would not be feasible for him to trace the thousands of patients he has

treated, yet this is probably the most important contribution he could make. With such a large series over a long period of time it would be worth a considerable expenditure of time and effort to trace all or at least a randomly selected sample of his patients. These should be selected from among those treated more than 5 years ago rather than those treated in the last 3 years. While there seems to be no objection to repeated courses of HCG treatment, would this really be feasible for a lifetime? Simeons states that 70% of his patients had no relapse, but he gives no figures and does not state for how many years he has followed these patients. Patients are notorious for wandering on to other physicians when the disease for which they consulted the first physician recurs, and obese patients are probably more notorious than most in this respect. Simeons himself remarks that when a patient fails to lose weight on his regimen he assumes either that the patient ate more than the 500 kcal prescribed or different foods from those prescribed. "If the patient breaks down and confesses we melt and are all forgiveness and treatment proceeds. Yet if such performance is thought to be repeated more than two or three times we refuse further treatment. This happens in less than one percent of our cases." (2). The figure is undoubtedly greater than 1% for most physicians and methods, but the statement shows that even Simeons is not above the practice of dismissing the patient who fails. The failures in any treatment must be reported with exactly the same care as the successes.

It seems doubtful that the lifetime results of HCG treatment would be any less dismal than for any other known treatments. Most patients sooner or later regain the lost weight. The treatment, to be effective, must be practical to carry out for a lifetime. To date, no form of treatment has met this criterion.

Possible Mechanisms of Action of HCG

The study by Sohar (9) seems to prove beyond doubt that the weight loss resulting from HCG plus a 500-kcal diet is the same as that resulting from the 500-kcal diet alone. The effectiveness of HCG then must be either as a placebo in helping the patient to adhere to a very limited diet, or it must in some way make adherence to the diet easier. The latter is the point suggested by both Gusman and Simeons. The statements made by both of them, however, are difficult to substantiate. Various claims are made: HCG prevents hunger, it has a mood-elevating effect and causes euphoria, and it causes redistribution of fat, sparing normal fat but causing abnormal fat to be lost. These claims are based only on the testimonial of Dr. Simeons and have not been proven—indeed they would be difficult to subject to scientific testing.

A good scientific theory is not only one that works, as suggested by Gusman; it is one which can be subjected to disproof. Robert A. Good (10), in addressing the American Society for Clinical Investigation as its president in June, 1968, separates the credibility of a postulate from the creation of that postulate. Regarding the establishment for credibility, he refers to Popper (11) who "long ago pointed out that postulates have scientific value not as a consequence of their explanatory power but by virtue of their refutability. This characteristic is the essence of testability. Satisfactory fittings or observations which agree with a hypothesis do not in any way establish its worth or even strengthen it as a scientific instrument. It is only the hazard of refutation, the susceptibility to disproof which distinguishes a scientifically powerful and useful hypothesis from a scientifically useless one." The hypothesis of Simeons as repeated by Gusman belongs in the realm of creativity—the hypothesis has been created on the basis of clinical



impression, but no author so far has established scientific credibility for this theory. The hypothesis that HCG somehow helps in the treatment of obesity needs to be reworded in a series of scientific statements that potentially can be disproved.

The first statement—that HCG plus diet causes more weight loss than the same diet alone—appears to have been disproved by Sohar (9) and is not really claimed by Simeons. The second statement, that adherence to a 500-kcal diet is easier with HCG treatment than without it, as stated by Simeons and by Gusman, would probably need psychiatric testing as well as the double-blind technique to rule out the powerful placebo effect of nearly daily injections and of daily interviews with the physician.

Even if it were proven that Simeons' technique caused more pleasant weight loss than other regimens, the possibility would have to be considered that something in the nature of the diet itself, quite apart from the HCG, made adherence easier than to other diets. Simeons makes a strong point of rigid adherence to a rigidly prescribed and spaced diet, and explains failures in terms of minor infractions of the diet. However, Bortz et al. (12) have shown that except for minor fluctuations in weight due to shifts in fluid balance neither the spacing of the meals nor the composition of the diet (13) influences the rate of weight loss on hypocaloric diets of a specified number of calories.

Bortz's studies were carried out in strictly controlled metabolic ward surroundings. Whether patient adherence is better on one diet than another when the patient is at home or when he has the opportunity to "cheat" has not been shown for any diet and has certainly not been shown for the combination of Simeons' specific diet with or without HCG, or with or without the daily conferences with the physician. Therefore, the possibility still

exists that his diet might be easier to follow than others, either because of something intrinsic to the diet or to the addition of HCG.

Among factors intrinsic to the diet are its low calorie value and its composition. It was stressed by Keys and co-workers in extensive experiments during World War II that *semistarvation* is accompanied by demoralizing hunger while *total* starvation is as a rule not associated with hunger and may even be accompanied by a sense of euphoria (14). One might guess that the 500-kcal diet of Simeons is close enough to total starvation to eliminate hunger at least partially, when compared to the 1,400-kcal diets in the studies of Keys et al. (14). Gusman's comment that patients without benefit of HCG treatment have been unable to adhere to diets permitting twice the 500 kcal recommended by Simeons may thus be explained by the adaptive changes to very low calorie diets when compared to more generous diets, and not by any action of HCG.

A further feature that might make Simeons' 500-kcal diet more acceptable than others is that it contains very little carbohydrate—perhaps 30 g daily. Animal experiments have shown that the transition from the fed state, in which carbohydrate is the chief fuel, to the fasted state, in which fat metabolism prevails, is made more readily if carbohydrate intake has been previously greatly restricted (15). The animal so adapted to burning fat conserves the body's limited supplies of carbohydrate to meet the needs of the nervous system, which can burn only carbohydrate (16). Accordingly, tolerance to the brief periods of "starvation" between meals should be easier if the carbohydrate-conserving, fat-burning adaptation has been made in response to chronic restriction of dietary carbohydrate. Hypoglycemia with its attendant hunger would be avoided. Despite wide enthusiasm and publicity in the lay press, the long-term effectiveness of low



carbohydrate diets is untested and unknown.

Other mechanisms than dietary adaptation exist for conserving carbohydrate and favoring fat combustion, and such mechanisms would be expected to make calorie restriction more tolerable. The metabolic interplay between fat and carbohydrate metabolism might, by influencing the availability of glucose for the brain, contribute to a sense of well being, or even euphoria. Growth hormone and most of the other trophic hormones of the anterior pituitary as well as vasopressin of the posterior pituitary have a lipolytic effect on adipose tissue (17). Such fat mobilization by favoring fat combustion and, therefore, by conserving carbohydrate plays an important role in the adjustment to calorie restriction.

A possible role of growth hormone lack has been postulated in the etiology of obesity, since obese persons fail to show the rise in growth hormone with fasting that occurs in normal persons (18). However, this lack of growth hormone response appears to be secondary to the obesity and not the cause of it, for growth hormone response becomes normal with weight loss (19).

If HCG has an effect on obesity, it could be due to a direct lipolytic effect on adipose tissue, an indirect effect on the hypothalamus, or an effect on the gonadal hormones possibly released under its influence. The effect of HCG on human gonads is not well understood nor is the effect of sex hormones on the distribution of fat. That women have more subcutaneous fat than men is attributed to estrogen yet the weight gain commonly noted at menopause is not so explained. The mechanism by which estrogen influences adipose tissue is unknown. Progesterone, too, has some unexplained effects on obese persons such as the improvement in ventilation in patients with the obesity hypoventilation syndrome (20). The relationship of this finding to the statement of

Simeons that HCG treatment always improves the breathing of opera singers (2) piques the imagination.

Gusman and Simeons in considering the possible effect of HCG on the distribution of fat speak of abnormal fat cells, which lose their fat reluctantly, while the normal fat cells become depleted of fat during weight loss. They speak further of the ability of HCG to influence this discrepancy so that abnormal fat is lost and normal fat is retained. The evidence for abnormal fat cells, which yield their fat reluctantly, is not convincing. While fat is lost at a differential rate from different regions of the body, no scientific evidence exists that HCG has any more effect on one fat cell than another. The overstuffed adipose cells studied by Salans et al. (21) and alluded to by Gusman (1) were insensitive to insulin by virtue of being overstuffed and became normal on weight reduction. This cellular abnormality thus seems to be secondary to the obesity and not the cause of it. While the search for abnormal adipose cells continues, central regulatory factors appear to be more important than the type of cell.

The role of the hypothalamus and mid-brain in obesity has been recognized in experimental animals since the demonstration that hyperphagia and obesity follow damage to a specific region of the hypothalamus (22, 23). Among the many functions of the hypothalamus is the regulation of the pituitary (24). The ways in which the hypothalamus regulates the adipose organ and the possible effect of HCG on the hypothalamus are certainly valid subjects for contemplation and research.

While many possible effects of HCG on obesity might be entertained, at the moment the burden of proof that it does anything at all is on the shoulders of its proponents. Even if some effect is conclusively shown it will more likely be of theoretical interest rather than a practical tool for the life-long treatment of obesity. The



most difficult concept for both patients and doctors to grasp is that obesity is a life-long condition that requires life-long treatment.

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ADDENDUM

The study of HCG will be aided by recent advances in its purification (Bahl, O. P. Human chorionic gonadotropin. I. Purification and physical chemical properties. *J. Biol. Chem.* 244: 567, 1969). Studies on growth hormone might serve as a model for investigation of HCG. Rats chronically treated with growth hormone have a lower RQ, less body fat, and more body protein than pair-fed controls (Greenbaum, A. C. Changes in body composition and respiratory quotient of adult female rats treated with purified growth hormone. *Biochem. J.* 54: 400, 1953). A calorogenic effect of growth hormone in human subjects has recently been reported and may be mediated by the increase in circulating free fatty acids (Bray, G. A. Calorogenic effect of human growth hormone in obesity. *J. Clin. Endocrinol. Metab.* 29: 119, 1969).

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