Evidence Based Research Articles On The Benefits Of HCG Diet In Weight Management

Daniel Oscar Belluscio M.D

Medical Qualifications

• Medical graduate from Buenos Aires School of Medicine (1974)
• Specialist in Internal medicine
• Specialist in Bariatric Medicine
• Researcher - Bellevue Klinik - Switzerland.(12 years)
• Researcher - Marbert Laboratories - Germany
• Guest Researcher-Clínica Planas- Barcelona-Spain
• Visitor - University of Utrecht - Holland
• Visitor - Institute of Medicine II - Gothenburg - Sweden
• Visitor - Serono Laboratories - Milan - Italy
• Director: The oralhCg ™ Research Center - 1987– Present (24 years) Buenos Aires, Argentina
• Director - ISAUC (International Society for Alternative Uses of human Choriogonadotropin)
• Director and Coordinator: oralhCG ™ Training Program for Healthcare Professionals
• Director – Indexmedico
• Medical advisor- Unique Garden SPA- San Pablo Brazil
• Several reports on the issue of hCG and obesity published elsewhere.

A message from Dr. Daniel Belluscio

Many years ago (so many I'd rather not remember exactly), my medical specialty was Pediatric Plastic Surgery, within it, Plastic and Reconstructive surgery.

I used to assist a colleague, an adult Plastic and Aesthetic Surgeon, in his surgeries. In one of his trips to an International Congress, he assisted a conference about surgical body modeling in obese patients, which included, previous to the surgical procedure, a course of treatment to reduce body weight using a program based in the use of Human Chorionic Gonadotropin + a very low calorie diet (500 to be precise) . A Dr. Simeons had been the original proponent. The photographic results were simply stunning.

My colleague's proposal was very direct: we could develop a joint program using hCG and diet first, and then operate the patient in better conditions.

I read the book: Pound and Inches. I basically believed the doctor that published the manuscript. My impression was that he knew what he was talking about.

Timidly, I began treating some patients. The 500 calorie/ day diet seemed violent, and my biggest fear was that faced with such a restrictive caloric ingestion, my patients would not resist and would suffer. I controlled them on a daily basis.

To my absolute surprise, they felt better day after day. Happy, without hunger. A surprising discovery was right before my eyes. At that time I knew little about Gonadotropins. Pediatric surgeons such as me used it to treat a condition called cryptorchidia, which is the lack of testicular descent in male children. So I sent my assistant at the time to the Medical School Library to gather more information. I asked her to collect all references on hCG from Medline in order to later select the relevant information. When she asked, "What years?" I answered, "The last 5 years."

When she returned, she seemed shaken. "Doctor," she said, " there are over 6,500 references of gonadotropins on Medline, just in the last year!"

I felt I was before something important. I requested more information on Gonadotropin for obesity treatment from the pharmaceutical firm that manufactured Gonadotropin.

They sent me 11 papers. Only two reported positive results.

It was then I had to make a decision. Should I believe what I witnessed in my patients, or the negative studies?

I decided to believe my patients and my first-hand experience. This decision changed my professional life for the next 30 years.

I travelled to Switzerland, and worked in the Clinic with the most experience in the method, over 12.000 treated patients. I reviewed their statistics.

Ten years went by. In 1991 we began studies on a sublingual formulation of hCG, and I completed a double blind study. We submitted this study to the most important medical journals, but their reply was rubberstamped: the subject was not "interesting enough."

Meanwhile, more than 300.000 deaths piled up in the annual statistics, directly or indirectly caused by obesity.

I became tired of the hypocrisy and critiques of the method and hCG. We published our findings on the internet, releasing them to the public domain. And we waited.

In 2007, Mr. Kevin Trudeau once again opened Pandora's Box, publishing his book "The Weight Loss Cure." I am not in agreement with several points and with the selling techniques he used, but I commend him for bringing this subject back to public opinion.

Since that point, once again my life has changed. Due to the interest that has been awakened in the program, it now appears that the sublingual hCG formulation that we developed in 1991 is the preferred administration technique.

I am not facing this new challenge alone. Standing by me today, I have a team of fantastic assistants that have helped me to relight the flame of hope.

In today's world, the Internet has allowed the management of information to return to its original destinataries: the people. In this case, those people who suffer from the problem of obesity, who have been mistreated for many years, accused of gluttony, of being incapable of self-control, etc.

So the answer is: You are here because of me, and I am here because of you.

Thanks to:

- Dr. Simeons, who changed my professional life, and increased my understanding of Medicine as a whole.
- Dr. Trudy Vogt, who assisted in my training and has always been
..a fervent believer in the method.
- Mariela Carambia, our Nutritionist and daily collaborator.
- Dr. Sergio Vaney, our pharmacist.
- Dr. Alejandro Charosky, our lawyer.
- Dr. Mario Crescenzio, our financial advisor.

These are the people that accompany me in this battle against prejudices and the interests that prefer to keep this method in the shadows.

I also want to thank all of you who keep the faith in the protocol, and who support my work after almost 30 years and over 6,500 treated patients.

http://oralhcg.com/english/index.htm
http://www.hcgobesity.org/

Sincerely,
Daniel Oscar Belluscio, MD.
Founder and Director
The Oral hCG Research Center
Buenos Aires, Argentina

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1. Intrarectal administration of hCG (Human Choriogonadotropin) and fat loss as assessed by Dual energy X-ray absorptiometry (DXA in experimental animals (2012).

Intrarectal administration of HCG (Human Choriogonadotropin) and fat loss as assessed by Dual energy X-ray absorptiometry (DXA) in experimental animals.

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Abstract:

Our studies suggest that in experimental animals, submitted to a hypocaloric diet, the intrarectal administration of hCG (Human Chorionic Gonadotropin)decreases body fat and increases lean mass content in relative values to a greater extent that control animals who did not receive hCG

Objective:

To determine the modifications of DXA assessments (regarding lean mass, and body fat content) before and after the administration of four different doses of hCG (5, 10, 20, 40 IU / day) administered daily intrarectal for 6 weeks in conjunction to a hypocaloric diet in experimental animals.

Design and Methods:

For this study, 28 Sprague-Dawley rats were selected. All the animals were previously submitted to a cafeteria diet for a period of 5 weeks. After this "fattening" period all the animals reached an average of 35 % of weight increase.

Thereafter, animals were submitted to a hypocaloric diet (a third of the normal intake) for a period of 44 days, with water "ad-libitum" and environmental conditions similar to control animals.

Animals were splitted in five groups:

1. Control group (0): only hypocaloric diet
2. Group 1: hypocaloric diet plus the administration of intrarectal 5 IU of hCG dissolved in a cyclodextrin solution (16mg/ml.).
3. Group 2: hypocaloric diet plus the administration of intrarectal 10 IU of hCG dissolved in a cyclodextrin solution (16mg/ml.). .
4. Group 3: hypocaloric diet plus the administration of intrarectal 20 IU of hCG dissolved in a cyclodextrin solution (16mg/ml.).
5. Group 4: hypocaloric diet plus the administration of intrarectal 40 IU of hCG dissolved in a cyclodextrin solution (16mg/ml.).

The study lasted 6 weeks.

Procedures :

To determine the percentage body fat and lean body mass per body region, we performed Dual energy X-ray absorptiometry (DXA) on a Hologic Discovery A device, on days 0 (when starting the hypocaloric diet, after the cafeteria diet fattening period) and on day 44 (end of study). Also, during these determinations, three Regions Of Interest (ROI) were selected:

Region 1: Thorax and upper extremities
Region 2 Trunk
Region 3: Lower extremities and hips.

Personnel in charge of the study were blinded to the assignment of treatment groups.

Results:

At the end of the study the lowest mean value of body fat loss (absolute and relative) was recorded in group 4, both in all the regions (ROI) and the net content of body fat.

In addition, group 4 was more homogeneous regarding fat loss. However, the differences were not statistically significant.

The body fat decrease (absolute and relative) by region and total was slightly higher in the animals of group 4. This group also was more homogeneous.

At the end of the study, the highest values of total body fat content (absolute and relative values) were observed in group 1, both in regions 1, 2, 3, and total. However, when comparing to the rest of the groups, the differences were not statistically very significant.

When estimating fat loss in relative values, the body fat content decreases were

1. Between 12 % (Group 1) and 15% (Group 4) in region 1
2. Between 23% (Group 1) and 26 % (Group 4) in region 2
3. Between 11% (Group 1) and 16% (Group 4) in Region 3
4. Between 17 (Group 1) and 21 (Group 4).

Group 3 had a greater decrease of body fat content (absolute values) in different regions, whereas the absolute values from Group 1 showed the lower decrease.

However, the differences were not statistically significant. At the end of the study the lean body tissue content recorded was higher in group 4, both in all regions and absolute (weight) and relative (%) values results.

Conclusion

Given the small number of animals, no definite conclusions can be drawn. However, the results show a trend towards the decrease of body fat and an increase in lean mass in hCG treated animals as compared to control group, particularly in relative values (percentage). These difference results were dose-dependent of HCG administration.

An interesting finding of this study was that , compared to control animals who did not receive hCG, the intrarectal administration of hCG modified both the fat content and the lean mass in hCG-treated animals, as assessed by DXA, both in absolute and relative values.

We hypothesize that the enteral administration of hCG may be an alternative route providing results closely similar to injections, without the discomfort of an invasive procedure.

2. The hypothalamic genesis of obesity (2012).

The Oral hCG
RESEARCH CENTER

DIRECTOR:
DANIEL OSCAR BELLUSCIO MD

- **Training Course for Healthcare Practitioners**

- Why are we here?

We are here because you will have to make a choice

- **Either you believe in your patients:**

I need help! I keep gaining weight and i'm eating normally!

I don't know what to do to make this weight gain stop! Oh, and I also run for 40 minutes every morning on my treadmill at 6.3mph and do some light weights.

I'm so afraid that i am going to just keep gaining and i don't know what to do anymore!! I am so frustrated. I am still okay with my body now (i wear probably around an 8/10 now) but i definitely don't want to gain anymore

http://caloriecount.about.com/forums/weight-loss/need-help-gaining-weight-im-eating

OR…..

- ***Obesity Epidemic: Overeating Alone to Blame America's Obesity Problem Is caused by overeating rather than inactivity, new study says***

Friday 20 May 2011

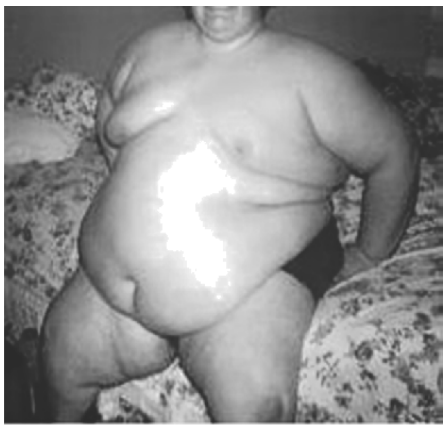
The Telegraph

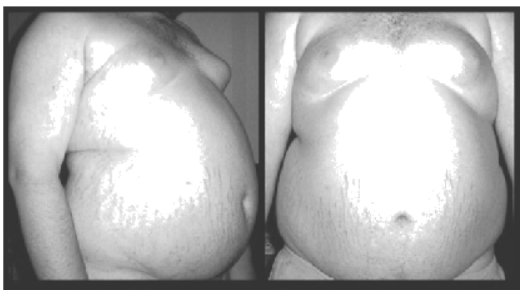
•Fat people are just greedy, says BMA chief

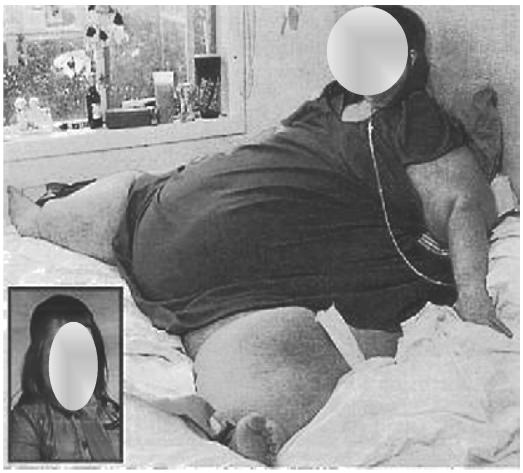
•*The head of the British Medical Association has sparked a row after claiming that fat people are simply greedy.*

•*Dr Meldrum said an obsession with labels may be stopping overweight people from tackling their problems. He said: "We are saying 'This patient has a hyper-appetite problem' rather than 'They are just greedy'."*

Just greedy, or gluttons?







Long – term results obesity treatment

Table 1
Features of Diet Studies With Long-Term Follow-Ups (and No Control Groups)

Study	Years of follow-up	N	% of N in follow-up	% self-reporting weight	% on additional diets (or mean number of diets)	% reporting regular exercise	Mean change from baseline to end of diet (kg)	Mean change from baseline to follow-up (kg)	% regain all lost weight (or more)
Anderson et al. (1999)	5–7	52	12	30	20[a]	–	−29.7	−5.2	–
Foster et al. (1996)	5	55	47	0	65 (M = 1 diet)	–	−21.1	+3.6	50% were > 5 kg above baseline
Graham et al. (1983)	4.5	60	43	0	(M = 3 types of treatments)	35	−4.5	−3.3	–
Hensrud et al. (1994)	4	21	88	0	>50[b]	22	−12.5	−1.6	37
Jordan et al. (1985)	5	111	25	100	–	–	−8.4	−5.2	–
Kramer et al. (1989)	4	152	77	7	(M = 1.3 diets/year)	–	−11.9	−3.1	38
Lantz et al. (2003)	4	54	48	0	–	–	−7.0	−3.3	–
Murphy et al. (1985)	4	25	33	0	38 (M = 1.6 programs)	46	−7.7	−0.5	–
Pekkarinen and Mustajoki (1997)	5.5	24	88	13	12% lost > 10 kg on other diets[c]	–	−22.9[d]	−5.8	29
Stalonas et al. (1984)	5	36	81	22	(M = 2 diets)	–[e]	−4.7	+0.7	46
Stunkard and Penick (1979)	5	26	81	63	–	–	−8.8	−5.4	31
Wadden and Frey (1997)	5	281	22	100	43	–	−25.6	−6.6	32
Wadden et al. (1989)	5	55	72	47	55	–	−14.6	−0.6	64
Walsh and Flynn (1995)	4.5	143	47	100	36	–[f]	−21.4	−5.1	–

- We sustain:

1. That **overeating is not the main cause for obesity, but its consequence**. Weight gain is the visible sign of an underlying regulatory disorder.

2. That the cause for obesity lies in the hypothalamic area.

3. That no dietary procedure will improve the disease, unless some type of correction of the diencephalic disorder is being simultaneously provided.

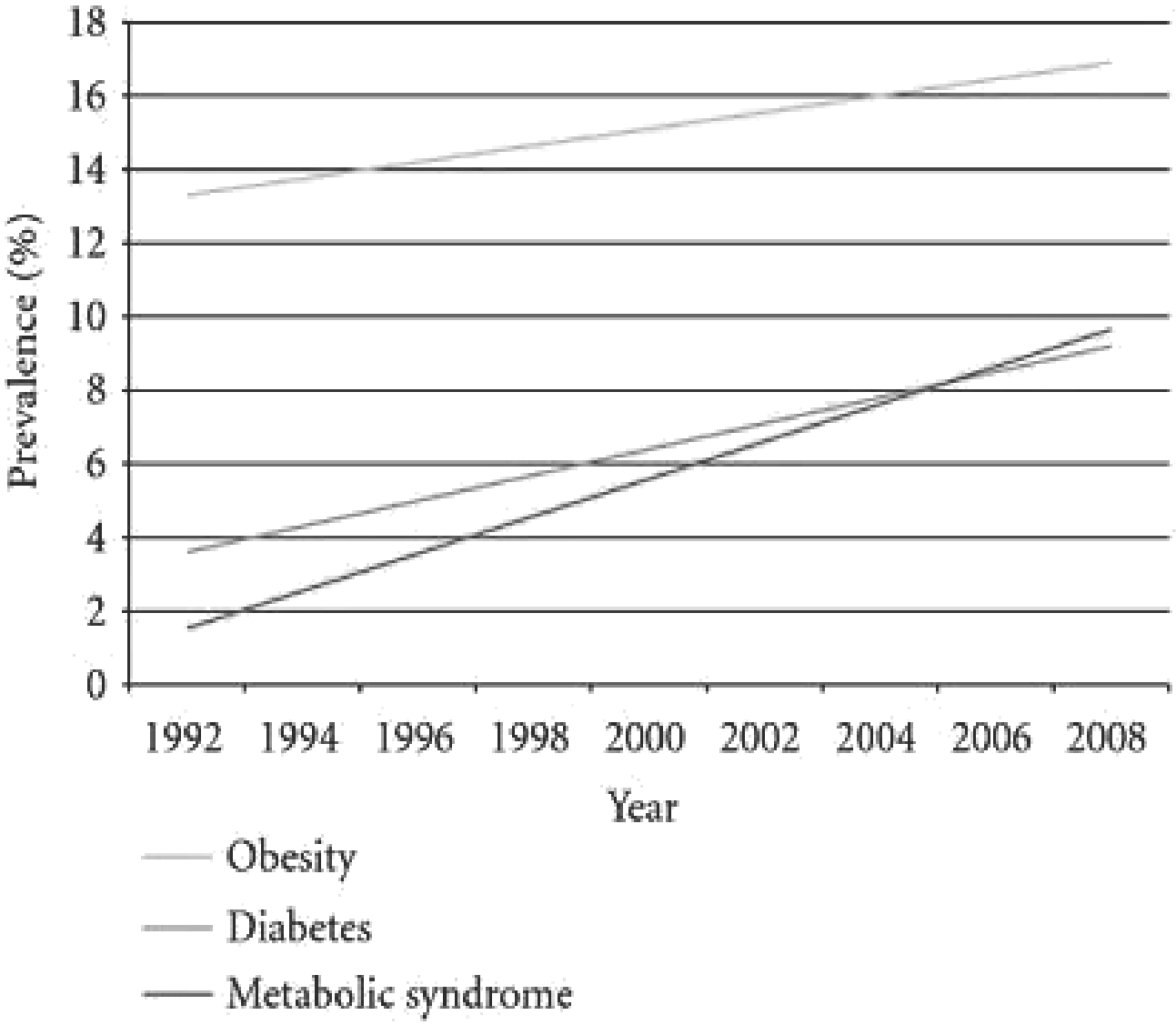
4. That, as by now, the only rational approach to treat the disease is the hCG method for weightloss.

Diseases associated to obesity

- Diabetes
- Cancer: Obesity increases the risk of cancer development by 25-33%. Obese person is likely to develop esophageal cancer, prostate cancer, breast cancer, kidney cancer, endometrial cancer or colon cancer.
- Congestive Heart Failure
- Heart Enlargement.
- Stroke
- Polycystic Ovarian Syndrome

- Pulmonary Embolism
- Gastro-esophageal Reflux or Heartburn
- Osteoarthritis
- Fatty Liver Disease
- Erectile Dysfunction
- Chronic Renal Failure
- Lymph Edema
- Urinary Incontinence
- Dislipidemias

- Depression
- Cellulitis
- Gallbladder Disease
- Gout
- Pickwickian Syndrome: Excess weight adds pressure on the pulmonary system, hence, leading to Pickwickian syndrome characterized by sleep apnea.
- Hernia: This condition is causes weak and enlarged diaphragm
- Metabolic syndrome


18
16
14
12
10
8
6
4
2
0
Prevalence (%)
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year
Obesity
Diabetes
Metabolic syndrome

- **OBESITY?**

Obesity according to current definitions

- Obesity definition is very straightforward: obesity is simply defined as a condition of being overweight.

Overweight according to current definitons

- In one sense it is a way of saying imprecisely that someone is heavy(?).

The other sense of "overweight" is more precise and designates a state between normal weight and obesity (?).

- **www.encyclo.co.uk/define/Overweight**

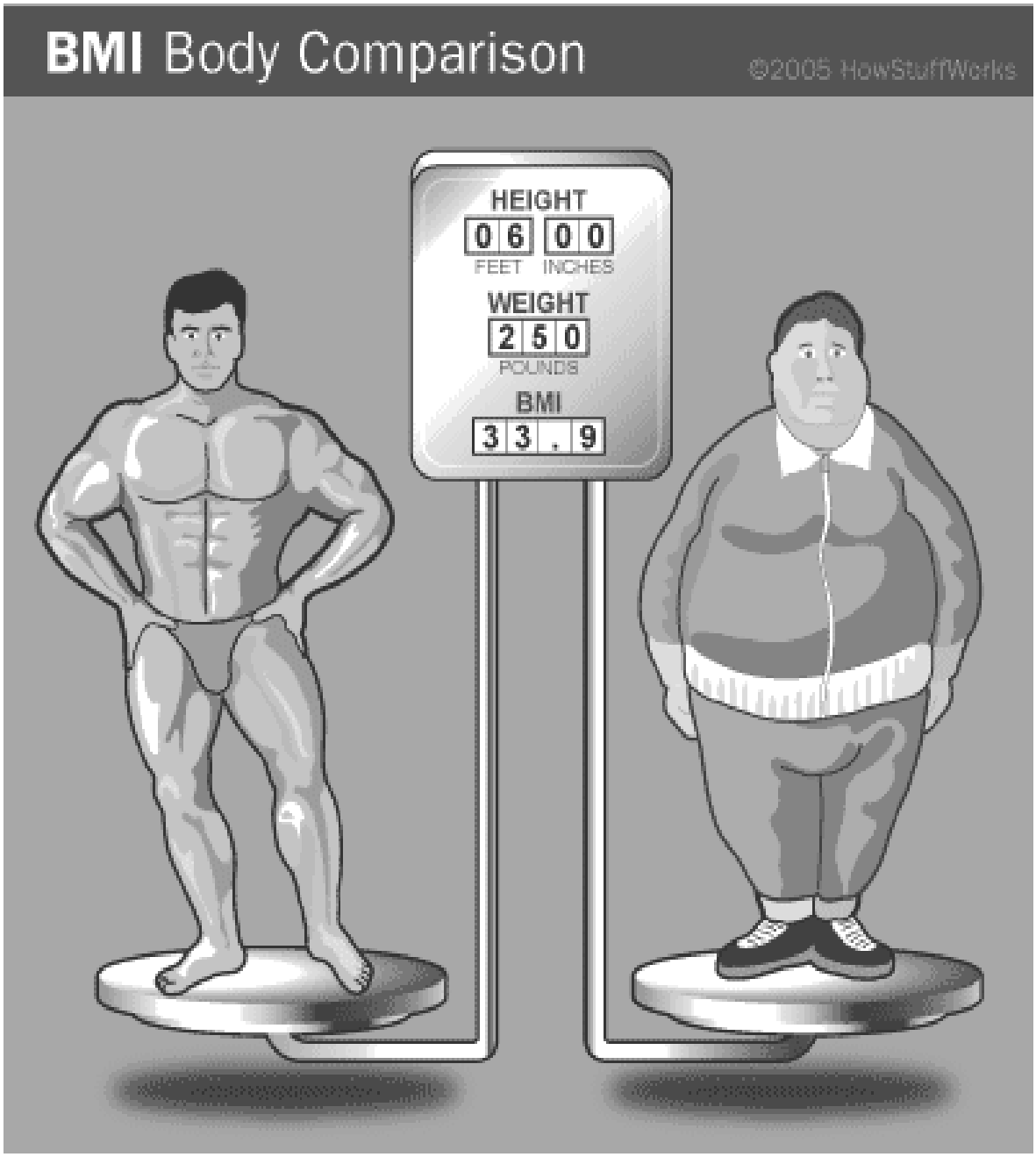
And, finally, obesity is…….

The state of being well above one's normal weight (overweight).

http://www.medterms.com/script/main/art.asp?articlekey=4607

- **Therefore, obesity and overweight are directly related terms. Right?**

No.



http://static.ddmcdn.com/gif/bmi-comparison.gif

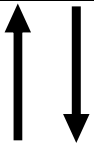
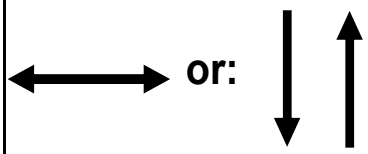
- **Obesity and overweight are not always related terms**

Let´s us redefine obesity….

- Obesity is a clinical disorder characterized by the capacity of the hypothalamus to acumulate fat well over daily requirements.

  These adipose tissue masses are located in conspicuous body areas

- Overweight, may or may be not, related to obesity.

	Diencephalic disorder	Adipose tissue mass
Normal weight	**No**	
Overweight not obese	**No (eventually later)**	
Obese no overweight	**Yes**	
Obese and overweight	**Yes**	

First Myth

- The hCG method is a medical procedure that can cure obesity, "resetting" the hypothalamus and allowing all types of foods after treatment.

What we <u>do</u> with the hCG method for weight loss:

- We provide a safe, time-tested, reliable and effective method for obesity treatment.
- Weight loss will be accomplished at the expense of adipose tissue and not lean mass.
- Our patients feel in a good mood throughout the entire treatment period.

What we <u>don't do</u> with the hCG method for weight loss:

- We do not cure obesity.
- We do not "reset" the hypothalamus.
- We do not allow all type of foods after the treatment.

Second Myth

- The hCG protocol is an unsafe and unreliable procedure for obesity treatment.

Obesity- Overcoming Myths

- Over 6,500 first-hand treated patients in our practice, and 14,000 patients reviewed at the Bellevue Klinik, in Switzerland.

- Twenty-nine years of personal experience on the method.

- No complications described.

Third Myth

- The scale is an useful tool to assess the efficacy of an obesity treatment.

Fat percentage

7%

10%

14%

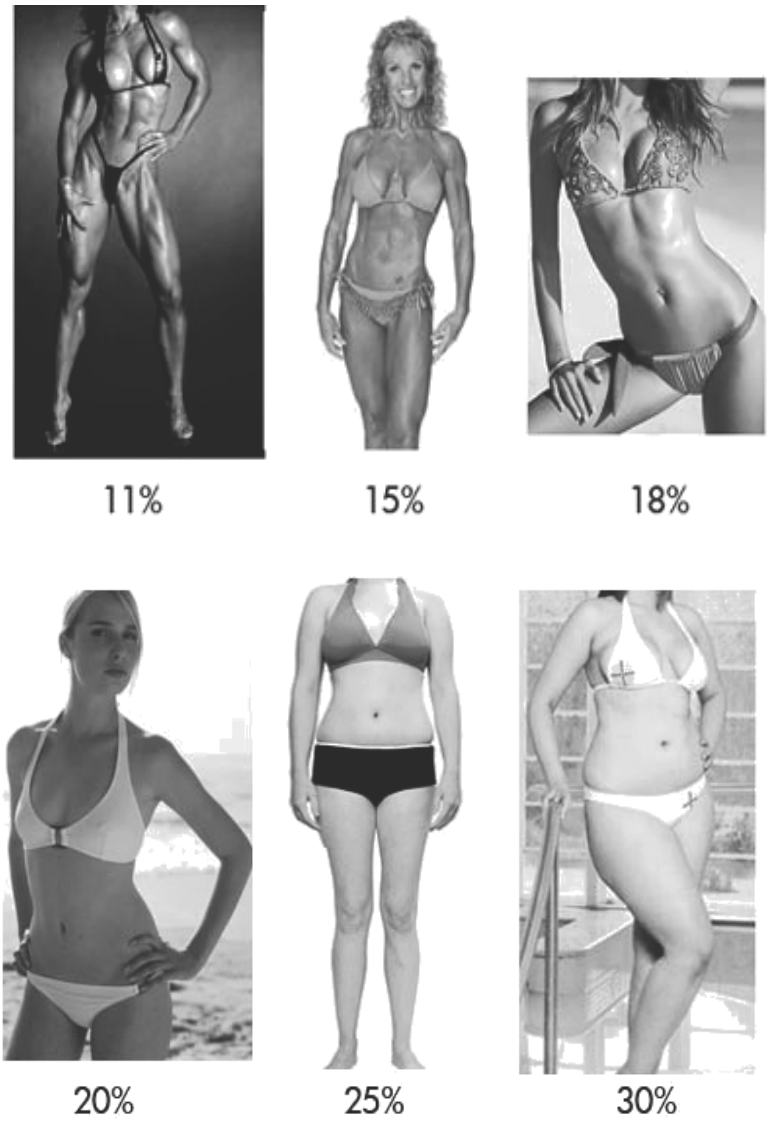
20%

25%

30%

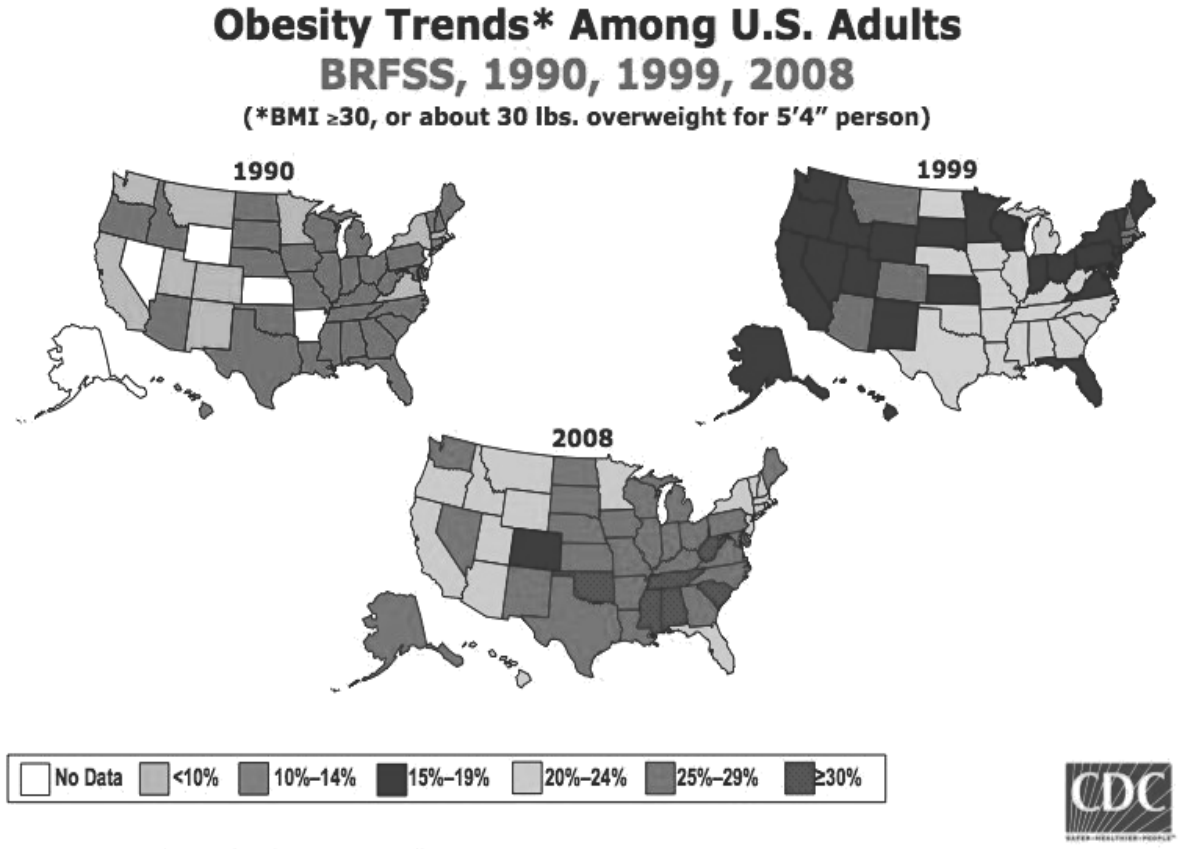
http://www.leighpeele.com/wp-content/uploads/2010/02/male-body-fat-percentages-pictures.jpg

Fat percentage



http://www.leighpeele.com/wp-content/uploads/2010/02/female-body-fat-percentage-pictures.jpg

- **The use of the scale to assess obesity is an unreliable tool to estimate the disease.**



Fourth Myth

- Exercising and "shutting your mouth" are the most effective tools for obesity treatment.

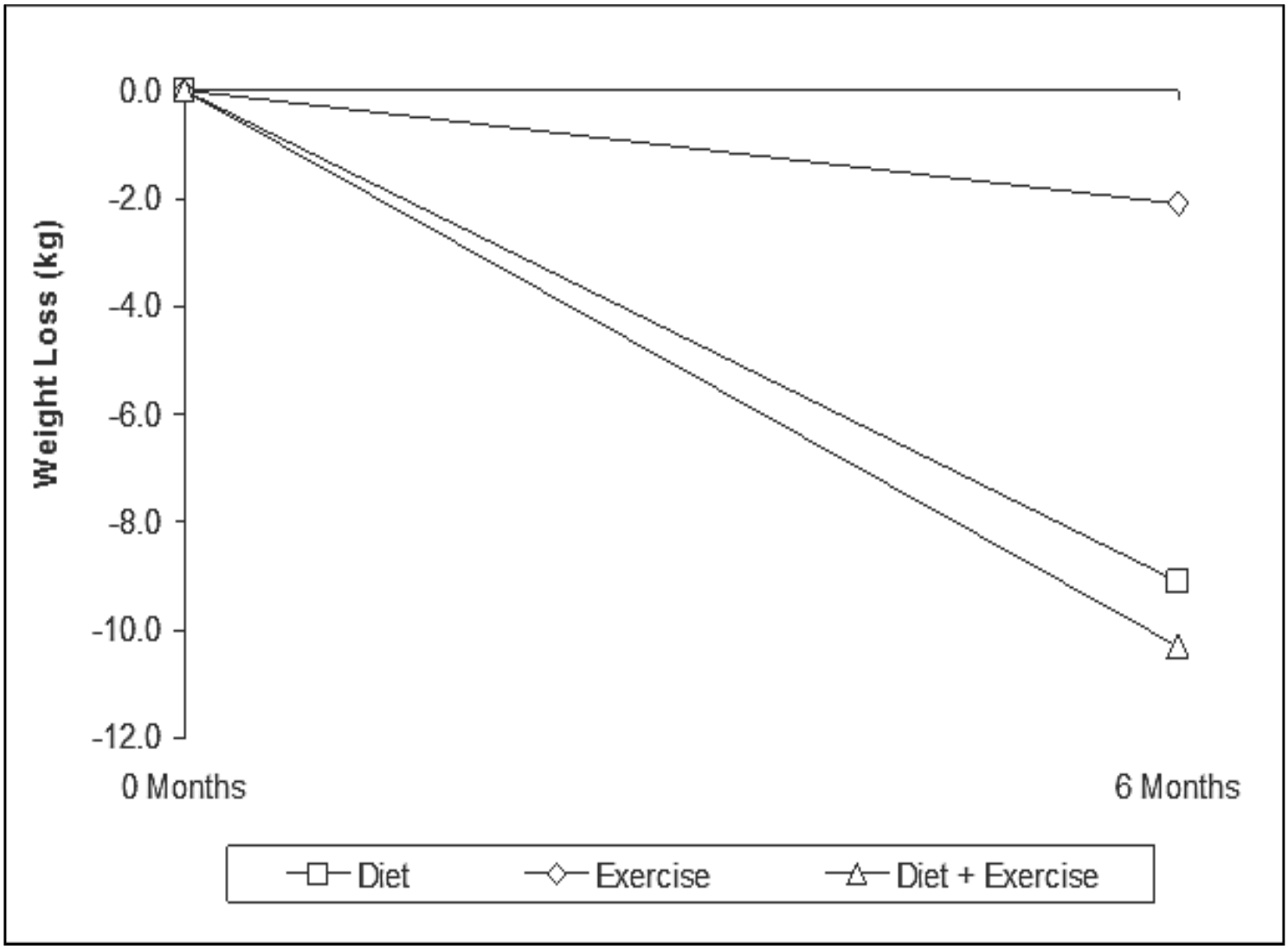
Exercise alone is probably insufficient to bring about significant fat loss except in individuals who are extremely motivated….

Although prolonged, intense physical exercise may promote weight loss, more moderate exercise, as practiced by non-athletes may not induce significant weight loss….

In some cases, weight gain has actually been reported.

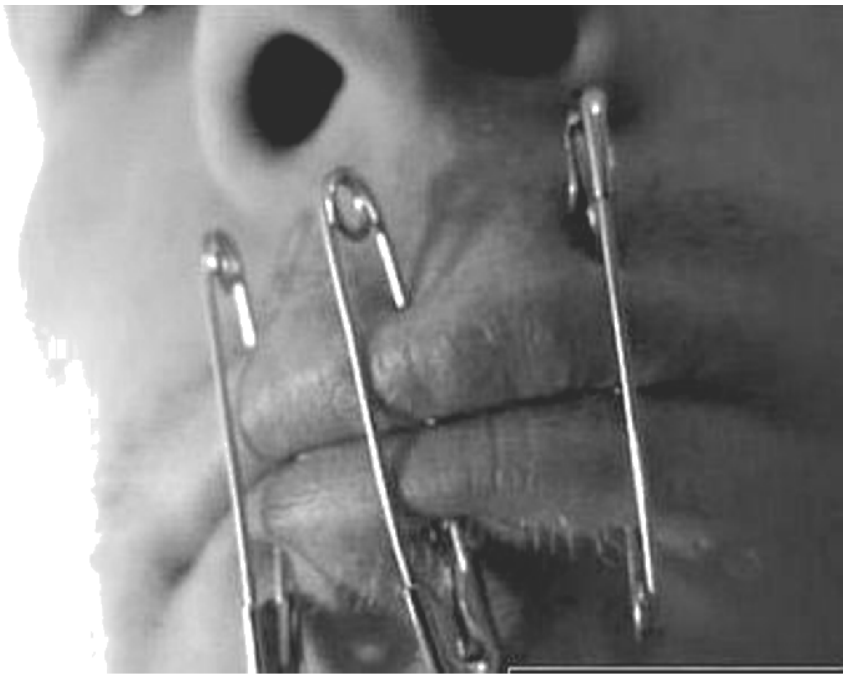
http://www.exrx.net/FatLoss/ExTherapy.html

Exercise or no- exercise for weightloss



- It seems the old mantra:

"Shut your mouth and exercise" were not effective for obesity treatment

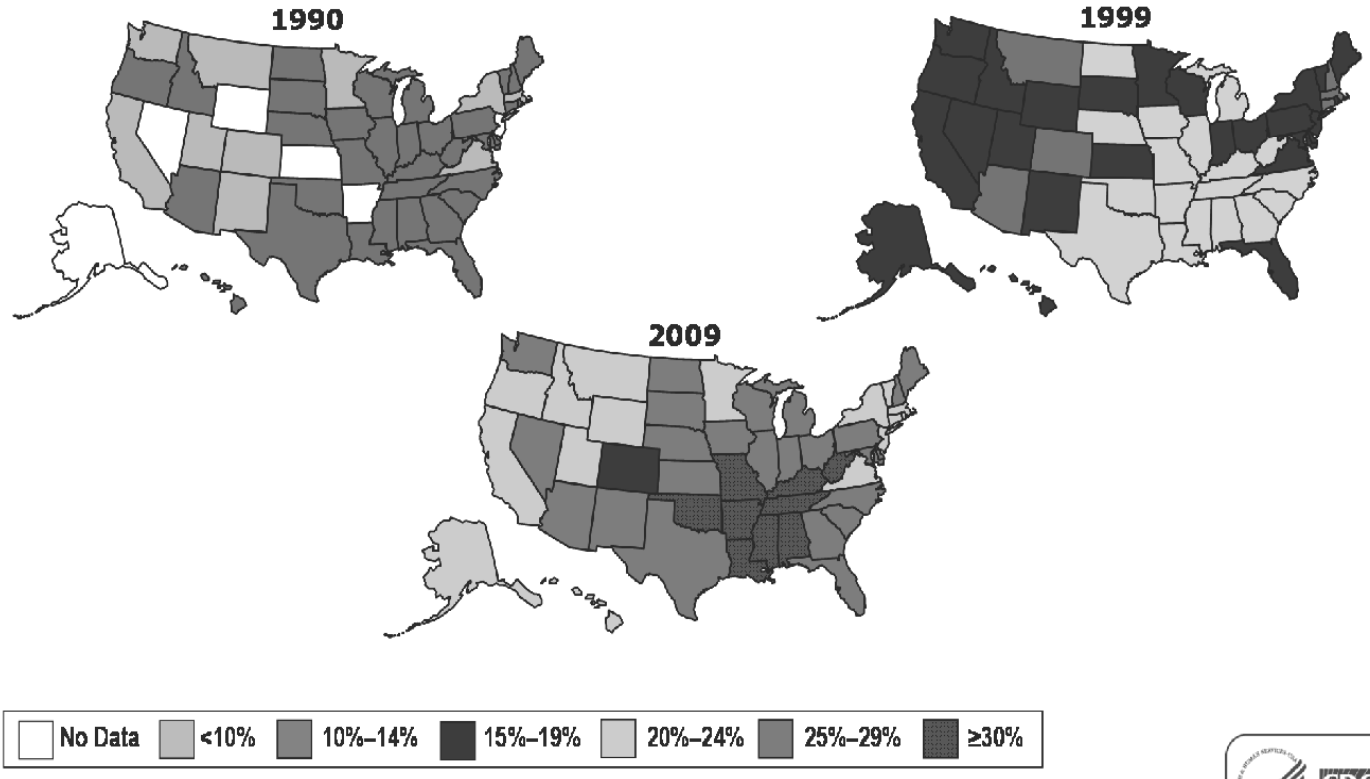


http://www.instablogsimages.com/images/2006/11/28/keep-your-mouth-shut_49.jpg

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1999, 2009

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Fifth Myth

- Overeating always results in weight gain.

J. Clin. Invest.

0021-9738/87/04/1019/07 $1.00
Volume 79, April 1987, 1019–1025

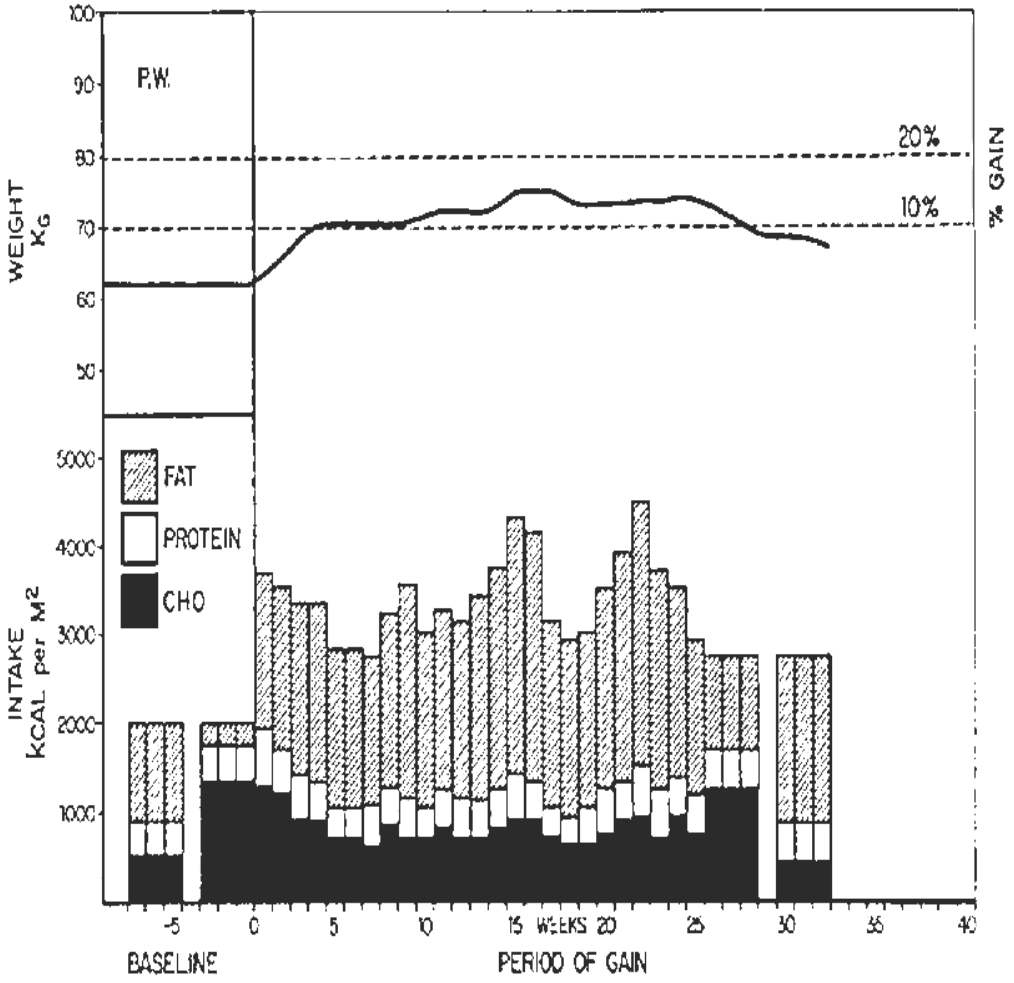


Figure 2. The dietary intake and weight gain in subject P. W., Group IV Protocol as in Figure 1. Note that this subject took a much greater excess of calories above the basal requirement, but failed to gain more than 14 per cent above his initial weight. 2700 kcal/M² in this instance was inadequate to maintain weight gained.

J. Clin. Invest.

0021-9738/87/04/1019/07 $1.00
Volume 79, April 1987, 1019–1025

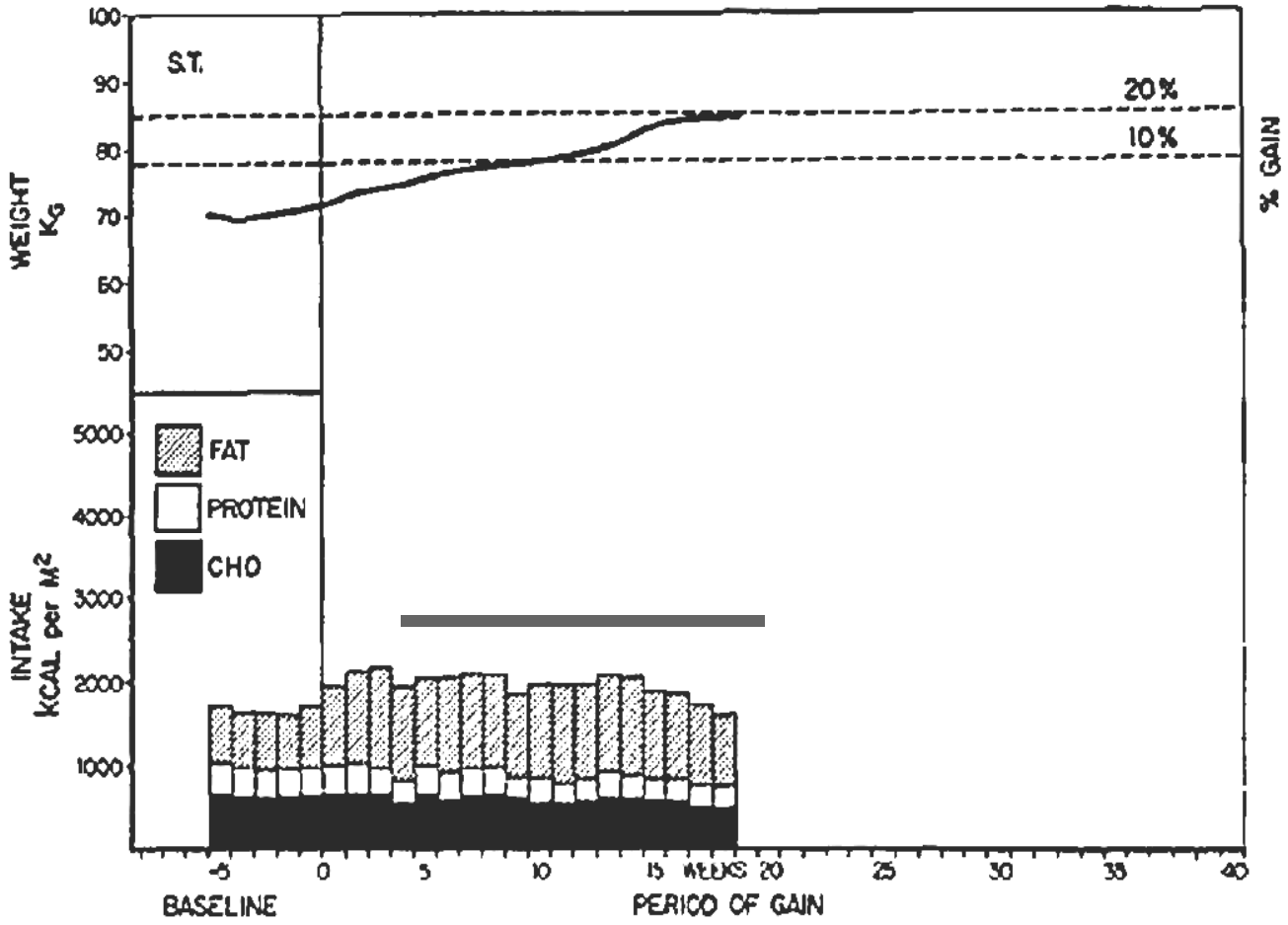


Figure 3. Weight gain from ingestion of an excess of dietary fat alone in subject S. T., Group V. Note that weight is apparently gained more efficiently than in the case of the subjects of Figures 1 and 2, taking a mixed diet. Also note that the excess weight is maintained by a caloric intake equal to the basal level.

Sixth Myth

- Obesity is a psychological disorder, characterized by anxiety, gluttony and/or greed.

- Therefore, psychotherapy or behavior therapy can provide relief to the disease.

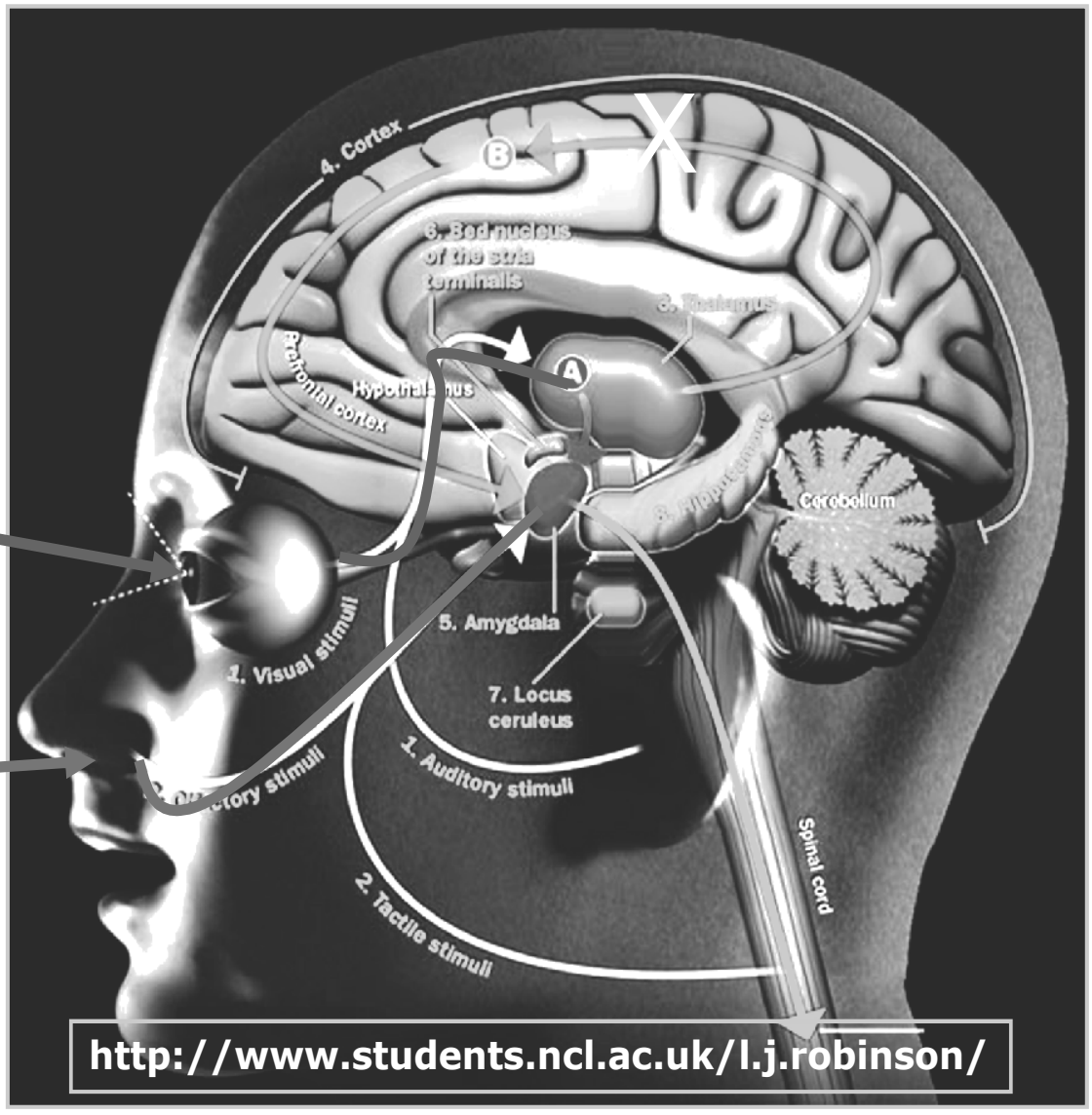
Are cats and rats obese because a psychological disorder?

http://www.nutrecareblog.com/wp-content/uploads/2010/05/fatcat.jpg

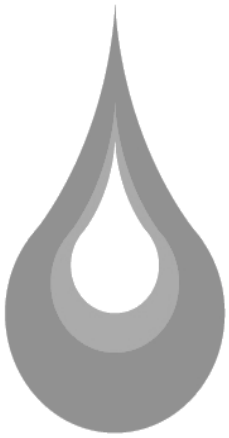
http://www.media.desicolours.com/2009/january/fatanimals07.jpg

The act of eating, may, or MAY NOT be related to a desire for food.

Rather, it suggests that a regulatory disorder is present in the hypothalamic area.


4. Cortex
B
X
6. Bed nucleus of the stria terminalis
3. Thalamus
A
Prefrontal cortex
Hypothalamus
8. Hippocampus
Cerebellum
5. Amygdala
1. Visual stimuli
7. Locus ceruleus
1. Auditory stimuli
2. Tactile stimuli
Spinal cord
http://www.students.ncl.ac.uk/l.j.robinson/

- The disorder responsible for obesity genesis is located BELOW the brain cortex.
- Therefore, no amount of psychological support may help obese patients.
- We are dealing with a hypothalamic regulatory disorder.
- Neuronal pathways of obesity closely resemble those related to an **addiction.**



The diencephalic theory of Obesity

The hypothalamus functions (I):

- Pituitary gland regulation.
- Blood pressure regulation.
- Hunger and salt cravings feeding reflexes.
- Fat deposition and release.
- Thirst.
- Body temperature regulation.
- Hydration and water preservation
- Heart rate.
- Bladder function.

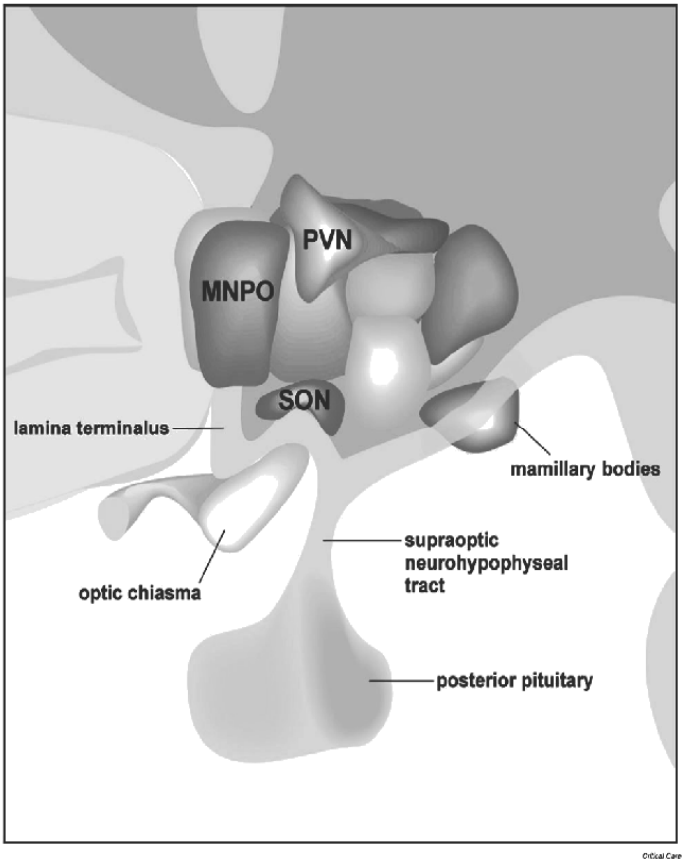
The hypothalamus functions (II):

- Hormonal/neurotransmitter regulation.
- Ovarian and testicular function.
- Mood & behavioral functions.
- Wakefulness metabolism.
- Sleep cycles.
- Energy levels.
- Adaptation to stress.

The hypothalamus - Obesity

- The hypothalamus functioning may become disrupted by a series of psychological (divorce, death of a relative, etc.) and physiological (concomitant diseases, etc.) agents.

- Once this disorder triggers one of the most sensitive areas within the hypothalamus are those related to adipose tissue metabolism.

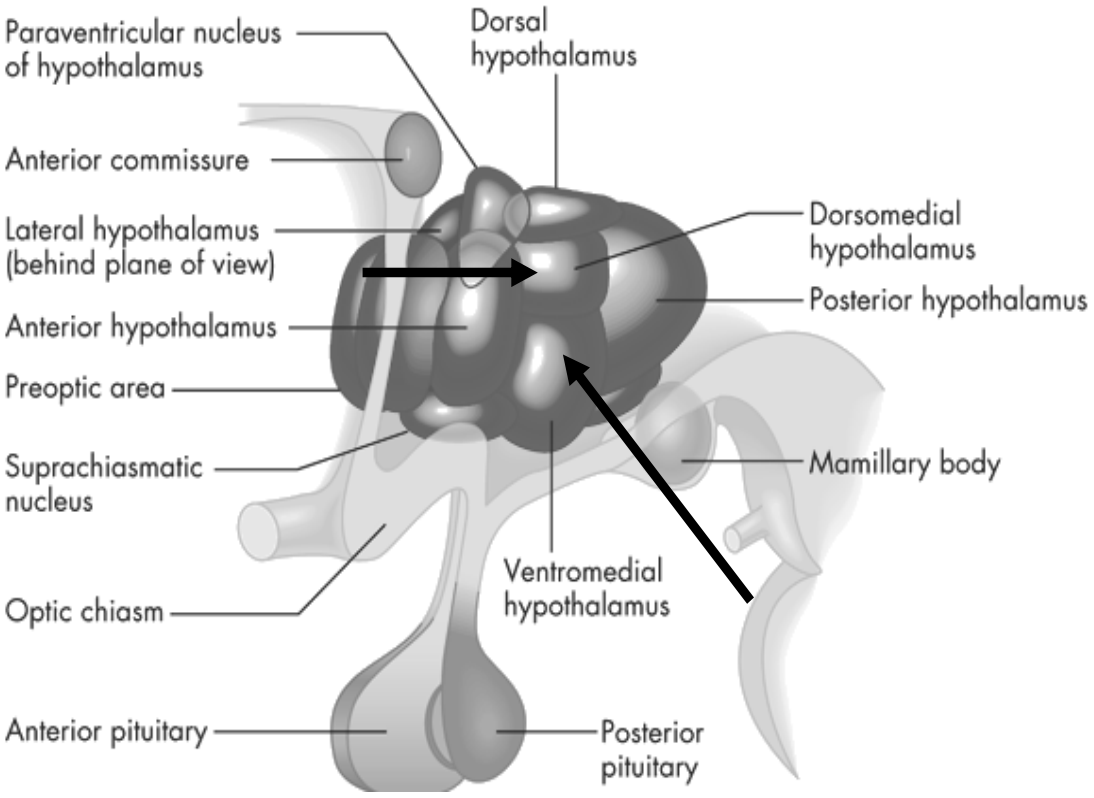


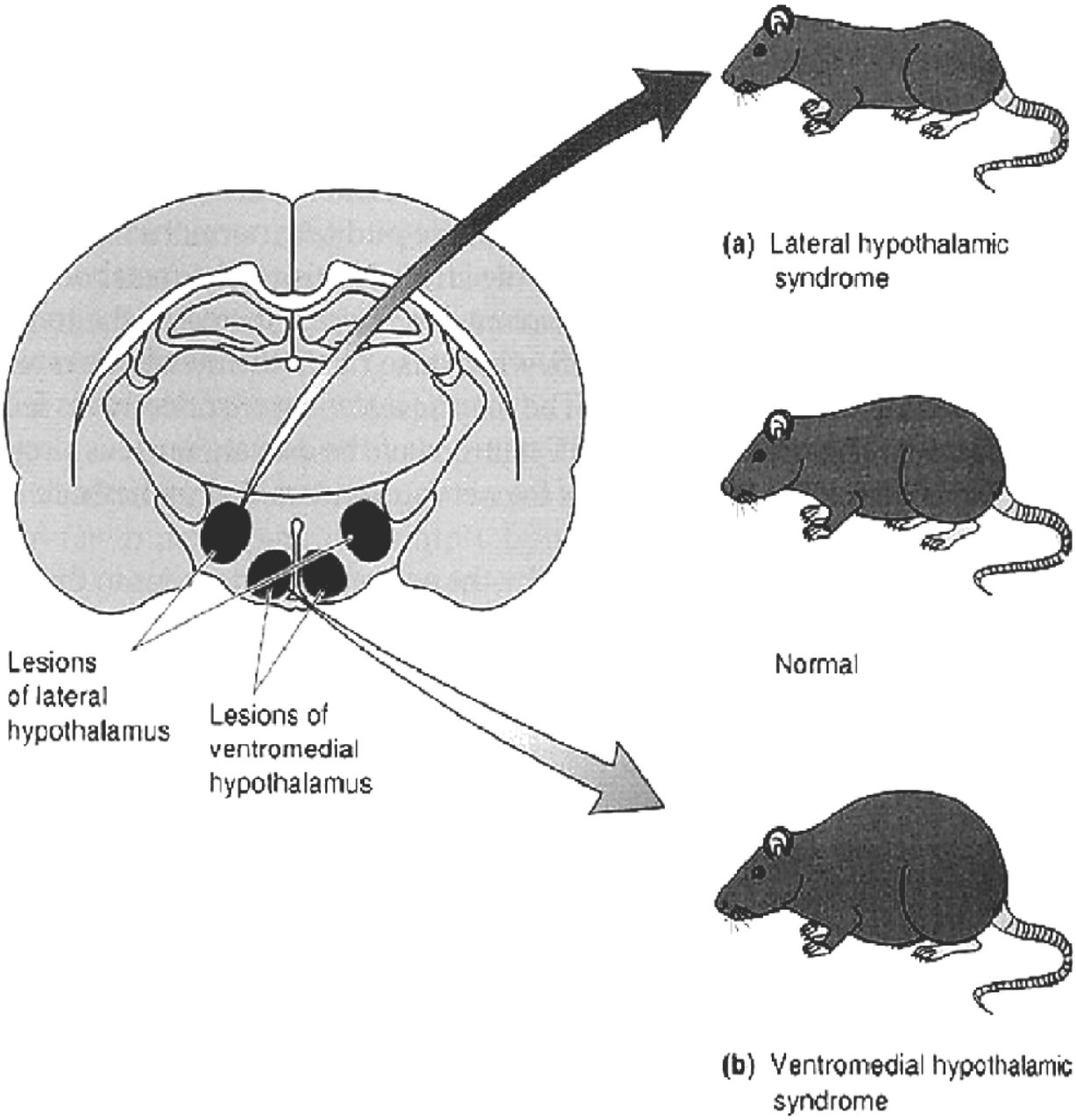
http://www.psycheducation.org/emotion/ltlHYPOTHL.jpg

http://www.psycheducation.org/emotion/ltlHYPOTHL.jpg

The hypothalamus - Obesity Experimental field

- Surgical destruction of Ventromedial and Lateral Hypothalamic Nuclei causes hyperphagia, hyperinsulinemia and obesity in experimental animals.





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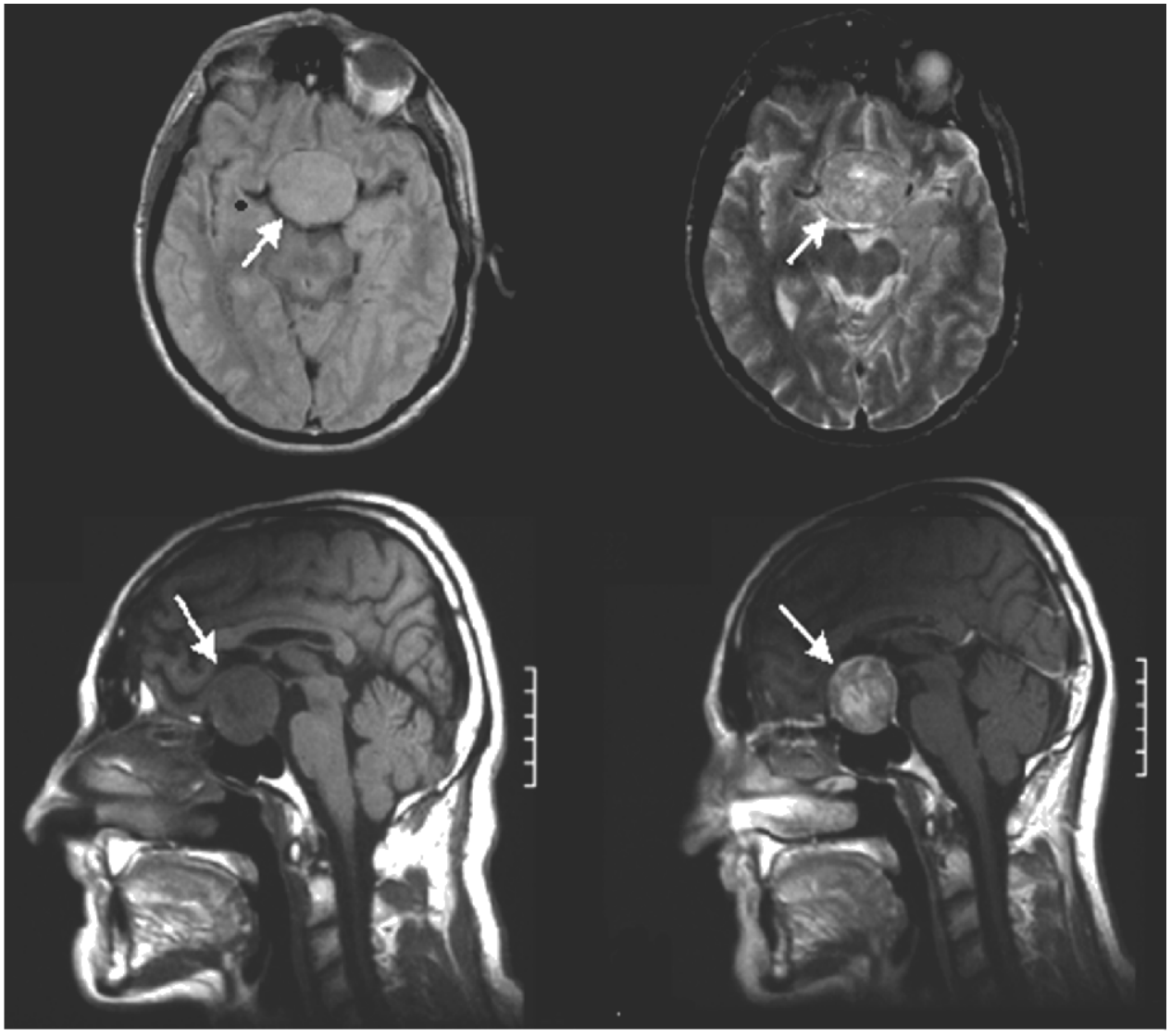
In humans



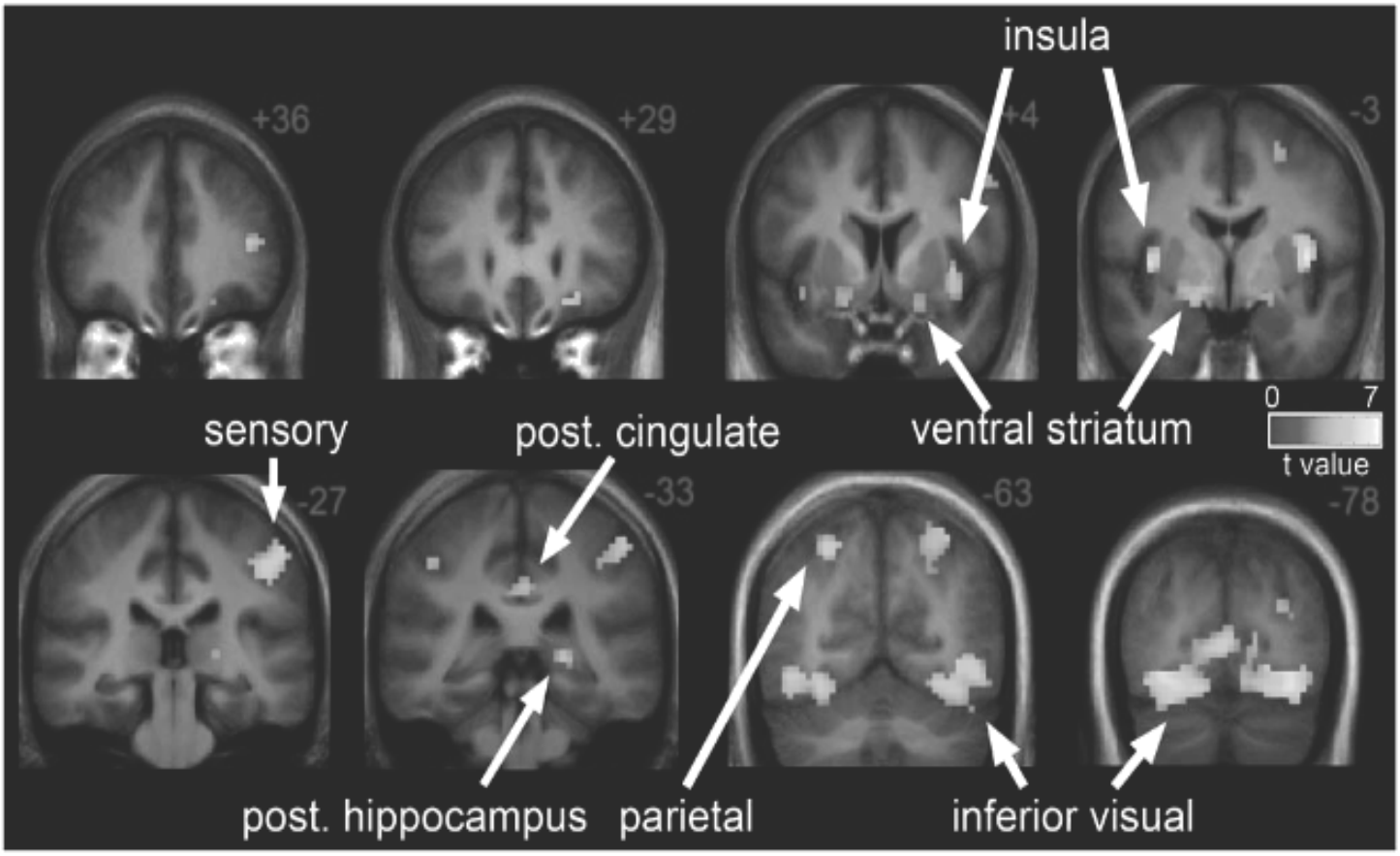


Figure 1. Neuronal response to visual foods cues in thin individuals in the eucaloric state. The neuronal response in thin individuals to visual stimuli of foods of high hedonic value as compared to non-food objects in the eucaloric state is shown (EU:H>O). Robust activation is observed in the insula, sensory cortex, posterior cingulate, ventral striatum, posterior hippocampus, parietal cortex, and inferior temporal visual cortex. Statistical maps thresholded at an FDR corrected threshold of $q<0.05$ and overlaid onto the group average anatomical image. Data are shown in the radiological convention (right hemisphere on the left).
doi:10.1371/journal.pone.0006310.g001

http://www.plosone.org/article/fetchObjectAttachment.action;jsessionid=BF45D92DDC6796CBAEAC9C3E13761A20?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0006310&representation=PDF

3. HCG Injections in a Randomized, Double-Blinded, Placebo-Controlled Trial (2012).

HCG Injections in a Randomized, Double-Blinded, Placebo-Controlled Trial

Sheri L. Emma, MD, Dr. Emma's Corporation, Brick, NJ

Abstract

Four week trials were conducted on a total of 59 females between the ages of 20 and 55, with no major medical illness. They were placed on a 500 calorie diet (50% protein). Measured parameters: weight, body composition via bioimpedance, blood pressure, and blood labs were performed. Subjects received daily hCG or saline (placebo) subcutaneous injections. After 4 weeks, the subjects body compositions were analyzed for overall change. There was significantly more muscle lost in the placebo group versus the HCG group. Overall weight loss was similar between the two groups. This lends support to the theory that HCG is acting to preserve lean body mass during a calorie deprived state.

Objectives

Objective: To elucidate the role that human chorionic gonadotropin (hCG) may have on body composition during weight loss.

This controversial topic has been under investigation for over fifty years. Repeated clincial trials have failed to show any significant difference in weight loss between HCG and placebo. The proposed theory is that HCG being a prohormone should serve to counteract muscle catabolism during a calorie deprived state. This trial was designed to analyze changes in body composition and therefore help to clarify whether or not HCG is in fact preserving lean muscle mass, thereby allowing for a more selective fat loss, by default.

Materials & Methods

59 females were randomized to HCG or Placebo Study Groups. All subjects were between the ages of 20 and 55, with no major medical conditions.

Recorded variables: weight, body composition, blood pressure, blood labs (CBC, complete metabolic panel, thyroid panel, hormones, and B-HCG), and in some patients, EKG. All were placed on a 500 calorie diet (approximately 50% protein) and were instructed to keep a diary of progress, hunger, and a food log. Subjects were randomized to HCG or placebo (saline) and injected between 200 and 300 IU subcutaneously daily for 4 weeks. Weekly follow-up visits were required during which patients received repeat weight, blood pressure, and medical evaluation. Blood tests were conducted every 2 weeks for electrolyte, hormone, and lipid monitoring.

Of the subjects, there were 30 HCG and 29 Placebo. Six subjects dropped out in each group. In the placebo group, five were noncompliant and one had a starting BMI less than 25, and thus were eliminated from analysis. In the HCG group, three were noncompliant (weight loss less than 5 lbs or extreme outlier (1) and one had a starting BMI less than 25, and thus were eliminated from analysis.

Median weight loss achieved in each group was 14 pounds. The mean was 14 pounds in HCG and 15 pounds in placebo.

Median fat loss was 11 pounds in HCG, 9.2 in placebo

Median muscle loss was 3.2 in HCG and 4.8 in placebo. The means were 2.7 and 5.4, respectively.

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Discussion

ANALYSIS: Mann-Whitney U Test Median Comparison: HCG vs. placebo. Primary endpoint: weight change. Secondary endpoints: change in muscle mass and change in fat mass. RESULTS: PRIMARY: no significant difference in weight loss between the two groups (p=0.5521), SECONDARY: Comparison of fat mass loss was not significant, with a p of 0.4189. Comparison of muscle mass loss was **significant at a p-value of 0.0303** with the HCG group retaining more muscle.

As was expected, on a 500 calorie diet, nearly equivalent amounts of weight will be lost. The difference is in that the body will preferentially burn fat for energy and protect muscle in the HCG group versus the placebo group.

Conclusions

HCG has been questioned as a weight loss aid due to the numerous dated studies that showed HCG had no impact on overall weight loss than placebo. To that we are in agreement. HCG demonstrates no significant stimulant properties or weight loss beyond diet alone. Rather it is a tool for creating a stable environment in the body during a VLCD to prevent the sarcopenia that occurs with use of such a diet. This muscle preservation is favorable due to maintenance of metabolism and physique, and therefore should be reconsidered as an aid to rapid weight loss methods.

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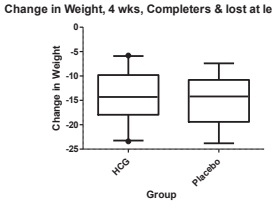
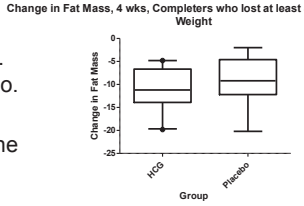
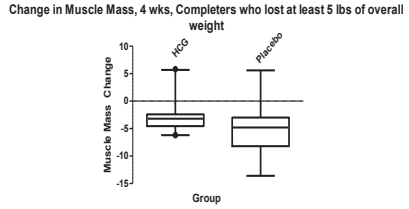
HCG vs. PLACEBO RESULTS:







4. Human chorionic gonadotropin (HCG) orally or for injection for the treatment of mood disorders and alcoholism (2008).

HUMAN CHORIONIC GONADOTROPIN (HCG) ORALLY OR FOR INJECTION FOR THE TREATMENT OF MOOD DISORDERS AND ALCOHOLISM

Mar 15, 2011

An HCG preparation for oral administration or for injection used either as a simple dilution or coupled to albumin or a cyclodextrin therapeutically effective in the treatment of mood disorders including (but not limited to) neurosis, irritability, depressive states and borderline states. HCG preparation as above described is also effective in the treatment of all types of alcoholism.

Skip to: Description Claims Patent History Patent History

Description

The present application is filed as a continuation application and claims priority of application Ser. No. 12/007,596.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to human chorionic gonadotropin (hcg) orally or for injection for the treatment of mood disorders and alcoholism, particularly HCG to be used as medical therapy for effective treatment of mood disorders as well as highly effective treatment of alcoholism.

2. Description of Prior Art

(HCG) was found and described for the first time' in pregnant women's urine by Ascheim and Zondek, about 1927. It was later found that this substance is produced in human placenta. Since it' was discovered in 1927, it was recommended for countless uses. At present, it is mostly prescribed for fertility problems and cryptorchidism (failure of both testicles to descend in children). HCG is currently supplied as a lyophilized substance for injection. Material is drawn from pregnant women's urine. It is available from several international pharmaceutical laboratories. About 1954 an English investigator published a paper containing his own experience with this substance in the treatment of obesity. The paper was welcomed and accepted by scientists generally until 1974-75, when the method became obsolete.

The method provided by the above-mentioned investigator had several problems: it was for injection, caused immunity after treatments longer than six weeks, had some secondary effects, such as fluid retention, among others.

BRIEF SUMMARY OF THE INVENTION

An HCG preparation for oral administration or for injection used either as a simple dilution or coupled to albumin or a cyclodextrin therapeutically effective in the treatment of mood disorders including (but not limited to) neurosis, irritability, depressive states and borderline states. HCG preparation as above described is also effective in the treatment of all types of alcoholism. HCG oral preparation provides the same therapeutic effects as psychotropic

substances commonly used in the treatment of the disorders as described above, but does not have the same technical and pharmacologic problems as such drugs. Moreover, it is an alternative to be considered in the cases of alcoholism since there is no effective treatment for this condition yet. The preparation can be used for long periods without secondary undesired effects.

BRIEF DESCRIPTION OF THE DRAWINGS

The figures included in the present application are charts representing the results of the test conducted to show the results of the use of HCG in the present invention.

FIG. 1 is a chart of the tests performed showing patient's mood during treatment.

FIG. 2 is a chart of the test performed showing irritability episodes

FIG. 3 is a chart of the test performed showing the arguments held during treatment.

DETAILED DESCRIPTION OF THE INVENTION

The standard lyophilized preparation supplied by pharmaceutical laboratories is used for HCG preparations. Originally, HCG is supplied as a lyophilized powder containing 2,000 to 10,000 International Units (IU) of HCG per vial. IU concept stands for an agreement whereby each IU represents the quantity that is adequate to cause maturity of an egg in experimental animals.

For the purposes of this invention, HCG is dissolved in 1% physiological saline with or without addition of human albumin or different buffers, to be administered as an injection or orally, placing it under the tongue and maintaining it there for an easier absorption by the rich sublingual venous plexus. Dilutions are prepared in such a way that each cubic centimeter of diluted HCG corresponds to a certain quantity expressed as IU.

Once Solution has been prepared in sterile conditions, it can be stored in the refrigerator for periods of 4 to 7 days. This period of time can be extended (7-10 days) if the solution is stored under cold chain conditions. Once the solution has been absorbed by the sublingual mucosa, a fraction of HCG is absorbed and carried into the circulation until it reaches the regulation centers of hypothalamic region, which contain appetite and satiation centers and fatty tissue metabolism.

Oral administration is more advantageous than injections one since it is easier to administer and equally effective. Since treatment is innocuous, it can be used for several months without problems and with equally effective results.

EXAMPLE

The following study was conducted in order to validate 105 obtained clinical results: Seventy (70) women were Screened (double blind study was conducted at site Gynecology Section. After signing the required consent, they where divided into two groups: Group A received saline alone, whereas group B received two different concentrations of HCG. The study was designed based on double blind study methods: neither the volunteers nor the staff knew who received placebo and who belonged to the HCG-administered group. The numbers assigned

to each volunteer showed the type of substance (placebo or HCG) to be administered. The envelopes containing the codes were opened at the end of the study.

Determinations

The following tests were carried out during the study:

A—Laboratory studies (Day O), and after the study.

B—Irritability test during treatment, which was evaluated through a questionnaire to be completed by patients once a week, including Hamilton test for depression and questionnaire for mood disorder evaluation. All evaluations were performed by the same observer throughout the treatment period in order to avoid observation differences due to different observers performing evaluations.

Study Period

Study period was five weeks, at the end of which the envelope containing the codes for each patient was opened, and the data obtained were used for statistical studies (regression and variance's studies).

Data Analysis

The following studies were performed:

Data were entered in a database and compiled in ASCII format.

Frequency, media, standard deviation and standard error analyses were conducted. Variance, co-variance and multiple regression analyses were conducted.

Results

Volunteers completed a questionnaire concerning their mood during treatment.

The following statistical differences between both Groups were found: HCG-administered patients felt better during study period ($p<0.03$ on the third week of treatment, and $p<0.01$ by the fifth week of treatment.

They had better and deeper sleep periods ($p<0.06$ on the third week of treatment.) They showed greater acceptance of points of view that were different from their own ($p<0.01$ on the fifth week of treatment). They were less irritable ($p<0.001$ from the fourth week of treatment). They got less upset every time things were not as expected ($p<0.05$.) They were less willing to argue for trifles ($p<0.05$.) They were less inclined to argue loudly ($p<0.005$ on the fourth week of treatment.) After four weeks' treatment 65% of the treated patients reported that they were in a better mood, less irritable, had longer and better sleep periods, had a tendency to avoid arguing for trifles, and their familiar relationships were more friendly.

On the other hand, volunteers that had problems with excessive alcoholic drinking reported they did not feel the urge to drink and that they could restrain from drinking even when social

pressures inciting to do so. This group also reported that they were able to refrain from alcoholic beverages drinking despite heavy social pressure

Approximately 10% of the patients completely quit alcoholic drinks spontaneously during treatment.

Conclusions

Nowadays mood disorders are a very common pathology in society, and the several or recommended treatments are not always implemented due to moderate to severe secondary effects. The use of HCG has demonstrated efficacy in the treatment of mood disorders without revealing undesirable effects, as well as the capacity to be administered for long periods. On the other hand, alcoholism is a serious social health problem for which there are no available therapeutic solutions. Since oral HCG has no secondary effects, its administration for the treatment of chronic alcoholism is an excellent and innocuous therapeutic aid.

Claims

1. A method of treating a human patient having mood disorders comprising the oral administration of an effective amount of a solution of human chorionic gonadotropin (hCG), to said human patient in need thereof.

2. The method of claim 1 in which a solution of hCG powder dissolved in a pharmaceutically suitable buffer is orally administered.

3. The method of claim 1 in which a solution of hCG powder dissolved in physiological saline is orally administered.

4. The method of claim 1 in which a solution of hCG powder dissolved in 1% pharmaceutically suitable buffer, is orally administered.

5. A method of treating a human patient having mood disorders comprising the parenteral administration of an effective amount of a solution of human chorionic gonadotropin (hCG), in a sterile injectable formulation to said human patient in need thereof.

6. The method of claim 5 in which a solution of hCG powder dissolved in a pharmaceutically suitable buffer is parenterally administered.

7. The method of claim 5 in which a solution of hCG powder dissolved in physiological saline is parenterally administered.

8. The method of claim 5 in which a solution of hCG powder dissolved in 1% pharmaceutically suitable buffer is parenterally administered.

9. A method of treating a human patient suffering from alcoholism comprising the oral administration of an effective amount of a solution of human chorionic gonadotropin (hCG), to said human patient in need thereof.

10. The method of claim 9 in which a solution of hCG powder dissolved in a pharmaceutically suitable buffer is orally administered.

11. The method of claim 9 in which a solution of hCG powder dissolved in physiological saline is orally administered.

12. The method of claim 9 in which a solution of hCG powder dissolved in 1% pharmaceutically suitable buffer, is orally administered.

13. A method of treating a human patient suffering from alcoholism comprising the parenteral administration of an effective amount of a solution of human chorionic gonadotropin (hCG), in a sterile injectable formulation to said human patient in need thereof.

14. The method of claim 13 in which a solution of hCG powder dissolved in a pharmaceutically suitable buffer is parenterally administered.

15. The method of claim 13 in which a solution of hCG powder dissolved in physiological saline is parenterally administered.

16. The method of claim 13 in which a solution of hCG powder dissolved in 1% pharmaceutically suitable buffer is parenterally administered.

Patent History

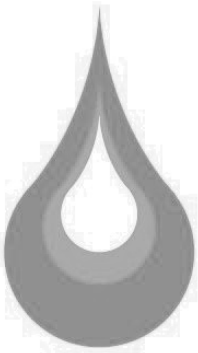
Application number: 20110224140
Type: Application
Filed: Mar 15, 2011
Issued: Sep 15, 2011
Inventor: DANIEL OSCAR BELLUSCIO (Buenos Aires)
Application Serial: 13/048,737

Classifications

Current U.S. Class: **Hormone Or Derivative Affecting Or Utilizing (514/9.7)**
International Classification: A61K 38/24 (20060101); A61P 25/32 (20060101); A61P 25/00 (20060101);

5. The influence of different excipients and storage procedures on hCG (human Chorionic Gonadotropin) as evidenced by spectrophotometry (2011).


The Oral hCG
RESEARCH CENTER



Pharmacology and pharmacodynamics of hCG solutions to be administered by the oral sublingual approach.

The influence of different excipients and storage procedures.

- **Authors**:

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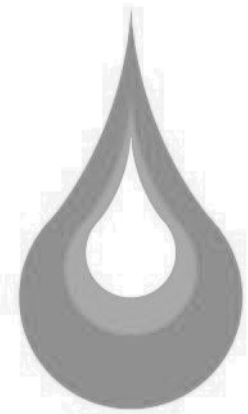
Introduction

- Currently Human Chorionic Gonadotropin (hCG), both the version obtained from urine of pregnant women or from recombinant DNA, can be obtained in the market in the form of liquid vials or lyophilized powder for injectable administration.
- Our current research provided us an insight to advance in the development for a new formulation, or pharmaceutical presentation for hCG, to be administered by the oral-sublingual route.
- Our objective is to develop a novel formulation or pharmaceutical liquid form of hCG with sufficient stability to grant a therapeutically effective presentation of hCG apt to be used by the oral/sublingual approach

Oral hCG formulation

- Theoretical Aspects:
  - Analysis and study of pharmacotechnical aspects to assess the ideal conditions for obtaining stability in the proposed Oral hCG formulation.



hCG stability study: analytical method and results.

HCG Stability Study: analytical method and results

Human Chorionic Gonadotropin in liquid pharmaceutical form

- Objective:
  - The following study aims to establish the conditions that will provide a stable pharmaceutical preparation of a liquid formulation of hCG for oral administration.

- Summary:
  - We propose an accelerated stability study in order to evaluate variables that could affect the chemical stability of hCG in a liquid solution.

HCG Stability Study: analytical method and results

Study Design: Objectives

- Gather information as regards the stability of hCG in a liquid environment.
- Need to establish variables or parameters evaluating the biological, physical and chemical properties of hCG under different conditions.
- These considerations will determine the analytical methods that will allow us to formulate those stability environments to quantifiable parameters.
- Perform preliminary studies to assess four study parameters or variables that in our opinion can affect the chemical stability of hCG in a liquid solution.

HCG Stability Study: analytical method and results

Defined Study Parameters:

1. PH.

2. Ionic Force (influence of electrolytes.)

3. Influence of Excipients.

4. Temperature.

HCG Stability Study: analytical method and results

Materials

- 5000 IU Human Chorionic Gonadotropin– lyophilized (GONACOR 5000 – Massone Institute)
- Phosphoric Acid 85% (Carlo Erba)
- Sodium Hydroxide (Merck – Analytical Grade)
- Sodium Chloride (Merck – Analytical Grade)
- Injectable quality distilled water (Roux Ocefa)

HCG Stability Study: analytical method and results

Method

- The samples under study were submitted to accelerated stability conditions: they are maintained at temperatures from 40ºC to 50ºC during approximately 12 weeks.
- We will define as quantifiable parameter the purity (hCG concentration) according to time.
- The quantificationof the concentration parameter will be established through an analytical method called HPSEC or High Performance Size-Exclusion (Molecular exclusion chromatography.)
- This chromatographic method allows the separation of substances according to their molecular weight and is used for the separation of proteins and substances with high molecular weight.

Standard working conditions

Phase A	0.1M phosphate ph 6,7 + 0.1M Sodium sulfate
Isocratic conditions	100% phase A.
Column	TSK G 2000 SWXL
Flow Rate	0.5 ml/min
UV Detector	214 nm
Injection Volume	40 microlite (5000 IU)

Sample Preparation

- All samples subject to the following study were elaborated according to operative conditions established in the following order:
  1. The hCG was diluted in the adequate solvent (injectable quality distilled water) and homogenized.
  2. The pH of the obtained solution was adjusted with Phosphoric Acid at 85% and Sodium Hydroxide 1M solution to reach pH7.
  3. The obtained solution was filtered through sterile syringe filters of 0.22 microns (Minisart 16534 K – cellulose acetate) to guarantee solution sterility.
  4. The obtained solution was bottled in 10 cc. vials and the vials were tapped with rubber tops and aluminum security precincts.
  5. All described operations were performed under laminar flux conditions.

HCG Stability Study: analytical method and results

Graphs results to evaluate the chemical stability of hCG according to the four established parameters or variables.

1 – PH

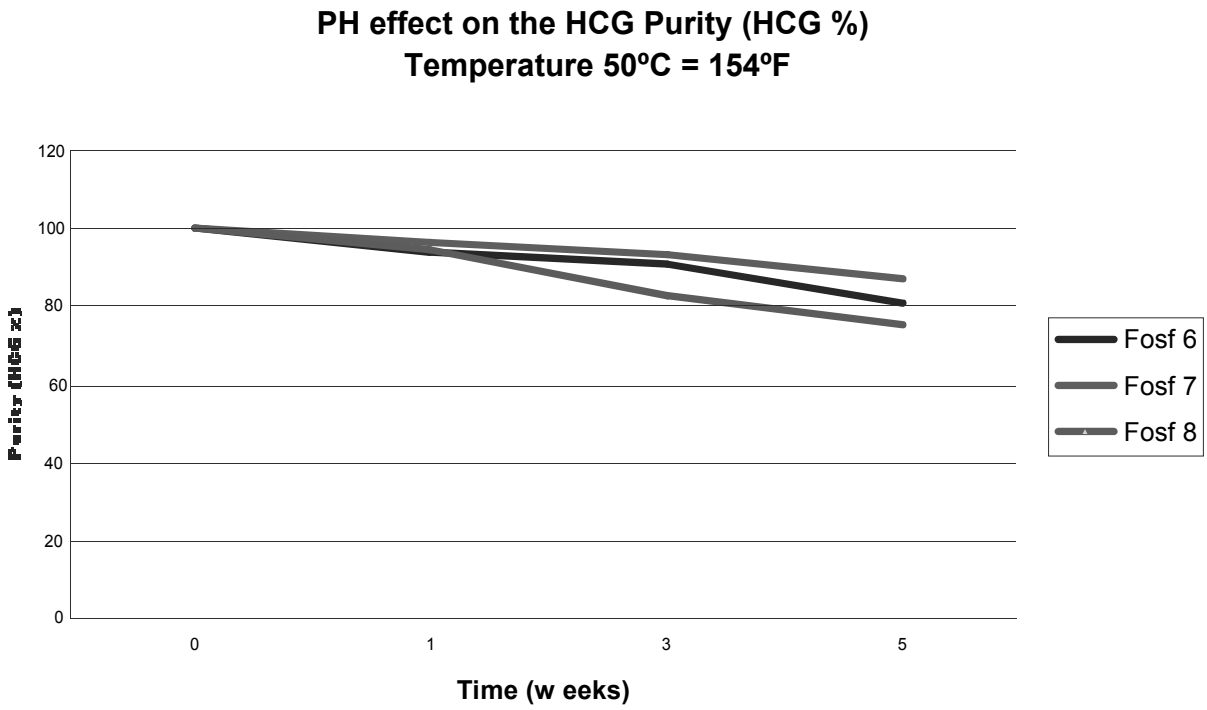
- To evaluate the effect of pH on the chemical stability of hCG in liquid solution, three samples were prepared. Their composition can be observed in Table 1:

Table 1

Samples	Composition
Fosf 6	HCG 5000 IU Phosphoric acid 85% 0.98mg Sodium Hydroxide solution 1M q.s to PH 6 Water injection q.s to 1 ml
Fosf 7	HCG 5000 IU Phosphoric acid 85% 0.98mg Sodium Hydroxide solution 1M q.s to PH 7 Water injection q.s to 1ml
Fosf 8	HCG 5000 IU Phosphoric acid 85% 0.98mg Sodium Hydroxide solution 1M q.s to PH 8 Water injection q.s to 1ml

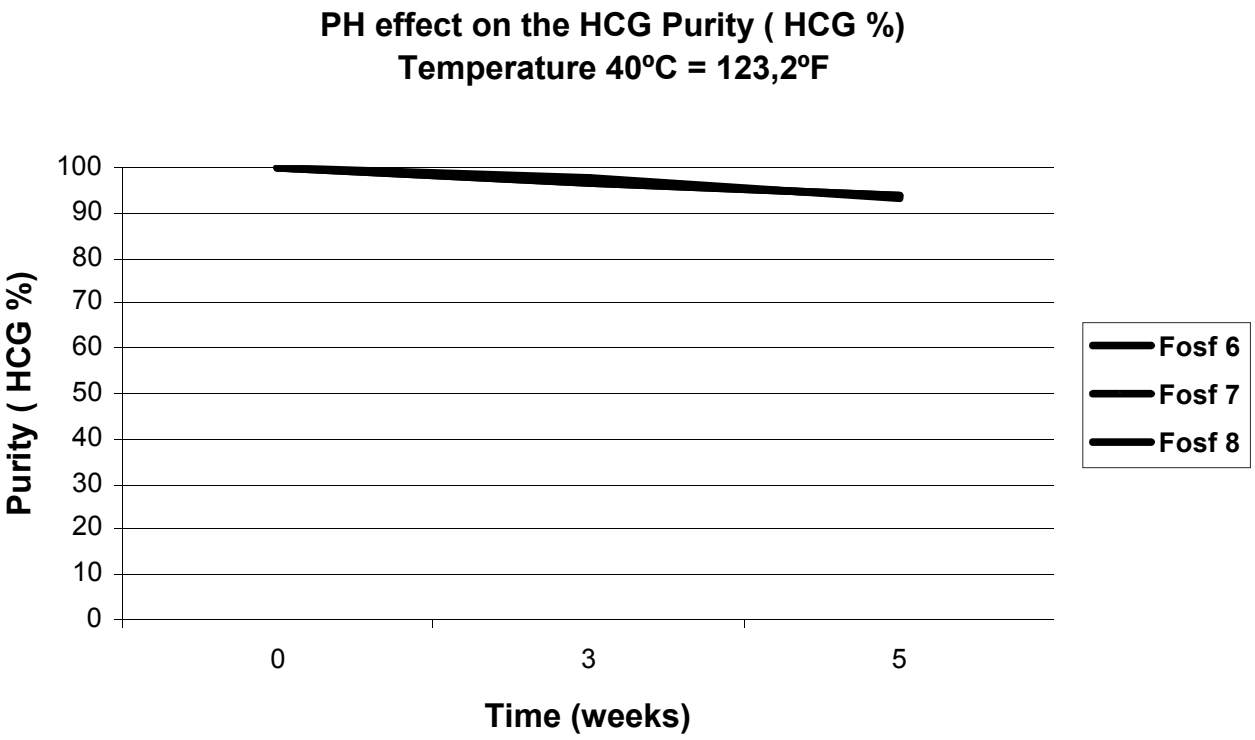
HCG Stability Study: analytical method and results

- Here in Graphs 1 and 2 we display the stability curves obtained for samples under experimental conditions:



Graph 1

Nature Precedings : doi:10.1038/npre.2011.5919.1 : Posted 21 Apr 2011



Graph 2

HCG Stability Study: analytical method and results

- Influence of pH on Purity (% hCG)

Temperature 50ºC = 154ºF				
Samples	**Time 0 week**	**Time 1 week**	**Time 3 week**	**Time 5 week**
Fosf 6	100	94.1	90.76	81
Fosf 7	100	96.09	93.12	86.93
Fosf 8	100	94.21	82.50	74.96

Temperature 40ºC = 123,2ºF			
Samples	**Time 0 week**	**Time 3 week**	**Time 5 week**
Fosf 6	100	97.5	93
Fosf 7	100	96.72	93.74
Fosf 8	100	96.77	93.55

2 – Ionic Force (influence of electrolytes)

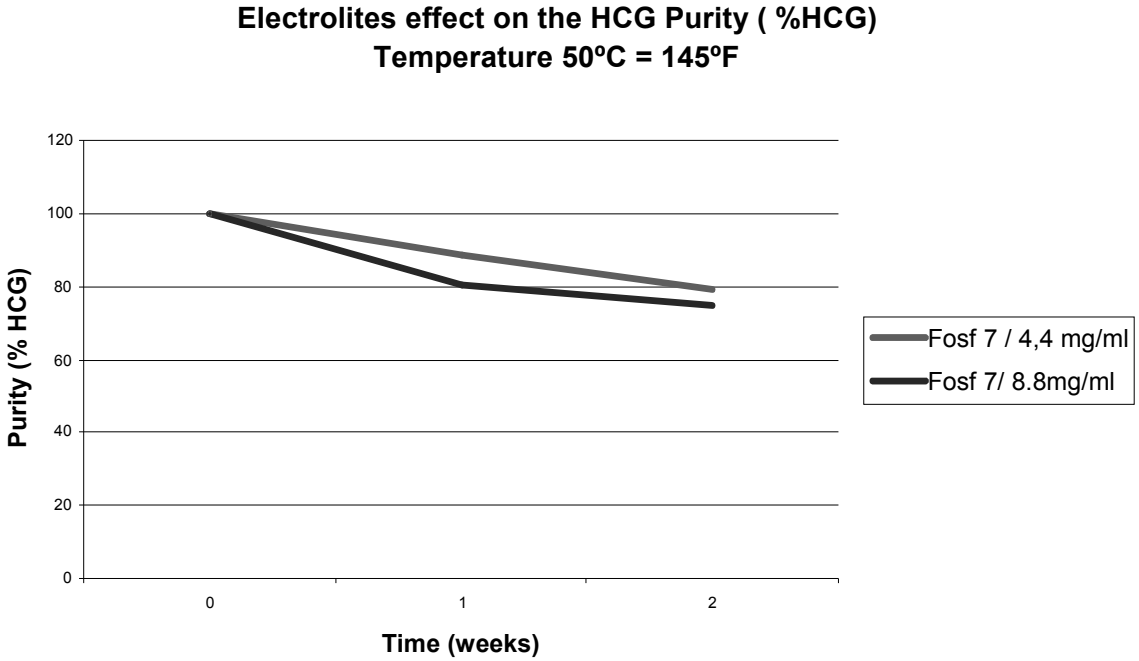
- To assess the influence of electrolytes on the chemical stability of hCG in liquid solution, 2 samples were prepared, their composition can be observed in Table 2:

Table 2

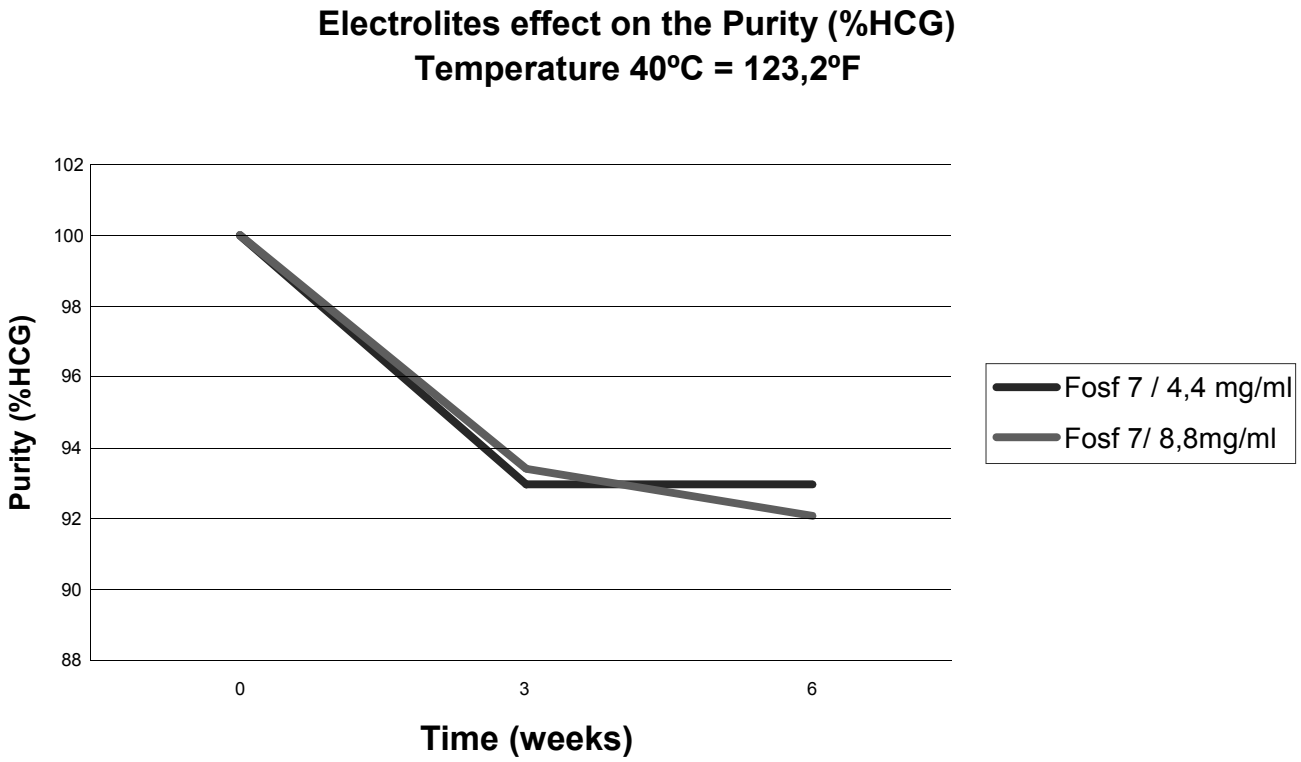
Samples	Composition
Fosf 7 / 4,4 mg/ml (150 mOsm)	**HCG 5000 IU / ml** **Sodium chloride 4,4 mg/ml** **Phosphoric acid 85% 0.98mg** **Sodium hydroxide solution 1M q.s to PH 7** **Water injection q.s to 1 ml**
Fosf 7 / 8,8 mg/ml (300 mOsm)	**HCG 5000 IU / ml** **Sodium chloride 8,8 mg/ml** **Phosphoric acid 85% 0.98mg** **Sodium hydroxide solution 1M q.s to PH 7** **Water injection q.s to 1ml**

HCG Stability Study: analytical method and results

- In Graph 3 and Graph 4 we can observe the stability curves obtained for both samples.
- The samples have been evaluated at temperatures of 25ºC and 4ºC, additionally to the proposed experimental conditions.



Graph 3



Graph 4

HCG Stability Study: analytical method and results

- Influence of Electrolytes (Ionic Force) on Purity (%HCG)

Temperature 50ºC = 154ºF				
Samples	**Time 0 week**	**Time 1 week**	**Time 2 week**	**Time 4 week**
Fosf 7 / 4,4mg/ml	100	88.5	79.2	72.2
Fosf 7/ 8,8mg/ml	100	80.5	75	67.9

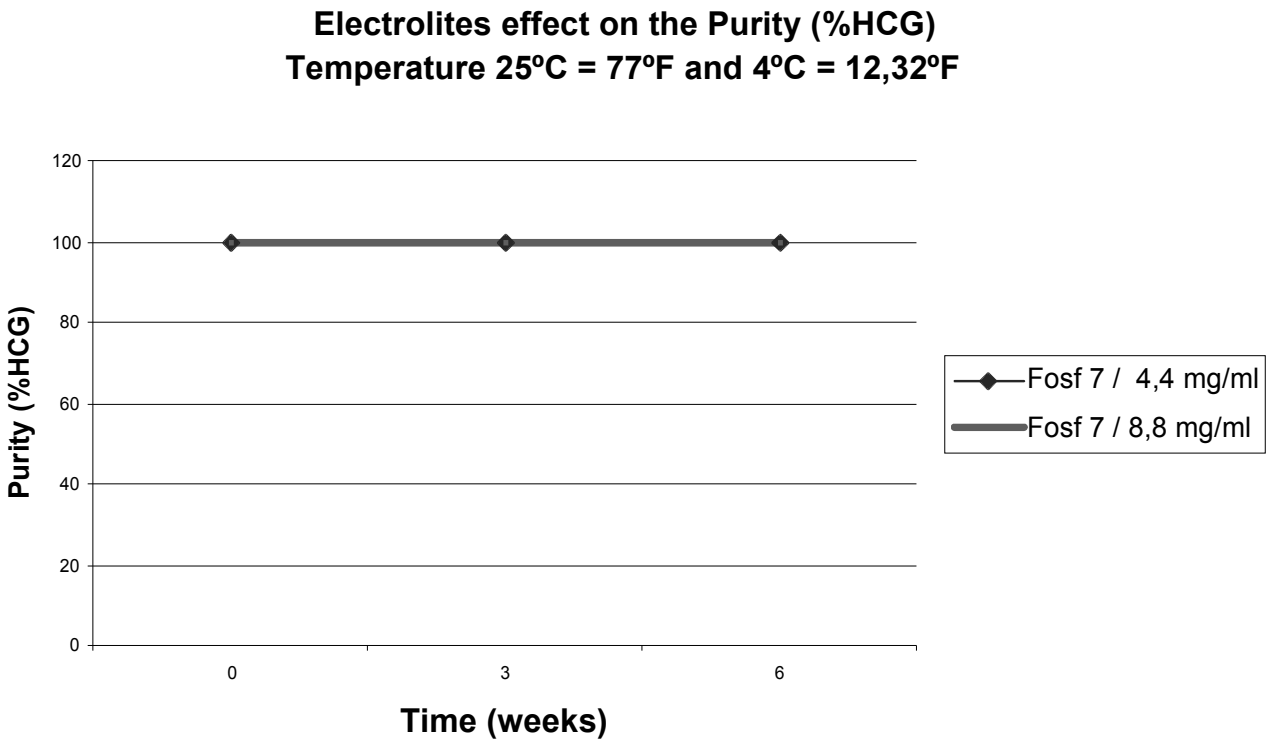
Temperature 40ºC = 123,2ºF			
Samples	**Time 0 week**	**Time 3 week**	**Time 6 week**
Fosf 7 / 4,4mg/ml	100	93	93
Fosf 7/ 8,8mg/ml	100	93,4	92,1

HCG Stability Study: analytical method and results

- Influence of Electrolytes (Ionic Force) on Purity (%HCG) (2)

Temperature 25ºC = 77ºF			
Samples	Time 0 week	Time 3 week	Time 6 week
Fosf 7 / 4,4mg/ml	100	100	100
Fosf 7/ 8,8mg/ml	100	100	100

Temperature 4ºC = 12.32ºF			
Samples	**Time 0 week**	**Time 2 week**	**Time 4 week**
Fosf 7 / 4,4mg/ml	100	100	100
Fosf 7/ 8,8mg/ml	100	100	100



Graph 5

Conclusion

- In proposed experimental conditions (temperatures of 50ºC and 40ºC) we observe that an increase in concentration of electrolytes negatively affects purity (%hCG) of Human Chorionic Gonadotropin in liquid solution.

- No changes are observed at temperatures between 25ºC and 4ºC.

Comparative Study- Effect of different Electrolytes: Silver

- In order to qualitatively evaluate the influence of electrolytes on the chemical stability of hCG in liquid solutions, two samples were analyzed by ultraviolet spectrophotometry. Their composition is observed in Table 3:

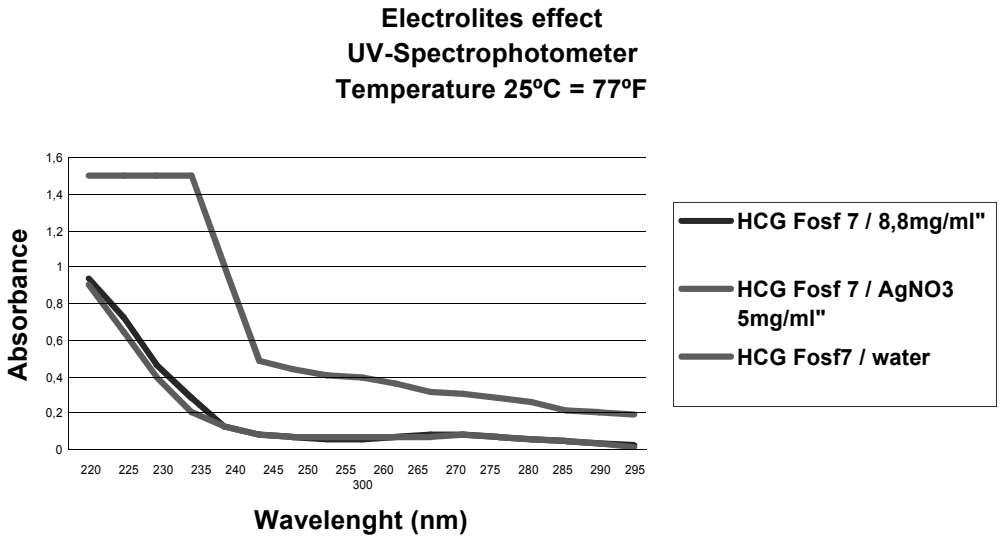
Table 3

Samples	Composition
Fosf 7 / Nacl	**HCG 5000 IU / 10ml Sodium chloride 8,8 mg/ml Phosphoric acid 85% 0.98mg Sodium hydroxide solution 1M q.s to PH 7 Water injection q.s to 10 ml**
Fosf 7 / $AgNO_3$	**HCG 5000 IU / ml Silver nitrate 5 mg/ml Phosphoric acid 85% 0.98mg Sodium hydroxide solution 1M q.s to PH 7 Water injection q.s to 10ml**

HCG Stability Study: analytical method and results

Working Conditions

- The samples under study were analyzed by a Beckman 25 spectrophotometer, scanning between 300nm–220nm, using quartz buckets of 10 mm of width and maintaining temperature between 22ºC–25ºC in a thermostatic bath.
- The obtained specters of both samples are displayed in Graph 5:



Graphic 5

Conclusions

- The spectrophotometric comparative study of both samples evidences that the use of sodium chloride as electrolyte favors the chemical stability of hCG in liquid solution.

- By contrast, the use of silver salts in liquid solution degradates the hCG molecule.

3 – Influence of Excipients

- To compare the effect of excipients on the chemical stability of hCG in liquid solution, two samples were prepared.
  Their composition can be observed in Table 4.

Table 4

Samples	Composition
Fosf 7 / mannitol	**HCG 5000 IU / ml** **Mannitol 54 mg/ml** **Phosphoric acid 85% 0.98mg/ml** **Sodium hydroxide solution 1M q.s to PH 7** **Water injection q.s to 1 ml**
Fosf 7 / Sucrose	**HCG 5000 IU / ml** **Sucrose 102 mg/ml** **Phosphoric acid 85% 0.98mg/ml** **Sodium hydroxide solution 1M q.s to PH 7** **Water injection q.s to 1ml**

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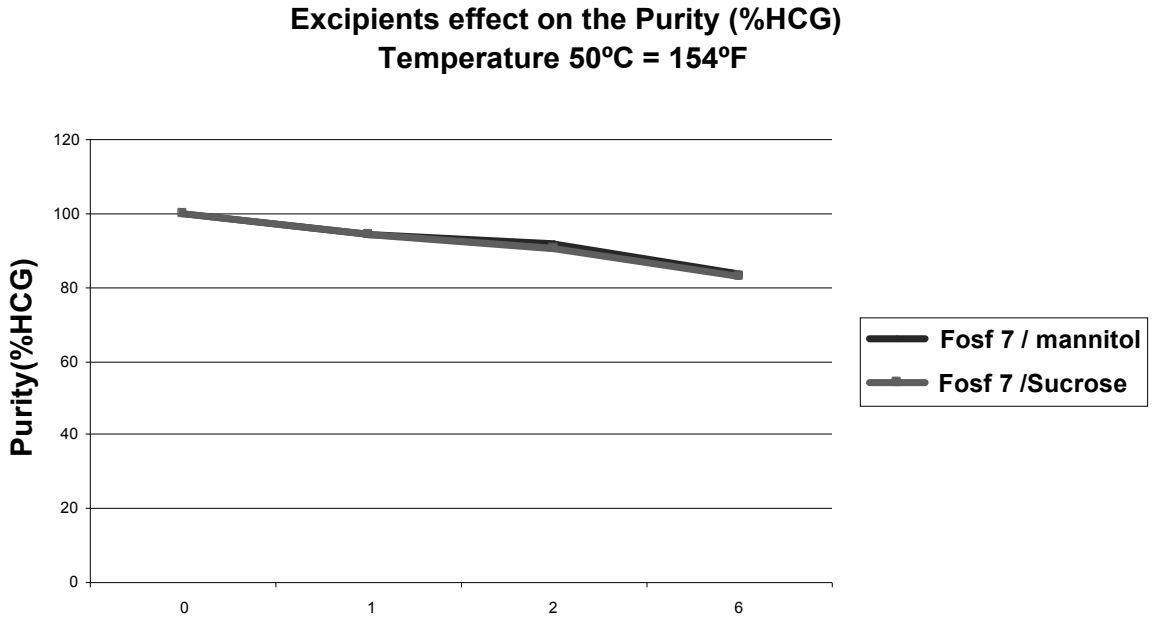
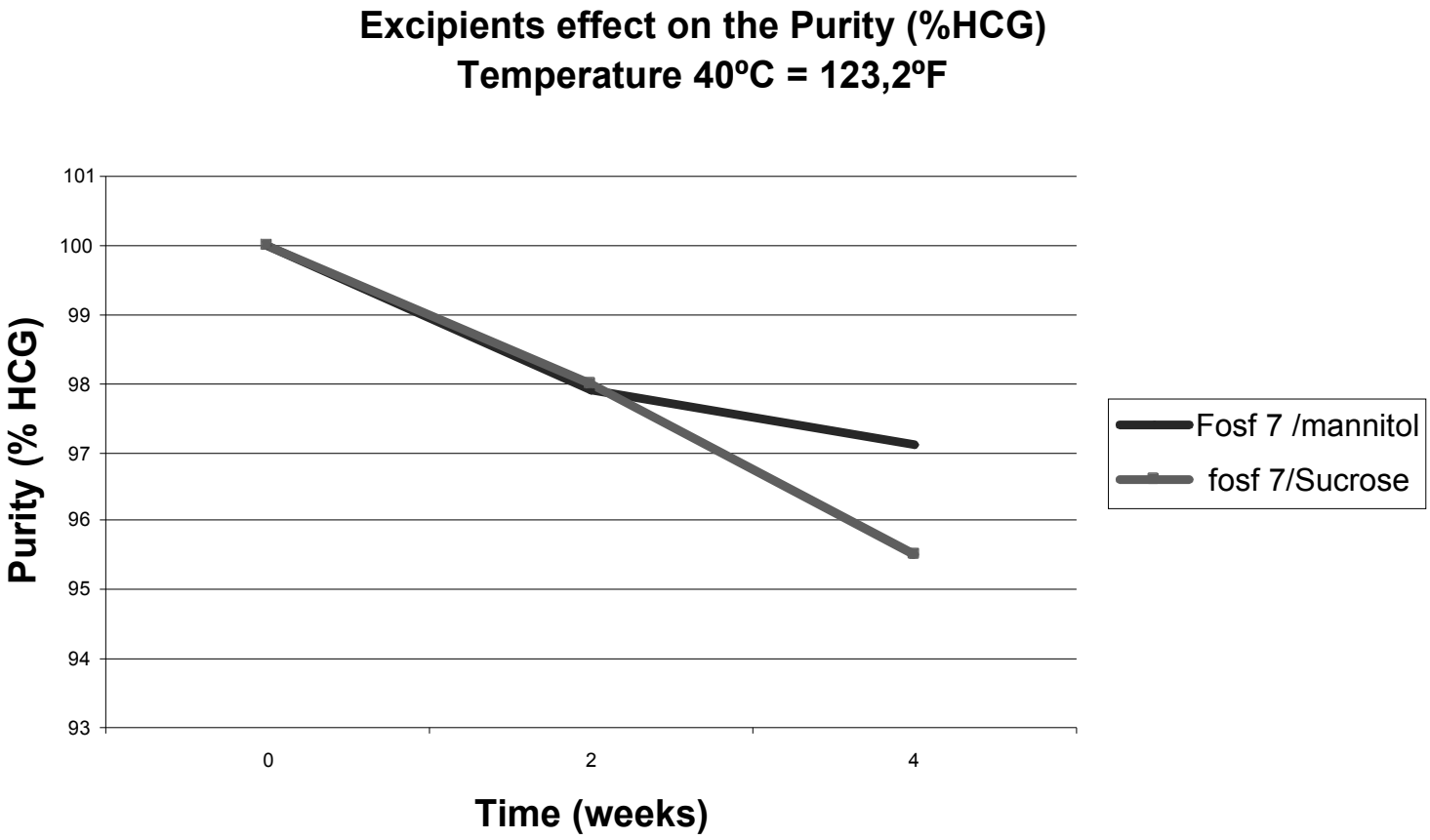
HCG Stability Study: analytical method and results

- We can observe the stability data obtained for both samples in Graph 7 and Graph 8.
- Samples were also subjected to temperatures of 25ºC and 4ºC.



Graph 7



Graph 8

Nature Precedings : doi:10.1038/npre.2011.5919.1 : Posted 21 Apr 2011

HCG Stability Study: analytical method and results

- Influence of excipients on Purity (%hCG)

Temperature 50ºC = 154ºF				
Samples	Time 0 (weeks)	Time 1 (weeks)	Time 2 (weeks)	Time 6 (weeks)
Fosf 7 / mannitol	100	94	91.7	83.5
Fosf 7 / Sucrose	100	94.1	90.3	83

Temperature 40ºC = 123,2ºF			
Samples	Time 0 (weeks)	Time 2 (weeks)	Time 4 (weeks)
Fosf 7 / mannitol	100	97.9	97.1
Fosf 7 / Sucrose	100	98	95.5

HCG Stability Study: analytical method and results

- Influence of excipients on Purity (%hCG) (2)

Temperature 25ºC = 77ºF			
Samples	Time 0 (weeks)	Time 3 (weeks)	Time 6 (weeks)
Fosf 7 / mannitol	100	100	100
Fosf 7 / Sucrose	100	100	100

Temperature 4ºC = 12,32ºF			
Samples	Time 0 (weeks)	Time 2 (weeks)	Time 4 (weeks)
Fosf 7 / mannitol	100	100	100
Fosf 7 / Sucrose	100	100	100

Comparative Study – Excipients

- To qualitatively evaluate the influence of excipients on the chemical stability of hCG in liquid solutions, two samples were analyzed by ultraviolet spectrophotometry (400nm–200nm) Their composition is observed in Table 5:

Samples	Composition
HCG Fosf 7 / Water	HCG 5000 IU / 10ml Phosphoric acid 85% 0.98mg Sodium hydroxyde solution 1M q.s to PH 7 Water injection q.s to 10 ml
HCG Fosf 7 / Ethylic alcohol	HCG 5000 IU / ml Ethylic alcohol 5% v/v Phosphoric acid 85% 0.98mg Sodium hydroxide solution 1M q.s to PH 7 Water injection q.s to 10ml

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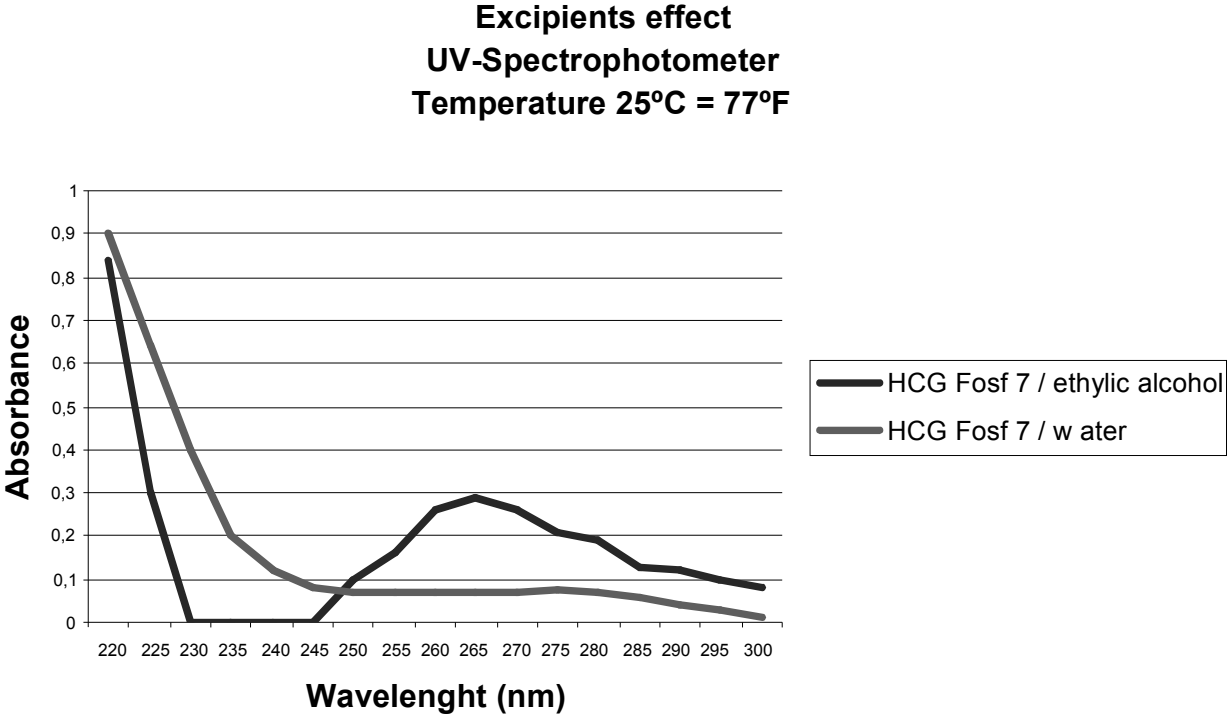
HCG Stability Study: analytical method and results

Working Conditions:

- The samples under study were analyzed by a Beckman 25 spectrophotometer, scanning between 300nm–220nm, using quartz buckets of 10 mm of width and maintaining temperature between 22ºC–25ºC in a thermostatic bath.
- The obtained specters of both samples are observed in Graph 9:



Graph 9

Conclusion:

- The spectrophotometric comparative study of both samples evidences that the use of ethyl alcohol as excipient has a negative effect of the chemical stability of hCG in liquid solution.

4 – Temperature

- To assess the effect of temperature on the chemical stability of hCG in liquid solution, two groups of samples were prepared as observed in Table 6.
- Both groups were submitted to temperatures of 25ºC, 55ºC, 65ºC, 80ºC and then analyzed by HPLC or High Performance Liquid Chromatograph

Table 6

Samples	Composition
A, C, E, G.	HCG 15000 IU / ml Buffer Phosphate 0.01M Sodium hydroxide solution 1M q.s to PH 7 Water injection q.s to 1 ml
B, D, F, H.	HCG 15000 IU / ml Sodium chloride 0.15M Sodium hydroxide solution 1M q.s to PH 7 Water injection q.s to 1ml

Working Conditions

Elution	Solution 0.1M potassium phosphate, PH 7 + solution 0.15M sodium chloride
Column	TSK – G 3000 SW
Flow Rate	1 ml/min
UV Detector	280 nm
Injection Volume	10 microliter

HCG Stability Study: analytical method and results

Stability of Human Chorionic Gonadotropin (HCG)

Temperature effect

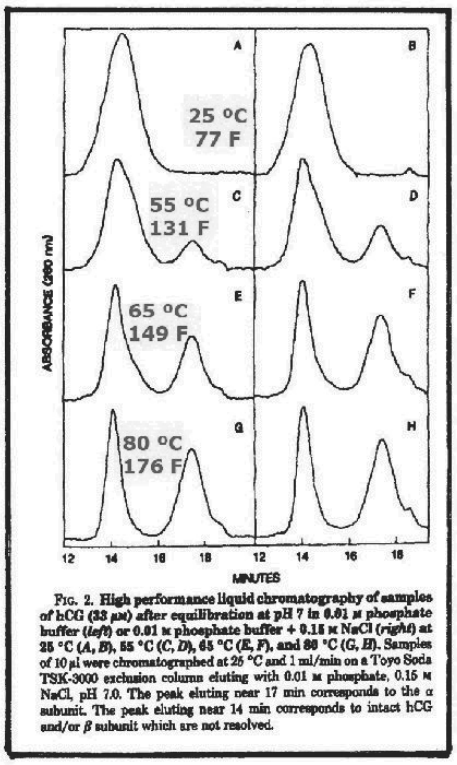


FIG. 2. **High performance liquid chromatography of samples of hCG (33 μM) after equilibration at pH 7 in 0.01 M phosphate buffer (*left*) or 0.01 M phosphate buffer + 0.15 M NaCl (*right*) at 25 °C (*A, B*), 55 °C (*C, D*), 65 °C (*E, F*), and 80 °C (*G, H*).** Samples of 10 μl were chromatographed at 25 °C and 1 ml/min on a Toyo Soda TSK-3000 exclusion column eluting with 0.01 M phosphate, 0.15 M NaCl, pH 7.0. The peak eluting near 17 min corresponds to the α subunit. The peak eluting near 14 min corresponds to intact hCG and/or β subunit which are not resolved.

Graph 10

- Graph 10 shows chromatographic results obtained for both sample groups.
- In both cases we can observe that temperatures above 25ºC initiate the process of pharmacologic modifications of the hCG molecule.
- These changes are evidenced as signs or peaks that appear in different elusion times (14 and 17 minutes) and correspond to the dissociation of the hCG molecule into its alpha and beta subunits.

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HCG Stability Study: analytical method and results

Stability of Human Chorionic Gonadotropin (hCG) Kinetic Analysis

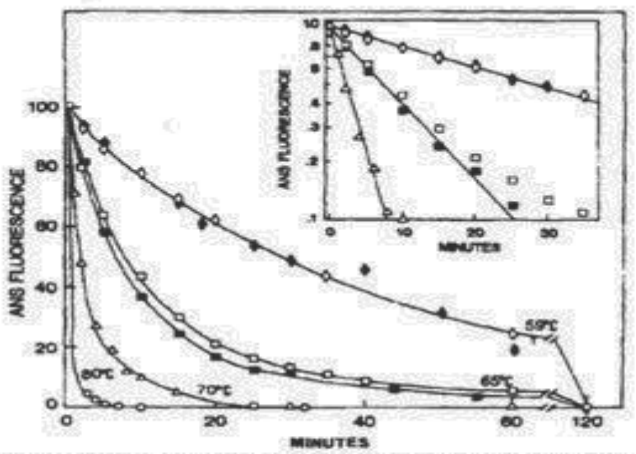

FIG. 5. The time course for the dissociation of 3.3 μM hCG at pH 7 in the presence (*filled symbols*) and absence of 0.15 M NaCl at 59 °C (◇), 65 °C (□), 70 °C (△), and 80 °C (○). The *inset* shows the first order kinetic plots for the data. Each point corresponds to a separate 250-μl sample of 3.3-μM hCG which was incubated at the desired temperature in a 0.5 cm diameter cuvette. The sample was removed at the indicated time and place on ice to quench the reaction. A small volume of concentrated ANS was subsequently added to give a final concentration of 250 μM and the fluorescence measured at 25 °C.

Graph 11

- According to this we can propose the following expression:

$$HCG \underset{Kd}{\leftrightarrow} \alpha + \beta$$

(Kd = dissociation constant)

- This constant can be calculated by studying the kinetic reaction of hCG at different temperatures.

- In Graph 11 and 12 we visualize the curves obtained through fluorescence (analytical method that allowsus to measure light emissions- fluorescence) produced by certain substances in solution.

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HCG Stability Study: analytical method and results

- The capacity of substances in solution to produce fluorescence will depend on: concentration, PH, temperature, presence of electrolytes, presence of other fluorescent substances.

- The sample under study (hCG) is treated with ANS (1,8 anilinonaphthalene sulphonate) fluorescent substance, and its fluorescence is measured given time at a determined temperature. Composition of samples is shown in Table 7:

Table 7

Samples	Composition
A (black dots)	**HCG 1500 IU / ml** **Buffer Phosphate 0.01M** **Sodium hydroxide solution 1M qs to PH 7** **Sodium chloride 0.15M** **Water injection q.s to 1 ml**
B (white dots)	**HCG 15000 IU / ml** **Buffer Phosphate 0.01M** **Sodium hydroxide solution 1M q.s to PH 7** **Water injection q.s to 1ml**

HCG Stability Study: analytical method and results

- On the curves obtained we can see that the dissociation reaction corresponds to a kinetic curve of 1st order represented in the following equations:

$$\text{Log } C = \text{Log } C0 - kd \cdot t / 2.303$$

$$t\ ½ = 0.693 / kd \qquad t\ 90 = 0.105 / kd$$

- Applying the Arrhenius equation to results obtained in Graph 9, we obtain Graph 10:

$$\text{Log } K2 / K1 = - Ea / 2.303\ R\ (1/T2 - 1/T1)$$

K2 = dissociation constant at T2

K1 = dissociation constant at T1

HCG Stability Study: analytical method and results

Observations

- According to the straight line obtained in Graph 12 it is possible to infere (by extrapolation) that the value of the dissociation constant at a temperature of 37ºC has a value of 0.003 (minutes -1).

- Our conclusion is that in physiological conditions of PH and Temperature, the half life of hCG is of approximately 40 hours.

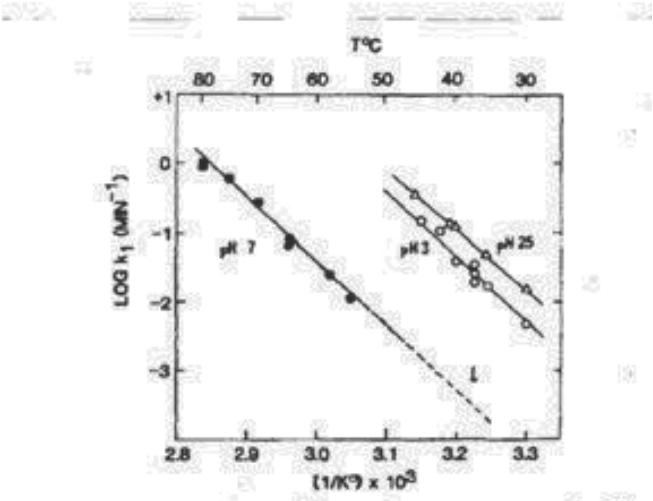

FIG. 6. Arrhenius plots of first order rate constants for dissociation of hCG subunits at pH 7 (●), pH 3 (○), and pH 2.5 (△). The values at pH 7 were determined from the data in Fig. 5. The values at pH 2.5 and 3.0 were determined in separate experiments not shown. The *dashed line* shows extrapolation of the pH 7 data to 37 °C (*arrow*) where a $t_{1/2}$ of 40 h is predicted.

Graph 12

Conclusions

- ✓ **1) PH**
- hCG resulted more stable in a liquid solution at a pH of 7, over pH 6 and pH 8.
- ✓ **2)Temperature**
- The hCG molecule is thermolabile. Thus, at a temperature above 25ºC its alpha and beta units are dissociated.
- ✓ **3)Electrolytes**
- The presence of electrolytes or salts such as Sodium Chloride synergize the dissociation of the hCG molecule.
- ✓ **4)Half-life**
- In physiological conditions of PH and temperature, the half life of hCG is of approximately 40 hours.

- Conclusions (II):

✓ **5)Ionic Force (influence of electrolytes)**

- The chemical stability of hCG is negatively affected by the presence of electrolytes at temperatures of 50ºC and 40ºC. However, at temperatures between 4ºC and 25ºC the chemical stability depends on the electrolyte present in the solution.

- The comparative spectrophotometric study between two electrolytes (sodium chloride and silver nitrate) demonstrated that the use of sodium chloride favors the chemical stability of hCG in liquid solutions.

Conclusions (III):

- ✓ **6)Excipients**

- The chemical stability of hCG is not modified by the actions of reduction sugars or poly alcohols at temperatures between 4ºC and 25ºC.

- ✓ **7)Alcohol- Silver**

- The use of ethyl alcohol and/or silver as excipients have a negative effect of the chemical stability of hCG in liquid solution.

6. Metabolic Activity of Human Chorionic Gonadotropin (hCG) on Glycemia and Leptinemia in Experimental Animals Fed a Cafeteria Diet 2 (2011).

Metabolic Activity of Human Chorionic Gonadotropin (hCG) on Glycemia and Leptinemia in Experimental Animals Fed a Cafeteria Diet

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Running title: hCG Affects Glycemia and Leptinemia in Animals

ABSTRACT

Objectives: To elucidate the relationship of hCG administration to glycemia, Non Esterified Fatty Acids (NEFA), leptin and adiponectin levels on experimental animals previously submitted to a cafeteria diet, and then to a Low Calorie Diet (LCD). **Design:** Forty-one rats were selected (21 females, 20 males) and divided into seven (0-6) groups. Animals from groups 1 to 6 were fed a "cafeteria diet" with a mean energy content of 10% protein, 30% carbohydrate and 60% fat. Animals from group 0 were fed the standard laboratory diet. After the fattening period, animals from groups 1 to 6 were submitted to a restricted diet consisting of one-third the average daily intake for rats. hCG was administered for five weeks according to a specific protocol. The effects of hCG treatment were evaluated using analysis of variance (ANOVA). **Results:** These assessments were compared: (1) glycemia, adiponectins, leptins and non-esterified fatty acids (NEFA); (2) weight; (3) formulation effect; and (4) dose effect. Differences in leptins were observed between the Control group and Injectable A (p=0.026), Intrarectal Suspension A (p=0.20), Intrarectal Suspension B (p<0.001), and Intrarectal Suspension C (p<0001) groups. In all cases, the average values were higher for the control group. Significant differences were found in the groups treated with Injectable B, Intrarectal Suspension B (p=0.025) and Intrarectal Suspension C (p=0.037). Groups receiving Intrarectal Suspension B or C showed significantly lower mean leptin values. Differences in glycemia were detected between the Control group and Intrarectal Suspension A (p=0.021) and Intrarectal Suspension B (p=0.020) groups. Groups treated with Intrarectal Suspension A or B showed lower mean blood glucose values. **Conclusions**: Results show the activity of hCG (both urinary and recombinant) on glycemia and leptins levels in

experimental animals in different formulations, but specifically when administered intrarectal. hCG administration significantly decreased blood sugar and leptin levels, whereas adiponectins were only relatively sensitive to hCG treatment.

Keywords: Human chorionic gonadotropin (hCG); Leptins; Glycemia; Adiponectin.

INTRODUCTION

Human chorionic gonadotropin (hCG) was discovered in 1927 by Ascheim and Zondek in the urine of pregnant women and was used for the treatment of conditions such as infertility, cryptorchidism, and obesity [1-3]. Several extragonadal therapeutic actions have been attributed to hCG, including (but not limited to) Kaposi sarcoma, glaucoma and BPH (Benign Prostatic hypertrophy). One of the most controversial indications was its use in the management of obesity, until a series of double blind studies conducted in humans concluded that weight loss under hCG was no better than placebo. The standard administration route was intramuscular. Its efficacy in obesity treatment was debated for years until some studies found it was not useful for treating this condition [4-8]. In 1987, Vogt and Belluscio published a study concluding the hCG protocol originally designed by Simeons [3] for obesity treatment was a suitable and safe approach to manage this condition [9]. The authors also reasserted the role of the hypothalamus as a possible intermediate organ for the lipolytic action of hCG [9].

In 1999, Belluscio et al. worked on a modification of the hCG administration route as a strategy to modify its biological activity. They investigated the sublingual route, proposed a change in the administered dose, and in a double-blind study demonstrated the pharmacological activity of hCG in the reduction of adipose tissue total mass in volunteer subjects [10] [11].

Leptin was discovered in rats in 1994. Subsequently, the human Ob gene was located on chromosome 7. It is a cytokine that plays a key role in the regulation of energy balance. It is believed to act as a lipostate: when the amount of fat stored in adipocytes increases, leptin is released into the bloodstream and results in a negative feedback signal that acts

on the hypothalamus to inhibit appetite. When adipose tissue mass increases beyond the point of equilibrium, the synthesis and secretion of leptin increases. This, in turn, stimulates several compensatory effects in the hypothalamus such as: anorectic peptide production and suppression of orexigenics, increase of energy expenditure, increase of basal metabolic rate and body temperature, and modification of the hormonal balance point, thereby reducing lipogenesis and increasing lipolysis [12-19]. The regulation of leptin secretion is associated with variations in body mass and insulin-stimulating effects. However, many obese people have high serum concentrations of leptin or resistance to it, indicating that other molecules such as ghrelin, serotonin, cholecystokinin and neuropeptide Y also have an effect on satiety and contribute to body weight regulation [20-25]. The molecular basis of leptin resistance is poorly understood; although the most accepted hypothesis is its inability to cross the blood brain barrier or the result of defects in the leptin receptor [26].

Adiponectin is a peptidic hormone abundantly expressed in mature adipocytes that circulate in high concentrations in plasma. Adiponectin expression decreases in all processes related to inflammation and insulin resistance such as obesity and diabetes mellitus. Plasma adiponectin decreases before the onset of obesity and insulin resistance in primates, suggesting that hypoadiponectinemia contributes to the pathogenesis of these diseases. Adiponectin levels increase when insulin sensitivity improves, either due to the reduction in body weight or to treatment with insulin sensitizing drugs [27].

The purpose of this study was to determine by plasma biochemistry analysis the metabolic activity of different hCG formulations, either urinary or recombinant, as well

as its relationship to glucose, NEFA, adiponectin and leptin metabolism, and to assess its safety (particularly gonadal) through histological observations of target organs.

SUBJECTS AND METHODS

The study was conducted between December 12, 2008 and June 15, 2009 at the BIO FUCAL S.A. Center located at Acceso Norte km. 42.5, Del Viso, Buenos Aires, Argentina, and sponsored by Daniel Belluscio MD. Forty-one rats (Rattus norvegicus, Sprague Dawley strain) were selected comprised of 21 females and 20 males and divided in seven (0-6) groups. Animals in groups 1 to 6 were fed a hypercaloric and highly palatable cafeteria diet [28], in contrast to animals from group 0, which continued with the standard laboratory diet. The amount of food provided with this diet was "ad libitum" and extended from December 12, 2008 (day 0 of treatment) to January 27, 2009. After the fattening period, animals in groups 1 to 6 were subjected to a restricted diet consisting of one-third of the average daily intake of balanced food for rats, calculated separately for both males and females.

hCG administration lasting five weeks was performed according to the following protocol. Group 0 received no medication or diet and continued with the standard diet throughout the course of the study. Group 1 was submitted to a hypocaloric diet without hCG administration. Group 2 was submitted to a hypocaloric diet and received 125 International Units (IU) of hCG (urinary, Massone Laboratories, Buenos Aires, Argentina) dissolved in normal saline (NaCl 0.9%), administered intramuscularly and daily, including Sundays (Injectable A). Group 3 was submitted to a hypocaloric diet and received 125 IU of r-hCG (recombinant, Ovidrel®, Serono Laboratories, Buenos Aires,

Argentina) dissolved in normal saline (0.9% NaCl), administered intramuscularly and daily, including Sundays (Injectable B). Group 4 was submitted to a hypocaloric diet and received 300 IU of hCG (urinary, Massone Laboratories, Argentina) in intrarectal emulsion containing 8 mg/ml of cyclodextrin (Laboratory Roquette Freres, Lestrem, France) as enhancer, daily, including Sundays (Intrarectal Suspension A). Group 5 was submitted to a hypocaloric diet and received 300 IU of hCG (urinary, Massone Laboratories, Argentina) in intrarectal emulsion containing 16 mg/ml of cyclodextrin (Laboratory Roquette Freres, France) as enhancer, daily, including Sundays (Intrarectal suspension B). Group 6 was submitted to a hypocaloric diet and received 300 IU of r-hCG (recombinant, Ovidrel®, Serono Laboratories) as intrarectal emulsion containing 8 mg/ml of cyclodextrin (Laboratory Roquette Freres, France) as enhancer, daily, including Sundays (Intrarectal Suspension C).

Injections were administered using 1 ml syringes and 16 x 5needles to the rear limbs between the semimembranosus and semitendinosus muscles, alternating one member per day. For intrarectal administration of the suspensions, the same syringes were used attached to an oesophageal probe for oral administration. The emulsion was deposited over the entire rectal surface, proximal to distal, keeping the anus closed for 1 minute. Both suspensions and injections were renewed every week and kept refrigerated at all times to ensure their biological activity.

Observations were systematically recorded on each treated animal once a day throughout the duration of the trial. Body weight was assessed on days 0, 3, 6, 14, 21, 25, 33, 39 (beginning of the treatment), 46, 53, 63, 77 and 82. The following serological determinations were assessed in each group at both baseline (day 39) and on the final day

(82), pre- and post- treatment, respectively: Glycemia (g/L) (Colorimetric end-point technique Autoanalyzer Hitachi 902 Wiener); adiponectin (ng/mL) (Rat adiponectin ELISA kit-ELISA manual- Catalog Nº K4903-100-Lot40203-Biovision Incorporated); leptin (ng/mL) (Mouse Leptin-Quantikine Immunoassay-ELISA-Lot 259828-Catalog Nr. MOBOO R&D Systems) and NEFA (mEq/L) (Mouse Non-ester Fatty Acid (NEFA) ELISA Kit Product No.: CSB-E13618m-CUSABIO BIOTECH Co). Regarding the safety of hCG, histological evaluation of a general necropsy was performed. The following organs and tissues were removed to perform the pertinent histopathological studies: brain (half in buffered formaldehyde at 5% and half-frozen at -20° C), ovaries (formaldehyde 5%) and testicles (5% formalin).

Statistical methodology

The effects of hCG treatment were evaluated using analysis of variance (ANOVA). The Kolmogorov-Smirnov test was also used to assess normality of distributions. Nonparametric analysis of variance was used to compare weights between treatments at the beginning and end of treatment. Descriptive analysis of adverse events was performed. SPSS® software V. 11.5 (Cary, IN, USA) was used to assess the determinations.

RESULTS

We compared basal and final determinations as follows.

General

Basal determinations

Figures 1 A-D show baseline results (before treatment) in the seven groups. To estimate their homogeneity, values were compared among the six groups submitted to high-calorie diets. No significant differences were found between groups: leptin (Fig. 1A), p=0.056; glycemia (Fig. 1B), p=0.291; adiponectin (Fig. 1C), p=0.364; and fatty acids (Fig. 1D), p=0.722.

Final determinations

Figures 2 A-D show final results (post treatment) in the seven groups. No significant differences were observed in adiponectin (F=2,130, p=0.076) (Fig. 2C) or fatty acids (F=1,056, p=0.408) (Fig. 2D), but statistically significant differences were observed in leptin (F=7,066, p<0.001) (Fig. 2A) and glucose (F=3,012, p=0.018) (Fig. 2B). Differences in leptin were observed between the Control group and the following groups: Injectable A (p=0.026), Intrarectal Suspension A (p=0.20), Intrarectal Suspension B (p<0.001) and Intrarectal Suspension C (p<0001). In all cases, the average values were higher for the Control group. Significant differences were also found in the group treated with Injectable B and in the Intrarectal Suspension B (p=0.025) and Intrarectal Suspension C (p=0.037) groups. Groups receiving Intrarectal Suspension B or C showed significantly lower mean leptin values. Differences in glycemia were detected between the Control group and the Intrarectal Suspension A (p=0.021) and Intrarectal Suspension B (p=0.020) groups. Groups treated with Intrarectal Suspension A or B showed lower mean blood glucose values.

Treatment effect

Differences were first assessed between the Control group (Group 0), the group that was submitted to the hypocaloric diet (Group 1), and groups treated with hCG (Groups 2-6) (treatment effect).

Leptin

Significant differences were found in leptins among the treatments groups (F=9,694, p<0.001). The average value in the Control group was 3.05, 1.92 in the group treated only with hypocaloric diet, and 1.12 in groups treated with hCG. The most significant differences were found between the Control group and groups treated with hCG (p<0,001), while no significant differences were found between the two groups that did not receive hCG.

Glycemia

Significant differences were also observed in plasmatic glucose final values (F=8,099, p=0,001). The average value in the Control group was 1.78, 1.23 in the group treated with hypocaloric diet, and 1.15 in the groups treated with hCG. This difference is significant when comparing the Control group to the groups treated with hCG (p=0,001). Even though adiponectin plasmatic results were higher in the groups treated with hCG, differences were not statistically significant (F=1,388, p=0.262). The average value in the Control group was 2.69, 4.12 in the group treated with hypocaloric diet, and 5.80 in the groups treated with hCG. Statistically significant differences were not found in fatty acids (F=0.763, p=0.473). The average value for the Control group was 0.97, 0.85 in the hypocaloric diet group, and 0.90 in the groups treated with hCG.

Dose effect

To assess the effect of the administered dose, groups were matched as follows: Control with standard diet, Control with hypocaloric diet, Injection A/Intrarectal Suspension A, Injectable B / Intrarectal Suspension C, Intrarectal Suspension B.

Leptin

Significant differences in leptin were observed between the groups (Brown-Forsythe 5.473; p=0.009). The highest average values were recorded in the group that received the standard diet (3.05). Values were lower (1.92) in the group treated with hypocaloric diet, and even lower in the groups receiving hCG. Among those groups, the lowest mean values were recorded in animals receiving Intrarectal Suspension B. Differences were significant between the Control group and the groups receiving Injectable A/Intrarectal Suspension A (1.28, p=0.010), groups that received Injectable B/ Intrarectal Suspension C (1.30, p=0.012), and groups that received Intrarectal Suspension B (0.47, p<0.001).

Glycemia

Significant differences were observed in blood glucose between groups (F=4,078, p=0.008). Animals from the Control group showed higher average blood glucose values (1.78). A reduction in average values was observed in the group treated with hypocaloric diet (1.23) and in all subjects receiving hCG. When comparing animals under treatment, the lowest mean average values were observed in those receiving Intrarectal Suspension B (0.90). Significant differences were observed between the Control group and the group receiving Injectable A/Intrarectal Suspension A (1.05, p=0.016), the group receiving Injectable B/Intrarectal Suspension C (1.05, p=0.018), and the group receiving Intrarectal Suspension B (p=0.009).

Formulation effect

To estimate the effect of the administered formulation, groups were matched and analyzed as follows: Control with standard diet, Control with hypocaloric diet, subjects with Injectable A/Intrarectal Suspension, A/Intrarectal Suspension B, and subjects with Injectable B/Intrarectal Suspension C.

Leptins

Significant differences in leptin levels were observed between the groups (Brown-Forsythe 4978; p=0.020). The highest average values (3.05) were observed in the Control group with standard diet. Values were lower (1.92) in the Control group with hypocaloric diet and in the groups receiving hCG. When comparing groups, the lowest mean values (1.01) were observed in animals receiving Injectable A/Intrarectal Suspension A/Intrarectal Suspension B. Statistically significant differences were found when comparing the Control group with standard diet and animals receiving Injectable A/Intrarectal Suspension A/Intrarectal Suspension B (p=0,001) and Injectable B/Intrarectal Suspension C (1.30, p=0.009).

Glycemia

Significant differences were observed when comparing blood glucose levels between the groups (F=5.307, p=0.004). The highest average values (1.78) were detected in the Control group that received the standard diet, and values decreased in the Control group treated with the hypocaloric diet (1.23) and in groups receiving hCG (1.00 and 1.05, respectively). Differences were significant between the Control group with the standard

diet and the groups receiving Injectable A/Intrarectal Suspension A/Intrarectal Suspension B (p=0.003) and Injectable B/Intrarectal Suspension C (p=0.010).

Pharmaceutical formulation effect

To estimate the different effects of the pharmaceuticals formulations, groups were split as follows: Control group with standard diet, Control group with hypocaloric diet, a group with Injectable A/B and a group with Intrarectal suspension A/B/C.

Leptin

Significant differences were observed in leptins between groups (Brown-Forsythe 7.398; p=0.008). The highest average values (3.05) were recorded in the Control group with the standard diet. In the Control group with the hypocaloric diet, the observed value (1.92) was decreased and further reductions were observed in the groups receiving hCG. Among the groups receiving treatment, lower average values (0.75) were found in the intrarectal suspension A/B/C groups. Differences were significant between the Control group with standard diet, the group receiving Injectable A/B (1.72, p=0.041), and the group receiving Intrarectal suspension A/B/C (p <0.001). Differences were also significant between the groups with the hypocaloric diet and the Intrarectal suspension group (p=0.040), and the Injectable and Intrarectal suspension groups (p=0.034).

Glycemia

Significant differences were observed in blood glucose levels among the groups (Brown-Forsythe F=5,667, p=0.003). Animals with the standard diet showed higher average blood glucose values (1.78). Mean values dropped (1.23) in the group treated with hypocaloric diet and in all groups receiving hCG. Among the treated groups, the lowest

mean values (0.97) were found in those receiving intrarectal suspension A/B/C. Significant differences were found between the Control group with standard diet, groups receiving Injectable A/B (1.11, p=0.019), and groups that received the Intrarectal suspension A/B/C (p<0.001).

Weight assessment

Figure 3 shows modifications in the mean weight of the seven groups.

Treatment effect

Significant differences were found between the groups regarding weight modifications (F=13,254, p<0.001). The average percentage variation for the standard diet group was 0.4% (CI 95%; 8.8, 9.6). Results for the group with the hypocaloric diet were -24.7% (CI 95%; 29.9, 19.4) and for hCG-treated groups they were -16.8% (CI 95%; -20.3, -13.3). Differences were significant in all three comparisons: the Control group with standard diet *vs*. the hypocaloric diet group (p<0,001); the Control group with standard diet *vs*. hCG-treated groups (p<0,001); and the Control group with hypocaloric diet *vs*. hCG-treated groups (p<0.001).

Dose effect

To assess the effect of the administered dose, groups were matched as follows: the Control group with standard diet, the Control group with hypocaloric diet, the groups with Injectable A/Intrarectal Suspension A, Injectable B/ Intrarectal Suspension C, and Intrarectal Suspension B. Significant differences were observed in weight percent change among groups between day 39 (baseline; before treatment, after cafeteria diet) and day 82 (Brown-Forsythe=10,394, p=0 <0.001). Significant differences were also observed when

comparing the Control group under the standard diet (average percentage variation 0.4; CI 95%; 8.8, 9.6) *vs*. the Control group with the hypocaloric diet (-24.7, CI 95% -29.9, -19.4) (p<0.001); *vs*. the Injectable A/Intrarectal Suspension A group (-18.1, CI 95% -25.1, -11.2) (p=0,001); and *vs*. the Injectable B / Intrarectal Suspension C group (-18.3, CI 95% -23.0, -13.7) (p=0,001). There was also a significant difference between the Control group with hypocaloric diet and the Intrarectal suspension B group (-8.7, CI 95%;-16.7, -0.6) (p=0.037).

Formulation effect

To assess the effect of the administered formulation, groups were analyzed as follows: the Control group with standard diet, the Control group with hypocaloric diet, and the Injectable A/Intrarectal suspension A/ Intrarectal suspension B, Injectable B/ Intrarectal suspension C groups. Significant differences in average weight percentage variations were observed between day 39 (baseline) and day 82 between the groups (Brown-Forsythe=11.201; 0.4-8.8, 9.6 p=0<0.001). Significant differences appeared when comparing the Control group with the standard diet (average percentage variation 0.4; CI 95% CI; -8.8, 9.6) *vs*. the Control group with hypocaloric diet (-24.7, CI 95%; -29.9, -19.4) (p<0.001); *vs*. the Injectable A/Intrarectal suspension A/Intrarectal suspension B group (-15.6, CI 95%; -21.2, -10.0) (p=0.004); and *vs*. the Injectable B/Intrarectal suspension C (-18.3, CI 95% -23.0, -13.7) (p=0,001) group.

Histopathology

Significant morphological changes are summarized in Tables 1, 2 and 3.

DISCUSSION

Leptin plays a key role in the regulation of energy metabolism. In disorders such as overweight and obesity, it is often elevated in plasma, suggesting that resistance to its action results in an impairment of the regulation of adipose tissue metabolism. Weight gain also determines the presence of hyperglycaemia, a metabolic situation that clearly aggravates the underlying pathology (obesity). In this study, it was possible to observe relevant differences about the effects of leptins. While the Control group with the standard diet started the study with significantly lower mean values, the achieved reduction was significantly less. Significant reductions in leptins were observed in the Control group with hypocaloric diet and in the Injectable A and B groups. At the end of the study, leptin results continued to be significantly different among some groups. The Control group with the standard diet showed higher average values, while the Intrarectal suspension B and C groups showed the lowest values.

In addition, significant differences were also observed in mean blood glucose results. The Control group with the standard diet achieved the highest average values; higher than those of the groups treated with intrarectal suspension A or B. The Control group with the standard diet showed mean leptin and blood glucose values significantly higher than the groups treated with hCG. Moreover, no significant differences were found between the values of the Control group that received a standard diet and the Control group with the hypocaloric diet.

Adiponectins and fatty Acids are not very sensitive to treatment when evaluating different doses and formulations. However, it was observed that, in relation to adiponectin, its values were elevated in animals receiving the hypocaloric diet, and even more so in the groups treated with hCG. Leptin and glucose levels were sensitive to

treatment. Leptin levels were significantly higher in the Control group, were decreased in the hypocaloric diet group, and even more decreased in the animals that received hCG. When comparing analysis per dose, the group treated with intrarectal suspension B showed the lowest values: the Injectable A/Intrarectal suspension A/Intrarectal suspension B groups showed the lowest levels in the analysis of the formulation, and the Intrarectal suspension A/B/C groups showed the lowest levels in the analysis of the pharmaceutical form. It is emphasized that no significant differences were observed between the groups that did not receive hCG. A similar effect was observed regarding glycemia. Treated groups showed significantly lower mean values in animals treated with Intrarectal suspension B (per dose analysis), in the animals treated with Injectable A/Intrarectal suspension A/Intrarectal suspension B (in the analysis of formulation), and in the animals treated with Intrarectal Suspension A/B/C (in the analysis of pharmaceutical form).

These results demonstrate the activity of hCG (both urinary and recombinant) on glycemia and leptins levels in different formulations, but especially when administered intrarectal. Similarly to human studies performed by one of the authors (DOB), this activity did not correlate with a greater weight loss when compared to a population submitted to a standard hypocaloric diet. This result could either be attributed to the small number of animals in each group or it may also indicate a possible hCG effect on body composition, thereby favouring an increase in the lean mass component without modifying the total body weight. In addition, no significant adverse clinical effects were observed with the suprapharmacological doses administered (up to 400 times the dose/kg of body weight administered in humans).

These findings confirm the results from former studies in humans that show that weight loss under hCG is no different when compared to placebo-treated individuals. However, according to the authors, this is the first report that shows that hCG has a definite action on leptins and blood sugar metabolism.

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CONFLICT OF INTERST

Note: This investigation was entirely funded by the lead investigator. The author applied for a patent on the extragonadal use of hCG.

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TABLES:

Table 1. Adverse events in brain histopathology per group/sex

Brain Histopathology	**Group/sex**
Vascular congestion in meninges and parenchyma.	Group 4: 1 female Group 6: 1 female
Vascular congestion and erythrocyte extravasation in meninges.	Group 5: 1 female
Focal points of RBC extravasation in parenchyma	Group 0: 1 female
Marked vascular congestion in meninges	Group 5: 1 female Group 6: 1 female

Table 2. Adverse events in testicular histopathology per group.

Testicular histopathology.	**Groups**						
	0	1	2	3	4	5	6
Mild autolysis	2	2	3	2			
Moderate autolysis	1		1	3	3	3	1

Table 3. Adverse events in ovaries histopathology per group.

Ovary histopathology.	**Groups**						
	0	1	2	3	4	5	6
CL (Corpus Luteum)							1
Yellowish-brown pigmento focal points.			1				
Follicles in different maturation stages	2	1	3	2	3	5	2
Corpus Luteum in different maturation stages	1						
Interstitial cell hyperplasia.	2						
Interstitial cells hyperplasia and hypertrophy.	1	1	3	2	3	3	3
Interstitial cells mild hyperplasia.		2					
Luteomas	1	1	3	2	3	3	3
Pigment in CL				1	1		
Cysts			2	2	2		

FIGURES

Figures 1(A—D). Mean baseline determinations per group

Figure 1A. Mean leptin baseline levels per group

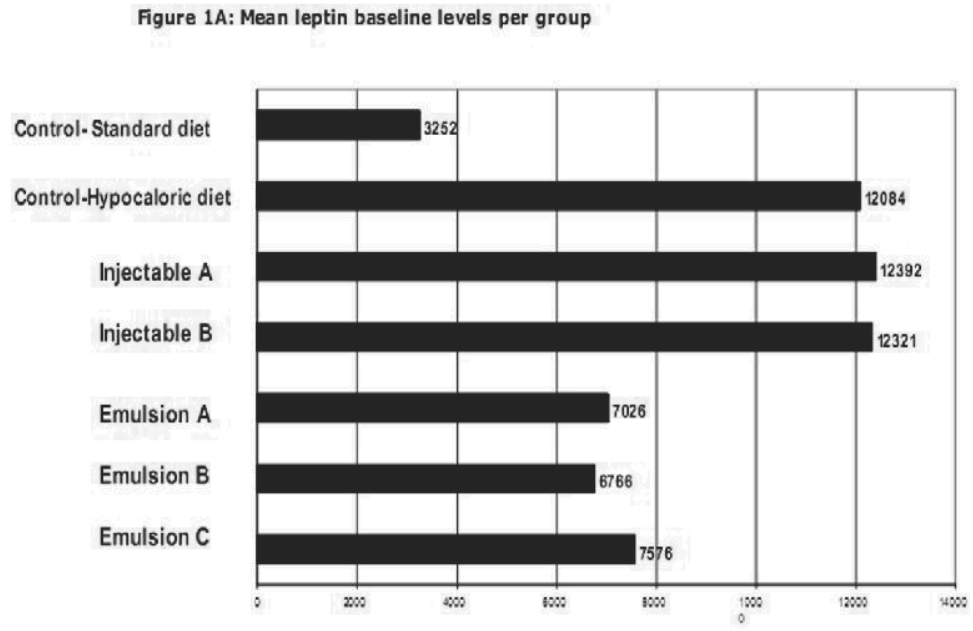


Figure 1B. Mean blood glucose (glycemia) baseline levels per group

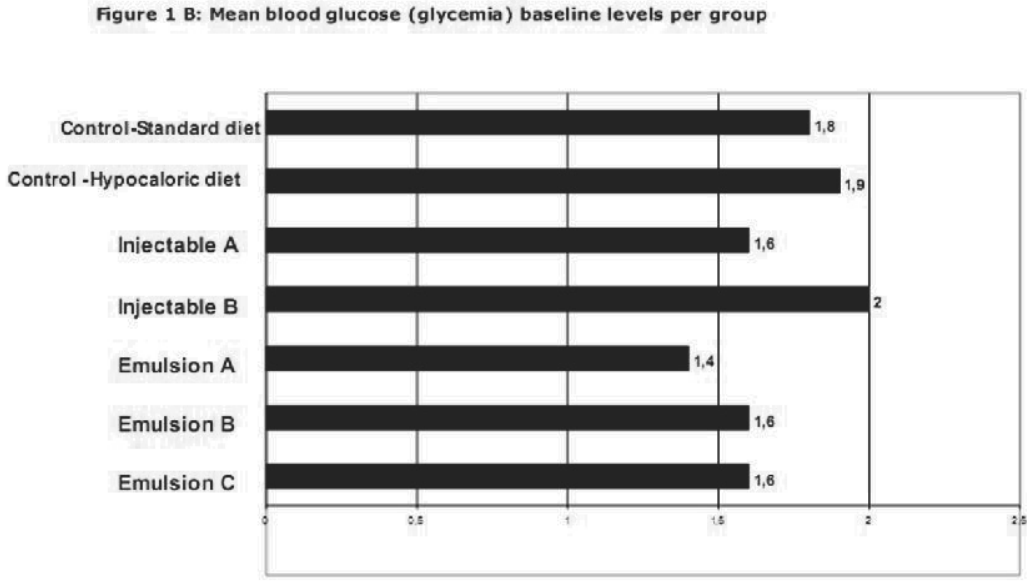


Figure 1C. Mean adiponectin baseline levels per group

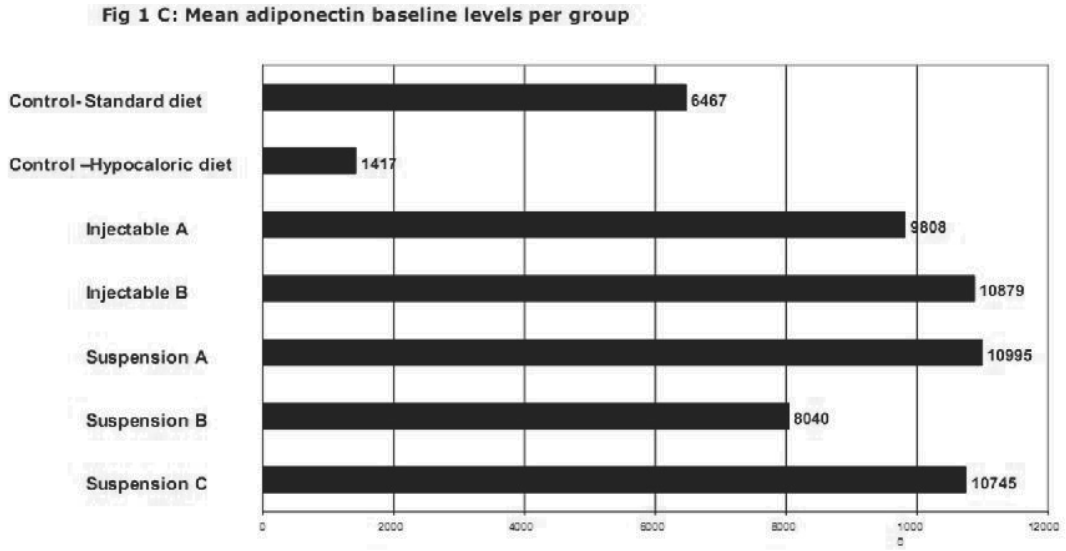
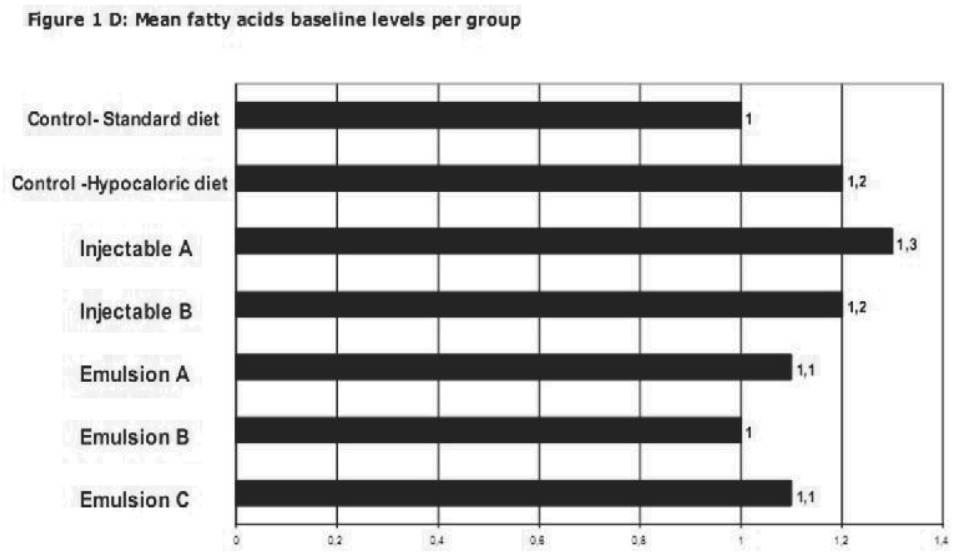


Figure 1D. Mean fatty acids baseline levels per group



Figures 2(A—D). Mean final determinations per group

Figure 2A. Mean leptin final levels per group

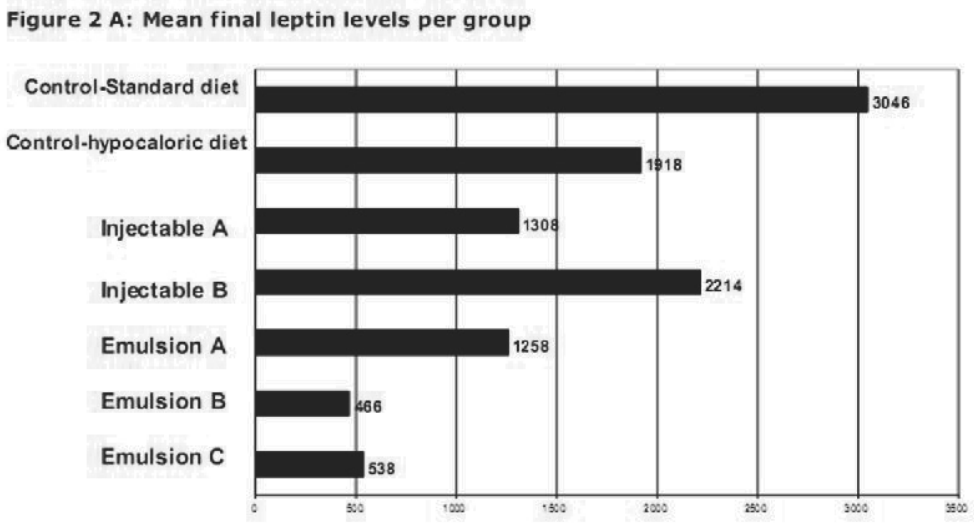


Figure 2B. Mean blood glucose (glycemia) final levels per group

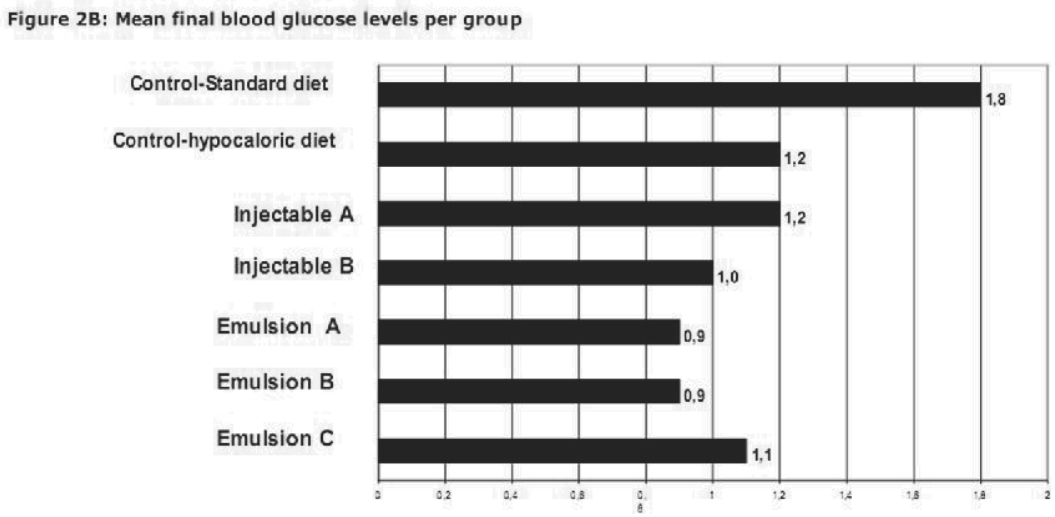


Figure 2C. Mean adiponectin final levels per group

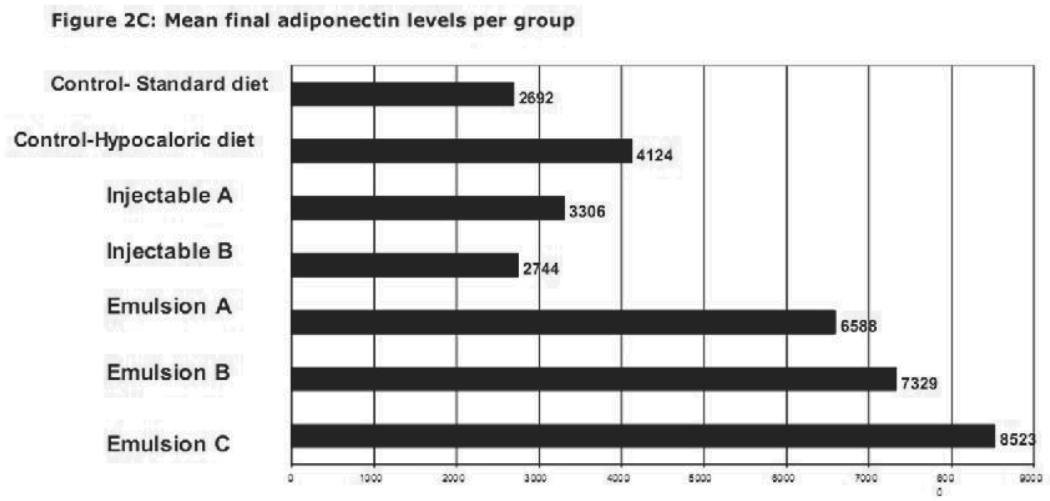


Figure 2D. Mean fatty acids final levels per group

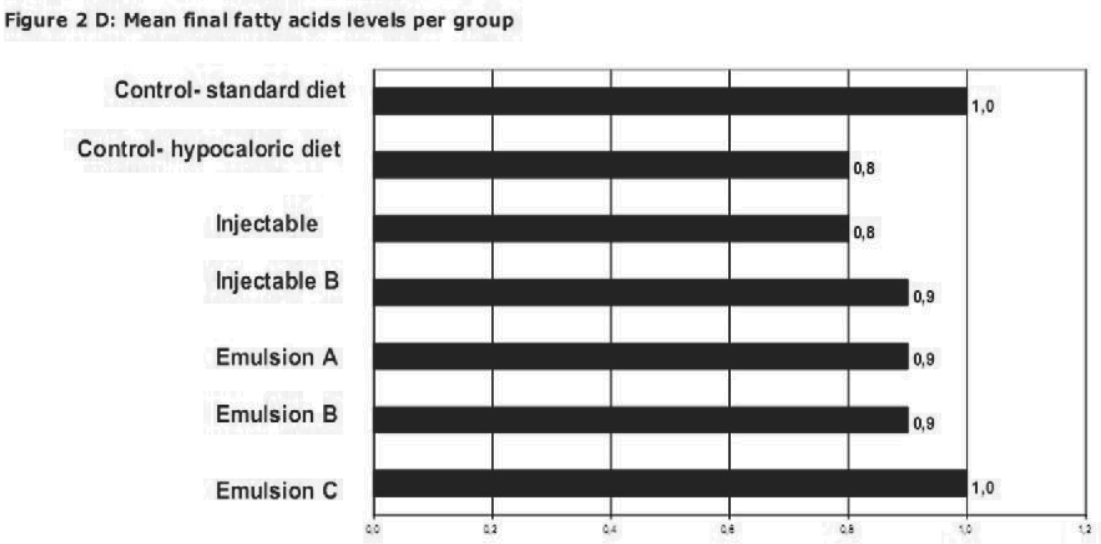
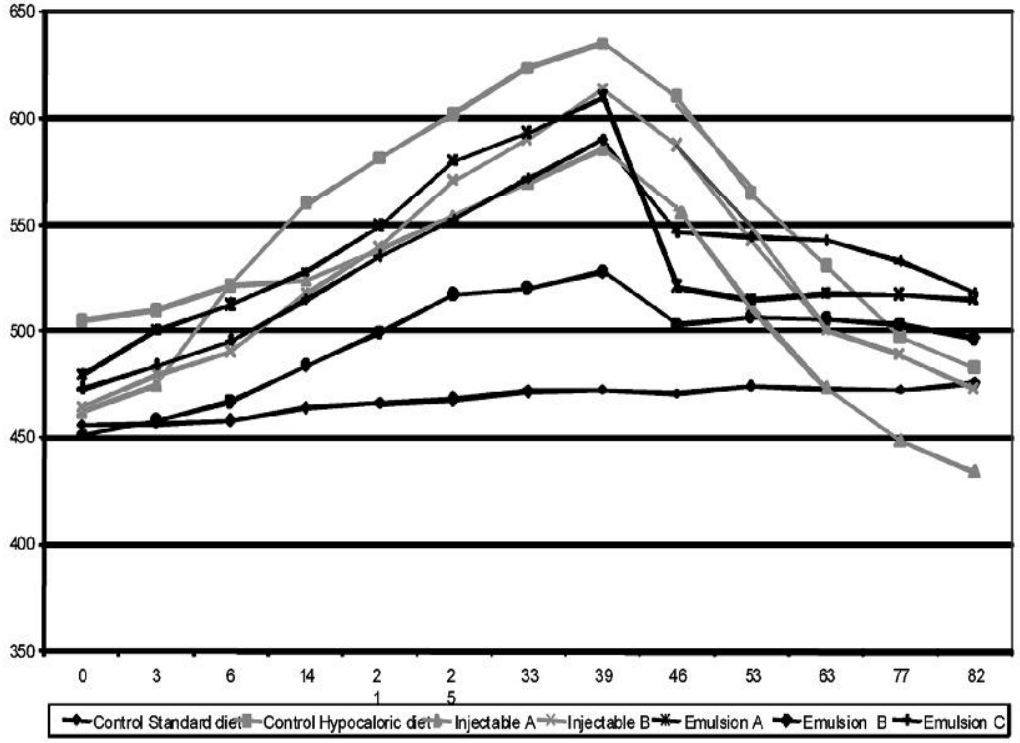


Figure 3. Body weight modifications per group

Figure 3: Body weight evolution per group



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Research Paper

Effect of Weight Reduction on Cardiovascular Risk Factors and CD34-positive Cells in Circulation

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Abstract

Being overweight or obese is associated with an increased risk for the development of non-insulin-dependent diabetes mellitus, hypertension, and cardiovascular disease. Dyslipidemia of obesity is characterized by elevated fasting triglycerides and decreased high-density lipoprotein-cholesterol concentrations. Endothelial damage and dysfunction is considered to be a major underlying mechanism for the elevated cardiovascular risk associated with increased adiposity. Alterations in endothelial cells and stem/endothelial progenitor cell function associated with overweight and obesity predispose to atherosclerosis and thrombosis.

In our study, we analyzed the effect of a low calorie diet in combination with oral supplementation by vitamins, minerals, probiotics and human chorionic gonadotropin (hCG, 125-180 IUs) on the body composition, lipid profile and CD34-positive cells in circulation.

During this dieting program, the following parameters were assessed weekly for all participants: fat free mass, body fat, BMI, extracellular/intracellular water, total body water and basal metabolic rate. For part of participants blood chemistry parameters and circulating CD34-positive cells were determined before and after dieting.

The data indicated that the treatments not only reduced body fat mass and total mass but also improved the lipid profile. The changes in body composition correlated with the level of lipoproteins responsible for the increased cardiovascular risk factors. These changes in body composition and lipid profile parameters coincided with the improvement of circulatory progenitor cell numbers.

As the result of our study, we concluded that the improvement of body composition affects the number of stem/progenitor cells in circulation.

Key words: weight reduction, body composition, cardiovascular risk factors, lipid profile, progenitor cells.

Introduction

Living in an environment characterized by calorie-rich foods and low physical activity, over two thirds of Americans are overweight [1]. This is a major public health problem, as obesity predisposes to a variety of age-related inflammatory diseases, including insulin resistance, type 2 diabetes, atherosclerosis and its complications, fatty liver diseases, osteoarthritis, rheumatoid arthritis, and cancer [2-4]. Clinical studies have identified a relationship between increased body weight and cardiovascular disease in-

cluding coronary atherosclerosis, congestive heart failure, arrhythmias, and stroke [5-11].

In addition to established cardiovascular risk factors, systemic inflammation, increased oxidative stress, and altered hemodynamics associated with excess weight may directly contribute to endothelial injury and dysfunction [12]. Progenitor cells, which are released from the bone marrow are sensitive to oxidative stress [13-16]. Circulating endothelial progenitor cell (EPC) numbers have been found to be lower in obese subjects compared to overweight or normal weight adults, and the colony-forming capacity of these cells is blunted [17, 18]. Alterations in endothelial cells and EPC function associated with obesity precede atherosclerosis and thrombosis [19-21]. Moreover, EPCs expanded from the obese subjects possessed reduced adhesive, migratory, and angiogenic capacity [22] and fail to respond to vascular endothelial growth factor. Mice treated with obese EPCs exhibited reduced EPC homing in ischemic hind limbs in vivo.

Etiology of obesity is complex, involving interrelated biochemical, neurological physiological, genetic, environmental, cultural and psychological factors. Adipose tissue can be considered as an endocrine organ that mediates biological effects on the metabolism and inflammation, contributing to the maintenance of energy homeostasis and the pathogenesis of obesity-related metabolic and inflammatory complications [4]. Endothelial damage and dysfunction is considered to be a major underlying mechanism for the heightened cardiovascular burden that occurs with increased adiposity.

The goal of our study was to examine how cardiovascular risk factors and circulating CD34-positive cell numbers correlate when overweight subjects attempt to lose weight through calorie restriction. The particular weight loss regimen we examined consisted of severe calorie restriction along with vitamin supplements and administration of human chorionic gonadotropin (hCG), a hormone that encourages metabolic utilization of visceral fat reserves [23-26].

Materials and Methods

Weight Loss Protocol

Our study consisted of fifty three participants, eighty percent of which were women, with ages ranging from 26 to 63. The starting body mass index of these subjects ranged from 30 to 67, while their body fat percentage ranged from 15% to 48% when they began treatment. All subjects gave written informed consent (as per Helsinki Declaration guidelines) and underwent the dietary program with the oversight of their primary care physician. Although, the program mainly aimed at overweight and obese people, it was open to anyone interested.

The weight loss program consisted of a 500 calorie per day dietary restriction in combination with the following:

1. Daily sublingual treatments by vitamin B12 (1,000 μg per day).
2. Oral supplements consisting of the following nutrients: 250 mg tyrosine, 2 mg β-glucan, 200 μg selenium, 1 mg folic acid, 5 mg iodine, 7.5 mg potassium iodide, 600 mg magnesium, 5 g vitamin D3, 60 mg coenzyme Q10, 150 mg lipoic acid, 340 mg acetyl-l-carnitine, 100 mg vitamin B complex, and a probiotic (2 billion CFU acidophilus with 2 billion CFU bifidus and 109 mg FOS).
3. Daily treatments of hCG nasal spray, at doses of 125 – 180 IU.

The very low calorie diet can be summarized as follows: breakfast consisted of coffee/tea with no sugar or one fruit serving, while lunch and dinner each consisted of 3.5 oz lean protein, a vegetable serving, bread serving, and a fruit serving. The program schedule was as follows: patients took supplements, B12, and hCG for two days prior to beginning a 36-day very low calorie diet. This was followed by a 35 day maintenance period during which calorie intake was gradually raised while restricting sugar and starch intake (at this point, hCG treatment stopped).

Subjects were supervised by a physician with weekly health evaluations. The following parameters were assessed weekly: body composition, including fat free mass (FFM), body fat (BF), total body water (TBW), intracellular/extracellular water, basal metabolic rate and body mass index (BMI). Blood chemistry parameters, including glucose, cholesterols, triglycerides and circulating CD34-positive cells were measured for nine subjects at the beginning and at the end of the study. Eight of the nine subjects who volunteered for blood work were female: they ranged in age from thirty to sixty-five years old. The lone male was forty years old.

Assay methods are described below.

Body composition

Body composition was measured by bioelectrical impedance analysis (BIA). The BIA is a non-invasive method for measuring body composition through reactance and resistance, the two components of impedance. Bioelectrical impedance analysis was performed by IMP DF50 (Company ImpediMed Limited). The fat–free mass, body fat, basal metabolic rate, total body water, extracellular water, intracellular

water and body mass index were determined for each participant before dieting intervention and each six days following intervention.

Assay of lipid profile

A fasting serum was used for measurements of the lipid profile (total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoproteins (LDL), triglycerides, very low-density lipoproteins (VLDV)) and glucose, by established clinical laboratory tests. Cholesterol, HDL cholesterol, and triglycerides were quantified by an auto-analyzer by an enzymatic method by using commercially available reagents (Genzyme Diagnostics). LDL cholesterol (in fasting samples) was determined by calculation.

CD34-positive cell measurements

The analysis of the CD34 positive cells was performed by adopting the gating strategy defined by the International Society of Haematotherapy and Graft Engineering (ISHAGE) guidelines [27]. The method of the selection of stem/progenitor cells consisted from several criteria. Cells were selected that expressed CD34+ antigen, did not express CD45 antigen and exhibited low side-angle light scatter characteristics of blasts cells. This subpopulation was defined as of endothelial progenitor cells. Our decision to considered CD34 positive/CD45 negative circulating cells as "circulating EPCs" was based on the work [28], in which blood–derived cells from which endothelial cells in culture were developed were described as cells expressing CD34 antigen. It has been hypothesized that endothelial progenitor cells and hematopoietic progenitor cells have common precursor, the hemangioblast and both may be subsets of bone marrow-derived progenitor cells expressing CD34. Moreover, recent studies demonstrate that CD34+ cells not expressing leukocyte antigen (CD45-) form endothelial colony-forming units and those expressing CD45 demonstrate hematopoietic properties [29].

Specific cell surface staining was accomplished by incubating duplicate samples of a biological specimen (separated white blood cells) with two color CD45-FITC/CD34-PE reagents (Stem kit reagents, Beckman Coulter). In an additional test, the samples were stained with CD45-FITC/IsoClonic Control-PE reagent to check the non-specific binding of the CD34-PE monoclonal antibody.

Statistical analysis

All data were analyzed by Systat software (Systat Inc) and KaleidaGraph software. Variables were presented as mean values ±SD. Statistical analysis was done by linear regression model and paired non-parametrical test. Statistical significance was accepted if the null hypothesis could be rejected at $p<0.05$.

Results

The distributions of mass loss and fat mass loss by all subjects during the diet are shown in Figure 1.

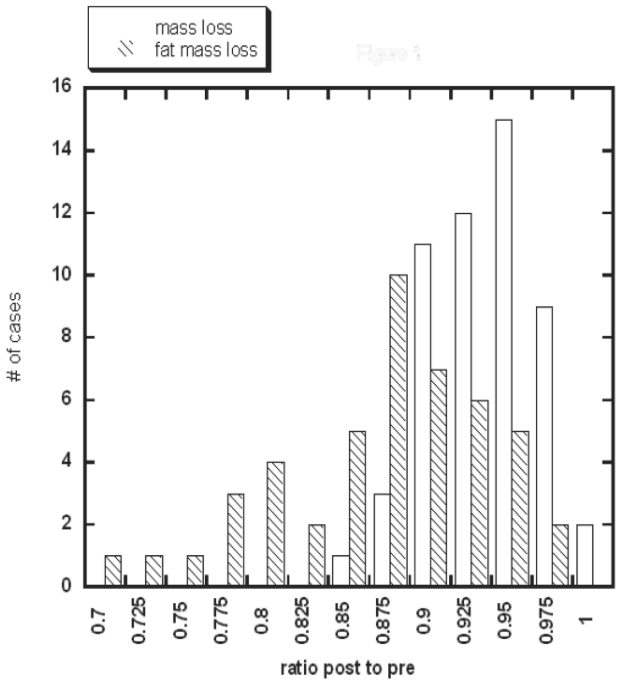

Figure 1. Distribution of the weight reduction and fat mass loss in all subjects participated in 36 days of the dieting program.

Subjects lost between 2.5 and 17.2 kg during the study, with the most weight loss occurring in subjects who started out the heaviest. All subjects achieved a decrease in body mass index during the study. The average BMI for participants at the start of the study was 34.0 ± 7.2 (SD), while that after the study was 28.5 ± 6.7 (SD). Using a paired Student's t-test, the difference is highly significant ($p = 0.0004$). This indicates that weight loss and changes in body composition did occur during the time course of the study.

The weight reductions during the hypo-caloric diet and maintenance period for several patients are presented in Figure 2.

Changes in body composition parameters are summarized in Table 1.

These percentages did not vary systematically with the initial mass of the subjects. The decrease in body fat was substantial, and in most cases larger than the corresponding loss in lean mass. According to our data, the average percentage loss of lean mass was 5.7±4.7 and the average change in body fat was

12.4±8.7. The percentage loss in body fat among the most subjects was significantly larger ($p = 0.04$) than the percentage loss in lean mass, suggesting an improvement in body composition.

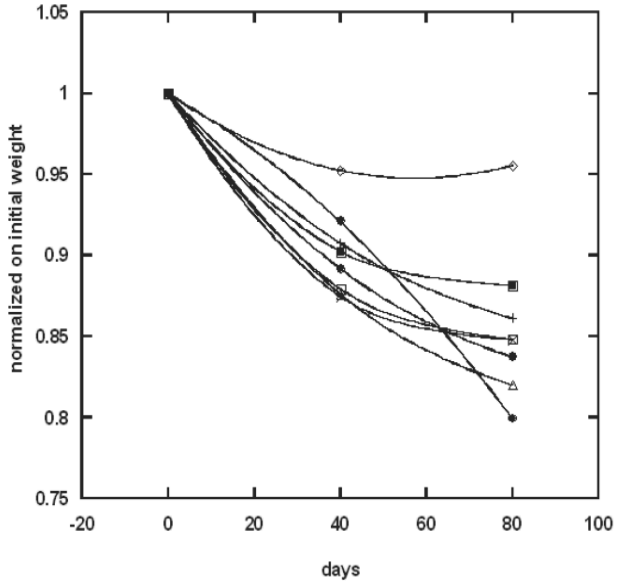

Figure 2. Examples of the effect of dieting and maintenance periods on the weight loss for several participants.

Table 1. Percent of decrease in total mass, fat free mass, intracellular/extracellular fluids and basal metabolic rate in subjects at the end of the study.

Parameter	Mean ±SD	Minimum value	Maximum value
Weight kg	8.1±3.3	1.8	16.9
Total Body Water Liter	5.7±4.7	-3.2	16.1
Total Body Water %	-2.6±4.1	-13.4	8.8
Intracellular Fluid Liter	5.7±6.3	-11.3	15.7
Intracellular Fluid %	0.0±3.0	-9.2	4.7
Extracellular Fluid Liter	5.8±4.6	-4.0	18.0
Extracellular Fluid %	0.0±3.1	-5.1	9.2
Fat Free Mass kg	5.7±4.7	-3.4	16.1
Fat Free Mass %	-2.6±4.2	-13.6	8.8
Fat Mass kg	12.4±8.7	-8.4	31.2
Fat Mass %	4.7±8.3	-11.2	26.7
Basal Metabolic Rate Mj	3.9±2.0	0.0	10.1
Basal Metabolic Rate CAL	4.1±2.0	0.9	10.1
Body Mass Index	8.1±2.0	2.0	16.9

The treated subjects showed a decrease in their body mass index in an average of 8.1%±2.0%.

Changes in total body water had inverse correlation with changes in fat mass (r=0.86) and positive correlation with an increase in fat free mass (r=0.78). The level of intracellular water (ICW) correlated with fat mass and fat free mass changes during dieting. Intracellular water levels showed linear relation with fat free mass (r=0.9) and an inverse relation with fat mass (r=0.6). As intracellular fluid decreases due to different pathological conditions, the increase in intracellular water suggests improvement in cell health and nutritional status.

Basal metabolic rate decreased slightly in subjects during their treatment (4.1%±2.0%). The percentage of the decrease in BMR correlated with the percentage of weight loss. The decreasing of BMR is not desirable for dieters; however, the BMR decrease seen in our study is modest.

Statistically significant decreases in serum cholesterol levels were observed during the treatment. Lipid profile data are summarized in Table 2.

Table 2: Averaged blood chemistry parameters before and after the diet regiment are given. † indicates significant difference between "Pre" and "Post" ($p < 0.05$ using paired Student's t-test).

Lipid profile	Pre	Post
Glucose (mg/dL)	91 ± 12	89 ± 7
Cholesterol (mg/dL)	206 ± 36	177 ± 24 †
Triglyceride (mg/dL)	119 ± 57	97 ± 36
HDL Cholesterol (mg/dL)	52 ± 13	52 ± 10
VLDL (mg/dL)	24 ± 11	19 ± 7
LDL(mg/dL)	130 ± 29	106 ± 21 †
Cholesterol / HDL	4.2 ± 1.2	3.5 ± 0.8 †
LDL / HDL	2.7 ± 0.9	2.1 ± 0.7 †

While glucose levels, triglycerides, very low density lipoproteins (VLDL), and high density lipoproteins (HDL) were not affected, subjects saw significant decreases in total cholesterol, low density lipoprotein (LDL), and overall in ratios of cholesterol and LDL to HDL. These variables are considered markers of cardiovascular disease. HDL protects arteries by transporting cholesterol away, while LDL can be deposited on arterial walls and clog arteries. Changes in the level of cholesterol and LDL for all participants are shown in Figures 3, 4.

For total cholesterol, the upper limit of the normal range is 200 mg/dL. Five of the subjects started the study above this threshold. All of these participants experienced cholesterol decreases during the

diet treatment, with two returning completely to the normal range. The upper limit of the normal range for LDL is 100 mg/dL. Eight of the nine subjects started with above normal LDL, with three of them returning to normal levels during the treatment. Similar trends were seen with the cholesterol/HDL ratio (upper limit of normal being 5.0) and LDL/HDL (upper limit of normal being 3.6).

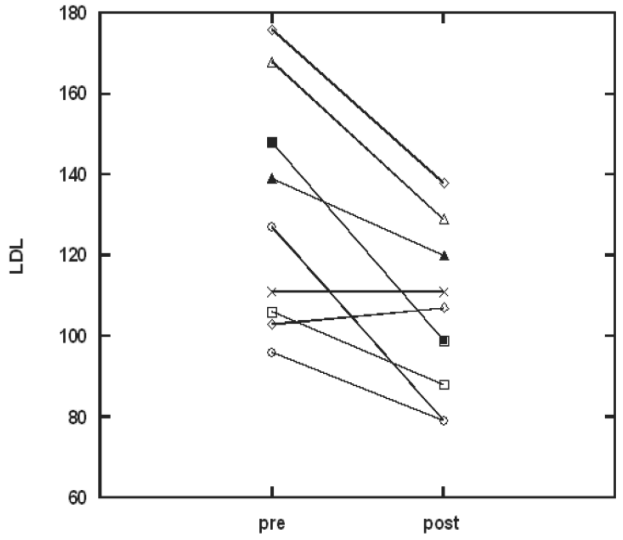

Figure 3. The effect of the dieting program on the level of LDL in plasma.

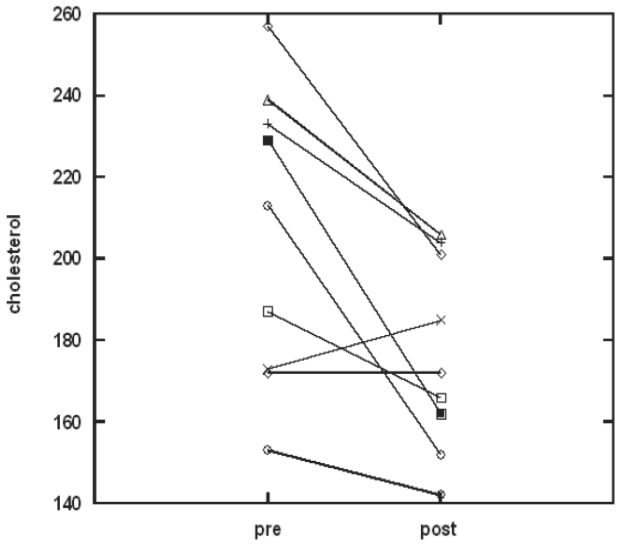

Figure 4. The effect of the dieting program on the level of cholesterol in plasma.

Regression analysis was conducted between body composition parameters and lipid profile parameters. The mass of body fat (BF) correlated strongly with the LDL to HDL ratio (r = 0.7), the cholesterol to HDL ratio (r=0.68) and inversely with HDL (r = 0.43).

Overall, these data indicated that the combination of a low calorie diet with hCG treatments reduced body fat as well as risk factors associated with cardiovascular disease.

Circulating CD34+ cells in peripheral blood, as a percentage of total leukocyte counts, were determined before and after the study. Weight loss was accompanied by a significant improvement in the number of circulating progenitor cells ($p < 0.01$). On average, the enhancement of progenitor cell numbers was roughly seventy percent. Figure 5 shows how CD34+ cell levels changed for each subject from the start to the end of the weight loss program.

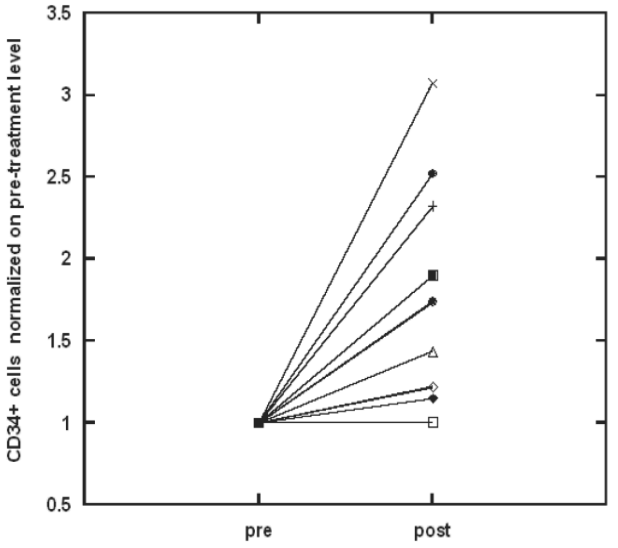

Figure 5. The improvement of CD34 positive cell number after diet.

Figure 6 shows the correlation between circulating CD34+ cell number (given here as the ratio of the percentage of cells after the diet to the percentage of cells before the diet) and the percentage of body fat lost by each subject during the study.

A correlation also exists between CD34+ cells and the proportion of fat free mass (r = 0.80) for each subject. The changes in body fat, and the changes in lipid profile parameters, coincide with improvements in circulatory progenitor cell numbers.

To rule out the possibility that changing numbers of circulating CD34+ cells were simply part of an overall change in circulating white blood cells, we ran complete blood counts before and after treatment on the nine subjects who consented to blood work. Changes in blood cell counts with treatment varied among the nine subjects, with five experiencing overall decreases (the maximum downward change was thirty percent). All subjects showed a decrease in

lymphocyte counts (the decrease ranged from eight to thirty-five percent).

The normalization of CD34-positive cell numbers to total peripheral blood mononuclear cell numbers, demonstrated that the numbers of CD34-positive cells per micro liter increase by an average of forty percent.

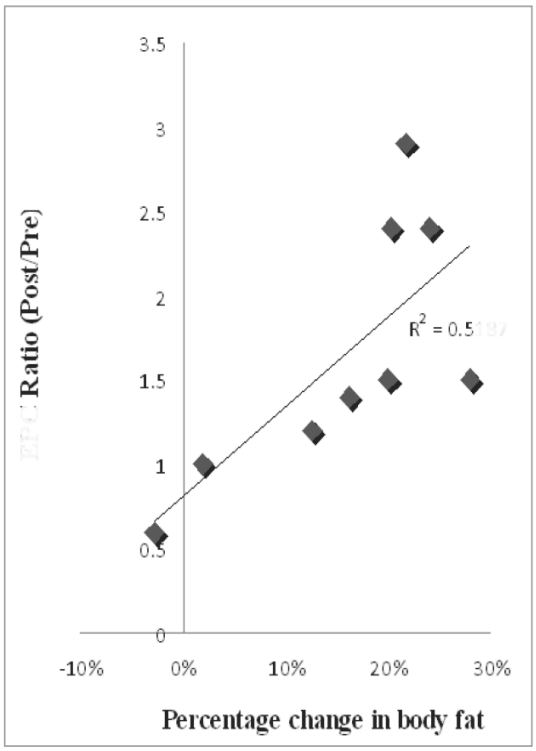

Figure 6. The ratio of CD34+ cells post diet to pre-diet as a function of percentage of body fat lost during the diet.

Discussion

Obesity is frequently associated with traditional cardiovascular risk factors such as type 2 diabetes, hypertension, dyslipidemia, altered coagulation/fibrinolysis, and the other components of the metabolic syndrome [30]. All these abnormalities create a state of constant and progressive damage to the vascular wall, manifested by a low-grade progressive inflammatory process and endothelial dysfunction [31, 32].

The endothelial cell damages due to dyslipidemia and proinflammatory cytokines have been demonstrated in studies [33, 34]. Increased levels of triglycerides and lipoproteins in obese or overweight subjects correlate with impairment of endothelial function [35, 36]. Endothelial cell damage due to dyslipidemia plays a critical role in the development and progression of atherosclerosis [37, 38].

Given the role of endothelial cell damage in obesity, our attention was turned to progenitor cells (CD34+/CD45- cells). These cells are thought to be early precursors of endothelial progenitor cells and function to replenish aging as well as damaged endothelial cells that line blood vessels. There is strong evidence of the role of circulating endothelial progenitor cells, including populations of CD34 positive cells presented in peripheral blood, in the maintenance of the vasculature and neovascularization [39, 40]. In several studies, the number of circulating EPCs and their migratory activity have been reported to be reduced in patients with risk factor for coronary artery disease and negatively correlated with the Framingham cardiovascular risk score [41-43]. Therefore, increasing the number of CD34-positive cells during treatment may provide an indicator of improvement of vascular health.

In our study, we analyzed the effect of weight loss on the improvement of lipid profile in plasma and the increase of the level of CD34+/CD45- cells in circulation.

The data from our study demonstrated that a combination of a very low calorie diet with hCG treatments, and supplements, decreases overall mass and body fat while improving lipid profiles. These benefits are accompanied by increases in circulating CD34+ cell numbers.

The weight loss protocol, which we used in our study, was developed in the 1950s [23, 24]. Several studies have been done to examine the efficacy of hCG in treating obesity, with mixed results [44, 45]. The main question has been whether the addition of hCG to a very low calorie diet enhances weight loss compared to dieting alone. While most studies report weight loss due to dieting, they disagree as to whether factors such as weight reduction, body proportion, and patient reported hunger level are affected by adding hCG to the diet. The issue is complicated by the fact that few of these studies were double-blind and placebo controlled. The experimental design used in the study [46] showed that the combination of the 500 calorie per day diet and hCG injections offered a significant benefit to dieters, offering increased weight loss and a decrease in hunger.

In our study, we did not compare hCG and diet to diet alone, but our work shows the direction that such a study should take, as we utilize additional measures such as body composition (fat free mass, body fat, total body water, BMI) for all participants and lipid profiles and circulating progenitor cell levels for a group of the patients to assess outcome.

Our study provided further evidence of this linkage, with fat loss showing a strong correlation

with changes in lipid profiles and increases in circulating progenitor cell numbers. For participants who represented weight loss and fat mass loss, the maximum reduction in lipids that have effect on overall cardiovascular health was 29% for cholesterol, 38% for LDL, 26% for cholesterol to HDL ratio and 35% for LDL to HDL ratio.

The average improvement of CD34+ cells in circulation during dieting program was 69% ± 50%.

In conclusion, the weight loss program analyzed in our study resulted in the improvement of the number of CD34+ cells in circulation and the decrease of the values of cardiovascular risk factors. According to our study, the circulating progenitor cell number can be improved by diet and weight loss.

Acknowledgements

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Conflict of Interest

The authors have declared that no conflict of interest exists.

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8. Use of human chorionic gonadotropin orally for the treatment of overweight (obesity) associated with high blood tension, non-insulin-dependent diabetes, hypercholesterolemia, dyslipidemias and lipodystrophy (2011).

USE OF HUMAN CHORIONIC GONADOTROPIN ORALLY FOR THE TREATMENT OF OVERWEIGHT (OBESITY) ASSOCIATED WITH HIGH BLOOD TENSION, NON-INSULIN-DEPENDANT DIABETES, HYPERCHOLESTEROLEMIA, DYSLIPIDEMIAS AND LIPODYSTROPHY.

Apr 01, 2011

Human chorionic gonadotropin administered by intramuscular route is traditionally used for the treatment of sterility and cryptorchidism. After numerous tests performed, a compound to be administered orally—sublingual—has been developed with such drug to treat patients suffering from overweight associated with high blood tension, non-insulin-dependant diabetes, hypercholesterolemia, dyslipidemias and lipodystrophy. It was determined that hCG acts satisfactorily upon high blood tension, non-insulin-dependant diabetes, hypercholesterolemia, dyslipidemias and lipodystrophy.

Skip to: Description Claims Patent History Patent History

Description

DETAILED DESCRIPTION OF INVENTION

The present application is filed as a continuation application and claims priority of application Ser. No. 11/826,214.

This invention relates to “THE USE OF HUMAN CHORIONIC GONADOTROPIN ORALLY FOR THE TREATMENT OF OVERWEIGHT (OBESITY) ASSOCIATED WITH HIGH BLOOD TENSION, NON-INSULIN-DEPENDANT DIABETES, HYPERCHOLESTEROLEMIA, DYSLIPIDEMIAS AND LIPODYSTROPHY.”

SCOPE

The compound is to be used for controlled treatment of overweight associated with high blood tension, non-insulin-dependant diabetes, hypercholesterolemia, dyslipidemias and lipodystrophy.

CURRENT TECHNIQUE

In the current technique, Human Chorionic Gonadotropin is administered by intramuscular route to treat sterility and cryptorchidism disorders.

PROBLEM TO BE SOLVED

When obese persons are healthy, overweight treatment is easier to administer through diets to be followed without difficulties by patients. However, where overweight is associated with health problems like high blood tension, diabetes, hypercholesterolemia, dyslipidemias and lipodystrophy, treatments are difficult and administration of additional drugs as coadjuvant therapy is necessary.

THIS INVENTION CAN SOLVE THE PROBLEM

After several assays testing, selecting and discarding drugs, Human Chorionic Gonadotropin was determined to act satisfactorily to solve the problem. On one hand, this drug acts inhibiting fat cell (adipocytes) lipogenesis, and on the other, Beta endorphin in gonadotropin molecule has action on the hypothalamus, thus allowing an improvement in patient's clinical condition during treatment, with rapid improvement on glycemia, lipid, cholesterol and blood tension levels. Finally, the most suitable administration form, and the one which showed the best results as well, was determined to be sublingual form.

ADVANTAGES

An advantage of this invention is the successful treatment of obesity in patients with high blood tension, non-insulin-dependant diabetes, hypercholesterolemia, dyslipidemias and lipodystrophy. The advantages of this invention, which should not be limited to the description above, will become more apparent and the invention itself better understood by reference to the following example of a preferred embodiment.

DESCRIPTION OF EMBODIMENT

“The use of human chorionic gonadotropin orally for the treatment of overweight (obesity) associated with high blood tension, non-insulin-dependant diabetes, hypercholesterolemia, dyslipidemias and lipodystrophy” is represented by the following formulation: Powder Human Chorionic Gonadotropin dissolved in physiological saline and administered placing it under the tongue. A preferred drug formulation consists of 500 international units of powder Human Chorionic Gonadotropin per milliliter solution.

ACTION

As stated elsewhere, the drug action inhibits fat cell (adipocytes) lipogenesis, and on the other hand, Beta endorphin in gonadotropin molecule has action on the hypothalamus, thus allowing an improvement in patient's clinical condition during treatment, with rapid improvement on glycemia, lipid, cholesterol and blood tension levels.

The advantages of this invention are plain from the description above, representing a beneficial technological improvement that warrants the inclusion of the invention in the law with the pertinent legal protection as per the appended claims.

Claims

1. A method of treating a human patient suffering from high blood tension, non insulin dependant diabetes, hypercholesterolemia or lipodystrophy comprising the oral administration of an effective amount of a solution of human chorionic gonadotropin (hCG), to said human patient in need thereof.

2. The method of claim 1 in which a solution of hCG powder dissolved in a pharmaceutically suitable buffer is orally administered.

3. The method of claim 1 in which a solution of hCG powder dissolved in physiological saline is orally administered.

4. The method of claim 1 in which a solution of 500 IU of hCG powder per millimeter of physiological saline is orally administered.

Patent History

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Inventor: DANIEL OSCAR BELLUSCIO (Capital Federal)
Application Serial: 13/078,474

Classifications

Current U.S. Class: Gonadotropin-releasing Hormone (gnrh) Or Derivative (514/10.3)
International Classification: A61K 38/09 (20060101); A61P 3/00 (20060101); A61P 9/12 (20060101);

9. Reversal of Prediabetes with a Very Low Carbohydrate/Calorie Diet (VLCD) and a Metabolic HCG Protocol (2011).

Reversal of Prediabetes with a Very Low Carbohydrate/Calorie Diet (VLCD) and a Metabolic HCG Protocol

Mayer Eisenstein MD, JD, MPH

Background and Purpose:

The American Heart Association estimates that 59.7 million Americans 20 years and older have prediabetes. People with IFG (impaired fasting glucose) and IGT (impaired glucose tolerance) are at increased risk for developing type 2 diabetes, heart disease and stroke. Long-term damage to the cardiovascular system may occur while a person has prediabetes, and a recent study indicates that prediabetes more than doubles the risk of death due to heart attack.[1]

An international committee composed of experts from the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation recommends that prediabetes testing include the **Glycated hemoglobin (A1C) test.** This blood test indicates your average blood sugar level for the past two to three months. It works by measuring the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. The higher your blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level between 5.7 and 6.4 percent is considered prediabetes. As a treatment plan the committee recommended that individuals with prediabetes should reduce their weight by 5% to 10% and maintain it long term.[2,3,4,5,6]

Dr. Sebastiaan Hammer et el in a study presented at the Radiological Society of North America (RSNA) **2011** Scientific Assembly found that obese patients with type 2 diabetes who consumed a severely restricted low carbohydrate diet of just 500 calories a day for four months were able to reverse their Type 2 diabetes, showed a reduction in pericardial fat, improved the function of their heart and they were also able to discontinue insulin injections.

The purpose of this study will be to add to the findings of Dr. Sebastiaan Hammer that a very low calorie diet can reverse prediabetes as well as diabetes.

Claims have been made that HCG (Human Chorionic Gonadotropin) along with a VLCD (very low carbohydrate/calorie diet) for 30 days in a medically supervised program can reduce weight by 10-20 lbs. per month along with a reduction of abdominal girth, lower HemA1C, lower blood

pressure, lower lipid levels, without experiencing hunger.[7,8,9,10]

Method:

Fifteen obese patients with an average weight of 262 lbs., average BME of 40.7 (morbidly obese) and an average Hemoglobin A1c was 6.4% (Prediabetic) were enrolled in the Homefirst® weight loss trial. No patients were prescribed appetite suppressants of any kind. All 15 patients finished 3 rounds of Phase I and 3 rounds of Phase II for a total of 6 months.

Phase I is sublingual pharmaceutical HCG[9,10] 200IU taken twice a day for 30 days along with a VLCD (500 calories per day, 300 calories from lean chicken or beef, 200 calories from fruits and vegetables and no calories from fat). This, along with other parameters such as increased water consumption, and daily weighing is the protocol.

Phase II is a maintenance period of 30 days. The protocol here is to increase the caloric consumption sufficient to maintain the current weight. The protocol is no HCG during the maintenance period.

Results:

The average BMI of our 15 patients when they joined was 40.7, after 180 days their average weight loss was 45 lbs. per person resulting in a BMI of 35.3. This represents 17.1% of their total body weight and a change from morbidly obese to obese.

The average Hemoglobin A1c of our 15 patients when they joined was 6.4 %(Prediabetic), after 180 days their average Hemoglobin A1c was 5.6 %(normal ranges).

Conclusions:

The initial three rounds of Phase I and Phase II of the HCG and VLCD protocol had the effect of significant weight loss as well as a reversal from a pre-diabetic state to a non-diabetic state. The Metabolic HCG program may be one treatment plan to lower overall obesity rates as well as to reverse prediabetes and thereby treat the two most significant factors (obesity and insulin resistance) of Metabolic Syndrome.

This adds to the findings of Dr. Sebastiaan Hammer and to the growing body of evidence that prediabetes as well as diabetes can be reversed in a short period of time with a very low carbohydrate/calorie diet.

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[9] Dr. Daniel Oscar Belluscio, Director- The Oral hCG Research Center

http://www.oralhcg.com/english/in7.htm#1.

[10] Utility of an Oral Presentation of HCG (Human Chorionic Gonadotrophin) for the management of Obesity: A Double-blind Study. Dr. Daniel Oscar Belluscio* M.D,

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LEARNER OBJECTIVES

1) A program to lower obesity rates.

2) A program to lower coronary artery disease, stroke, prediabetes and type 2 diabetes.

3) The role of the Glycated hemoglobin (A1c) test in prediabetes and type 2 diabetes.

4) Reversal of prediabetes and diabetes.

10. Utility of an oral presentation of HCG (Human Choriogonadotropin) for the management of obesity. A double-blind study (2009).

Utility of an Oral Presentation of HCG (Human Choriogonadotropin) for the Management of Obesity: A Double Blind Study

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Abstract

Female obese volunteers participating in a double blind study, and submitted to the administration of an oral presentation of hCG (Human Choriogonadotropin) plus a VLCD (Very Low Calorie Diet), decreased specific body circumferences and skinfold thickness from conspicuous body areas more efficiently than Placebo+VLCD -treated subjects.

Since a significant fat proportion from total body fat is subcutaneously located (50 to 65 percent, depending on sex and fat distribution), this hCG metabolic activity would result in a reduction of the total body fat mass, the main cause for obesity. We suggested that the combination of a VLCD and oral hCG could not only trigger clinically significant changes in subcutaneous fat stores but simultaneously decrease body weight and modelate body contour.

hCG oral administration proved to be a safe and effective procedure on obese treated volunteers. No side effects were observed during the study. There are no reports in the literature regarding this administration route to compare our findings.

Compared to placebo treated subjects, volunteers who were managed with an oral administration of hCG coped more efficiently with daily irritating situations, were in a better mood, and handled home conflicts without stepping up family discussions.

KEYWORDS: Gonadotropin(s), Chorionic; Obesity; Adipose tissue metabolism; fat; overweight; beta-endorphin; lypolisis; lipogenesis.

Introduction

Few substances have been so neglected and misunderstood regarding its potential therapeutic actions as hCG, the acronym for Human Chorionic Gonadotropin.

First discovered by Ascheim and Zondek as far back as 1927 in the urine from pregnant women[2], thousands of articles were published regarding its action on gonads, but comparatively quite a few investigated its vast therapeutics potentialities, encompassing Kaposi sarcoma,[34] asthma,[20,66] psychoses,[22] artheriopaties,[14] thalassemia,[57,7,19] osteopenia,[57] glaucoma.[54]

hCG is the glycoproteic hormone normally secreted by trophoblastic cells of the placenta during pregnancy.[67] It consists of two dissimilar, separately, but most presumably coordinately translated chains, called the alpha and beta sub-units.[12,26,47,27,18,30]

The three pituitary hormones LH (Luteinising Hormone), FSH (Follicle Stimulating Hormone) and TSH (Thyroid Stimulating Hormone) are closely related to hCG in that all fours are glycosilated and have a dimeric structure comprising the alpha and beta chains as well.[31,35,79]

The amino acid sequence of the alpha chain of all four human glycoproteic hormones is nearly identical. The amino acid sequence of the Beta subunits differs and accounted for by the unique immunological and biological activities of each glycoproteic hormone.[63] Beta hCG contains a carboxylic residue of 30 amino acids characteristic to hCG.[11,52]

Its denomination; (Human Chorionic Gonadotropin) dates back from the early days, when it was found. hCG rendered mature infantile sex glands in experimentation animals (Gonadotropin) and it was secreted by the placentary chorion (Chorionic).[2,91]

However, recent data suggest both terms can be misleading: normal human tissues from non-pregnant subjects,[88,74,48,86,87] trophoblastic and non-trophoblastic tumors,[33,6,90] bacteria,[49] and plants[46,69] express hCG or a hCG-like substance.

The first report on hCG and obesity was published back as 1954 in The Lancet, by a British physician, Dr. A.T.W. Simeons.[70] After its publication, hCG was advocated for several years as a useful approach to obesity. The pendulum of its popularity swang back and forth

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until a series of studies[1,3,8,17,36] but three concluded hCG was of no use to manage the disease.[3,25,80]

According to basic pharmacological postulates, the administration route may influence the biological activity of a drug. All previous studies were performed with a hCG preparation administered by injections. One of the authors of this study (DB) theorized that an increase in dose and a shifting in hCG administration to a sublingual-enteral route may modify the pharmacological activity of hCG.

The purpose of this study was to assess the utility of an oral presentation hCG for the management of obesity.

Materials and methods

The study design was of the double-blind type: neither treating physician nor patient knowing who was receiving hCG, or an inert substance (placebo). Female patients for the study were selected, since the clinic where the study was performed specializes in the diagnosis and treatment of gynecologic disorders. Details of the protocol were explained to eighty-three volunteers, who were solicited through a written announcement. Before entering the study, they signed an informed consent in front of a neutral witness.

Inclusion criteria

We required selected volunteers to meet the following criteria: being at least 25% BMI (Body Mass Index), overweight, and in general healthy condition. If taking medication for obesity, such as anorectics or amphetamines, they should discontinue the medication at least one month prior the initiation of the study. Drugs to control their clinical diseases (hypertension, hypothyroidism, etc.) were allowed. No patients under steroid, diuretics or hormones were entered the study. During the study, volunteers were also asked about starting the use of medical prescribed drugs or pharmaceutical preparations during the trial period.

Exclusion criteria

No teenagers or patients over 75 y.o. were admitted to the study. No patients with severe and/or uncontrolled clinical diseases (cancer, IDDM, heart attacks, infarcts sequelae) were accepted. After applying the inclusion/ exclusion criteria, we counted on 70 subjects to divide in treatment groups. These women were randomly assigned to groups Placebo (P, N=26) or hCG (N=44) by a simple randomized sampling method. This latter group was in turn split in two subgroups: G1 (N=36) and G2 (N=8), according to the hCG dose administered (see below).

Patients were Caucasian, ages ranging from 23 to 73 y.o. (group P: 41 ± 13; group G1: 42 ± 12; group G2: 41 ± 14), a range of heights of 162 cm. to 181 cm., and overweight ranging from 25 to 499 on BMI Tables.

Since there were no published reports on the oral use of hCG, except for one study posted by D.B. and L.R. on the Internet (http://indexmedico.com/obesitv/hcg.htm), group G2 was administered twice the dose of G1, to assess if hCG concentration may affect obtained results.

The pharmacist prepared two types of vials: one containing saline solution (Na Cl 0,9% w/v), and the other containing a diluted solution (saline) of commercial, standardized hCG (from Gonacor, Massone Pharmaceutical Industry). HCG Solution was prepared buffering the drug with Sodium Bicarbonate and glycerin.

Notice: after uploading this report to the Internet, further research we have performed on oral hCG preparations demonstrated that the addition of certain diluents, degrades hCG molecule, partially inactivating its activity.

Therefore, we have reverted to the use of saline solutions instead. Our results have significantly improved since then.

Vials were randomly labeled, each number corresponding to a patient. The pharmacist kept the codes in a sealed envelope. They were opened after completing the protocol.

Volunteers from group G1 were administered a diluted solution of hCG (125 IU) b.i.d. (twice daily; total: 250 IU). One of the doses was taken before breakfast (fasting). The remaining was administered 1 hr before dinner.

Volunteers from group G2 were given twice the amount of group G1: 250 IU b.i.d. (a total of 500 IU daily).

Patients were advised to maintain the solution at least two minutes in the oral cavity before swallowing (sublingual, to profit from the rich venous plexus existing in this region, also bypassing the liver). They were also told that medication has to be maintained under refrigeration at all times.

Diet plan

The same Very-Low-Calorie-Diet (VLCD), specific and detailed, was prescribed to all groups.

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Breakfast: tea or coffee in any quantity without sugar. Only one tablespoonful of milk allowed in 24 hr. Saccharin or other sweeteners could be used.

Lunch: 100 grams. of veal, beef, chicken breast, fresh white fish, lobster, crab or shrimp. All visible fat was carefully removed before cooking, and the meat weighed raw. Salmon, tuna fish, herring, dried or pickled fish was not allowed.

The chicken breast was removed raw from the bird. One type of vegetable could be only chosen from the following: spinach, chard, chicory, beet-greens, green salad, tomatoes, celery, fennel, onions, red radishes, cucumbers, asparagus, and cabbage. One breadstick (grissini) or one Melba toast was allowed, and an apple or an orange, or a handful of strawberries or one-half grapefruit.

For dinner: The same four choices as lunch.

The juice of only one lemon daily was allowed for all purposes. Salt, pepper, vinegar, mustard power, garlic, sweet basil, parsley, thyme, marjoram, etc., could be used for seasoning, but no oil, butter or dressing. Tea, coffee, plain water, mineral water were the only drinks allowed, but they could be taken in any quantity and at all times.

Clinicometric controls

Volunteers assisted twice weekly at the clinic to be controlled and weighed. The following evaluations were completed once a week:

I. Height and Weight, performed on a medical scale. Volunteers were weighed using normal underwear.

II. Body circumferences. Using a flexible, non elastic metric tape, the following anatomic areas were assessed:

- Wrist (WRT), at the level of flexion fold (wrist-forearm);
- Breast (BRE), submammary fold;
- Waist (WAT): at the hypogastric region level;
- Abdominal (ABD), at the navel level;
- Hips (HIP): pubic line;
- Thighs (THI): 8 cm. below pubic line;
- Suprapatelar (ROT), at the patella upper border;
- Ankle (ANK), at the flexion fold (peroneal protuberance).

III. Skinfold thickness. Using a Lange Skinfold Caliper (Cambridge Scientific Industries, Cambridge, Maryland), the following folds were examined:

- Tricipital (TRI), arm midline, posterior region and tricipital muscle zone;
- Anterior Axilar line (AXA), at the fold created when pinching the skin region at the level of the pectoralis muscle extending to the arm;
- Subscapular (SCA (i)): inferior scapular spine;
- Thoracic (TOR): at the fold created when pinching the region located immediately below the ribs, at the level of an imaginary line extending from anterior axilar line;
- Suprailiac (ILI), at the fold created 4 cm above the anterior superior iliac spine;
- Supraumbilical (UMB(u)), 3 cm above navel;
- Infraumbilical (UMB(i)), 3 cm below navel;
- Thighs (THI), internal aspect of thighs, eight cm below the pubic area;
- Patellar area (ROT), at the fold created when pinching the region located 6 cm medial to the internal patellar border.

IV. Bioelectrical impedance. Using Tetrapolar Bioelectrical Impedance (TBI) with a body fat analyzer Maltron, model BF-905 (Maltron International Ltd., Rayleigh, Essex).

Volunteers voided previous to the evaluation, placed on supine position, and allowed to rest half an hour before determination. Self-adhering electrodes were placed on extremities. Every determination was performed with a separate set of electrodes, discarded after single use.

The following TBI determinations were assessed:

1. Fat weight (FW)
2. Lean weight (LW)
3. Water weight (WW)
4. Calories (CAL)

V. ß-hCG determinations: all subjects enrolled in the trial were studied for plasmatic ß-hCG levels by an ELISA test (64) on 0-15-30 study days.

VI. Mood questionnaire: from the first study week on, patients were given weekly self-administered questionnaires to be completed at home. It consisted of twenty-four questions related to their mood changes in the course of the study, plus four questions related to adverse drug effects. They returned the data at the time of the subsequent visit to the clinic.

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Data Analysis

Variables were split as follows for a better data processing and statistical results presentation:

- **Category I**, BW plus four bioelectrical impedance records (FW, LW, WW and CAL),
- **Category II,** eight anthropometrical measurements (corporal circumferences WRT, BRE, WAT, ABD, HIP, THI, ROT and ANK).
- **Category III**, nine skinfold assessments (TRI, AXA, SCA (i), TOR, ILI, UMB(u), UMB(i), THI, ROT) (see long names and definitions for the studied variables at the beginning of this section).

Each set was analyzed with a two-way multivariate analysis of variance (MANOVA), comparing the obtained Wilks-lambda' F with the corresponding critical value.

TREATMENT (VLCD diet plus group-specific pharmacological intervention) was considered the between-subject factor with three levels (P, G1, G2), and WEEK of clinicometric control served as an additional within-subject factor with six levels: weeks 0 to 5.

To estimate how the differences between treatment groups depended on the trial time elapsed since week zero (comparison of pattern trend changes in function of treatment time) we obtained the MANOVA result for the effect of the INTERACTION (also displayed in the text as TREATMENT x WEEK).

Moreover, to prevent any possible influence of acute effects specifically associated to any VLCD program in the adaptation phase (first 5-7 days), we additionally evaluated with separate MANOVA analyses the differences between groups and within subjects in the course of the last four treatment's weeks.

After obtaining a statistically significant multivariate test for a particular main effect or interaction, we further examined the univariate F tests for each dependent variable. When parameters from these tests displayed significant modifications, data were further analyzed to ascertain which group (P, G1 or G2) was responsible for the previous p values obtained. We also compared data basal values from each group against those obtained in subsequent weeks (e.g., records of week 0 against week 1, thereafter against week 2, and so on). These pain/vise comparisons were statistically assessed applying *post hoc* Scheffé F tests.

Questionnaire responses were converted into percentages and submitted to a chi-square (2%) test to compare between-groups and within-groups (pairing off final vs. initial data) statistic results.

To attenuate the natural source of within-subject variation, inherent to all assessments of subjective symptoms, we averaged data results from identical questionnaires completed weekly during the initial first two study weeks. Thus, we obtained a more precise "initial questionnaire" (avoiding the potential "adaptation effect" common to any VLCD regime in the first treatment week).

To obtain the final mood behavior results over the last two treatment weeks, they were averaged using the same schema as detailed before. Criteria for significance was $p<0.05$. Statistica 4.2 (from StatSoft, Inc.) for Windows software was used in all processing.

Results

All volunteers were submitted to the same VLCD schedule lasting five weeks. The objective of this work was to gather data on the potential synergism between hCG administration and a VLCD plan. At the end of the study we counted a total of 4.3 % missing data due to the absence of subjects in control days (no one absent in more than two opportunities) as a consequence of personal situations not associated with the experimental conditions. No statistic differences were obtained between Placebo and hCG groups regarding missing data. No statistic differences were obtained among Placebo and hCG groups regarding missing data.

1. Regarding weight loss, similar results (with/ without hCG administration) were obtained. Bioelectrical impedance exhibited discrete modifications in tested groups.

As expected, for all types of clinicometric assessments, significant results were obtained through MANOVA analysis on factor WEEK. Figures 1 and 2 (bioelectrical impedance and anthropometrical data, respectively) show that the time-dependent changes were uniformly present in all tested groups. We therefore estimated that the decreasing observed patterns were the consequence of VLCD acting on overweight patients. However, regarding skinfold thickness findings (Figures 3 and 4), we detected in P group a noticeable tendency to attenuation of the within-subject variation during the last (third to fifth) study weeks. The data suggested us that this latter period might be the focus of our interest).

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Figure 1 (see page 209) shows data patterns resulting in all groups from three representative variables (BW, FW and LW) of the variable category I. The MANOVA analysis revealed nearly significant differences for the INTERACTION (TREATMENT x WEEK) [F(50,58) =1.35, p=0.13] without statistical significance on analysis of TREATMENT as main effect [F(10,98)=1.22, p=0.29].

When all groups were submitted to multivariate and univariate analyses taking exclusive data from weeks 2-5, we observed no significant difference result for the INTERACTION among group P and hCG-treated groups. This finding could be related to differences in mean basal body weights and treatment-dependent responses to the acute effects of VLCD during former weeks.

When the *post hoc* Scheffé test was applied to compare the result from each weekly record (weeks 1-5) to it's corresponding basal value (week zero), we found similar patterns for all groups concerning analysis of BW and TBI records (compare P vs. hCG-treated groups in every panel of Figure 1).

However, regarding the analysis of FW and BW data, we detected significant differences for the effect of the INTERACTION ($p<0.005$ and $p<0.05$, respectively). Comparing FW patterns from groups P and G1: $F(5,230)=4.55$, $p<0.001$. For the comparison P vs. G2, (BW and FW data), we obtained: $F(5,140)=4.20$ and 2.97, respectively ($p<0.01$ for both cases).

2. hCG+diet significantly decreased more waist and abdominal circumferences than diet alone.

Figure 2 shows the results for three (category II) body circumference assessments (WAT, ABD and HIP). MANOVA analysis showed significant differences for factor TREATMENT as main effect [F (16,92)=1.92, $p<0.04$], which we do not consider relevant due to the presence of higher basal records in group G2 when compared to the rest of the studied groups.

As a whole, the effect of the INTERACTION did not reveal statistical significance.

Nevertheless, significant differences were obtained after further analysis for the effect of the INTERACTION on variable WAT [F (10,265)=2.44, $p<0.01$, see panel A].

Data assessments from other circumferences did not show statistical differences for this effect among groups [as representative examples, see ABD ($p=0.35$) and HIP records in panels B and C, respectively]. When the records of weeks 0-1 were subtracted from MANOVA analysis, almost all p values were slightly affected. WAT and ABD measurements demonstrated to still be more affected by the INTERACTION: for WAT, $p<0.003$; for ABD, $p<0.08$. The INTERACTION significance increased when P controls were compared to subjects from group G2: comparing P vs. G2, and considering data from weeks 0-5, we obtained: $F(5,140)=2.87$ ($p<0.02$) for WAT, and $F(5,140)=1.80$, ($p=0.12$) for ABD. But when we analyzed data from weeks 2-5, we found the following: for WAT, $F(3,84)=3.43$ ($p<0.02$), for ABD, $F(3,84)=2.73$ ($p<0.05$).

3. Weak effects of hCG on a series of skinfold thickness reduction patterns.

Figures 3-4 show results from subcutaneous fat evaluations, as assessed by skinfold thickness, on nine selected skinfolds. Figure 3 presents three representative folds [TRI, SCA (i), ILI (U)3 out of five (those previous mentioned plus AXA and TOR)] that demonstrated to be slightly affected by the pharmacological treatment.

Analyzing skinfold data from weeks 0 to 5, the main effect TREATMENT showed statistical significance ($F(10,98)=2.39$, $p<0.02$). However, prevailing higher basal records in group G2 might account for this statistical significance. After studying the effect of the INTERACTION on skinfold results, statistics were as follows: TRI (see panel A), $p<0.08$; AXA, $p=0.98$; SCA(i) (see panel B), $p<0.005$; ILI (see panel C), $p=0.23$; TOR, $p=0.35$.

Performing pairwise comparisons between control P and hCG-treated groups, we observed that the higher significances obtained for SCA (i) and TRI skinfolds derived mainly from the comparison between P and G2: for TRI, $F(5,140)=2.55$, $p<0.04$, for skinfold SCA (i), $F(5,140)=6.02$, $p<0.0001$. MANOVA analyses run on weeks 2-5 data resulted in a significance increase for TREATMENT as main effect [$F(10,98)=2.55$, $p<0.009$]. In addition, the INTERACTION was enhanced on data from SCA(i) assessment ($p<0.00005$): by comparing data from groups P and G2 during weeks 2 to 5: for TRI, $F(3,84)=2.08$ ($p<0.04$), for SCA(i), $F(3,84)=9.31$.

4. Higher response rates in a different skinfold series by treatment with hCG plus a VLCD.

In Figure 4 we display skinfold thickness results

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obtained from another series of four examined skinfolds [UMB ($_U$), UMB ^ THI, ROT($_U$)]. MANOVA analysis resulted in a nearly significant INTERACTION [F (40,68)=1.55, p<0.06] in the absence of statistical significance for TREATMENT as main effect [F (8,100)=1.43, p=0.20].

When the specific effect of the INTERACTION was evaluated for each skinfold, highly significant differences were found. By computing F (10,265) values, we obtained the following results: UMB ($_U$) (see panel A), p<10-3; UMB ($_U$) (see panel B), p<10-5; ROT (see panel C), p<0.05; THI (see panel D), p<10-6. When we restricted the data analysis from weeks 2 to 5, we found nearly significant results for factor TREATMENT as main effect [F (8,100)=1.75, p<0.1] and for the effect of the INTERACTION [F (24,84)=1.55, p<0.06]. The INTERACTION was further studied pairing P group against each hCG-treated group in separate multivariate analyses.

By comparing P vs. G1, we found: for UMB(i), p<0.04, and for RQT , p<0.03 (UMB($_U$) and THI achieved nearly significant p values). Again, the strength of the INTERACTION [TREATMENT x WEEK] was higher when group G2 was selected for the comparison.

From the obtained data, it becomes clear that skinfolds determinations in Q2 subjects showed a differential response to VLCD schedule with respect to that of P controls (for INTERACTION, in these points of skinfold assessment, p<0.0005).

5. Selective response of some skinfolds to hCG was dependent on dose.

The experimental design of this investigation was not intended to determine the dose-response curve for hCG acting on diet-induced effects.

However, the effects of hCG on some of these skinfolds seemed to be dependent on dose, significant differences for the effect of the INTERACTION after the comparison between G1 vs. G2 groups for UMB (u) (p<0.001) and UMB (i) (p<0.005), and a nearly significant p value for THI (p=0.11).

Figure 4 also displays the percentages of skinfold thickness reduction from the beginning to the end of the clinical trial. We found skinfolds decreases for group G1 ranging from over 22% (for UMB (u), see panel A) up to over 115% (for THI, see panel D) over respective decreases in P group. These differences were still higher when G2-subjects were compared to P controls: by computing the ratio between decrease percentages, G2 had over twice (for UMB (u), see panel A) to over four-fold (for THI, see panel D) the skinfold records drops observed in group P (see each actual percentage, group by group, in Fig. 4).

Most of the differences among hCG-treated subjects and P controls regarding skinfold reduction rates were enhanced when data corresponding to week five was compared to records of week two instead week zero (data not shown).

6. Improvement in mood-related parameters by hCG.

In Figure 5, we display the responses to four representative questions asking about the occurrence frequency for specific mood-related events, according to a multiple choice designed questionnaire completed every treatment week by all the subjects enrolled in the trial.

Panels A to D display the initial and final questionnaire results, expressed as percentages for each optional response (covering a four-option frequency scale from never to frequent).

Using this procedure, we expected to find, in tested volunteers, skewness towards either sense concerning their behaviors and feelings in response to a diet and a pharmacological intervention. For all these questions, and compared to control subjects, hCG-treated volunteers (G1+G2) showed a trend to improvement of interpersonal contacts and mood control when confronting upsetting or conflicting situations. Pairing off final (f) vs. initial (i) distribution of percentages for optional responses, we particularly found statistical significance in two of these questions in group G (after\test: ^{2}X3=16.3, p<0.002, and ^{2}X3=7.82, p<0.05; see right sectors of panel A and B, respectively).

P group-subjects did not present temporal differences (see panel A), or were adversely affected in their mood during the trial ^{2}X3=14.4, p<0.002 (compare in panel B corresponding initial and final values for group P and G).

Furthermore, group P exhibited, in two other questions, certain skewness to the impairment of its mood (see left half of panels C and D, p<10-5); for group G we obtained the ^{2}X3 values 1.51 and 3.98, respectively (p>0.3), showing the absence of temporal mood changes.

For all other mood-related questions, no statistical sig-

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nificant difference among groups was found (data not shown).

We also included some questions intended to evaluate the potential occurrence of treatment-dependent clinical anomalies regarding hormonal, physiological or metabolic disorders. We found no significant difference after final vs. initial records' comparison (data not shown).

7. No detectable ß-hCG plasmatic levels in all tested groups.

On treatment days 0, 15 and 30 we have tested all volunteers, screening for the presence of plasmatic p-hCG. Concentrations were undetectable in all cases (data not shown).

Discussion

Concerning hCG and its utility for the management of obesity, this study introduces two new aspects, and adds new data for a third:

I. This is the first report assessing variables not included in previous reports;[38,51,68,89]

II. We report a new administration route for hCG management of obesity, the oral approach, which has never been reported before;

III. We have detected mood changes in hCG treated patients, regarding a better confrontation of daily emotionally conflicting situations.

I) Skinfold thickness (SKF) and Tetrapolar Bioelectric Impedance (TBI) records.

Both approaches have been extensively discussed in the literature. It was shown that the correlation between the values obtained with the two methods to be linear and highly significant for both sexes.[42,81,27]

There is general agreement that skinfolds calipers are particularly useful in the clinical setting,[56,82,16,76,10,65,9,15,75] particularly in view of the fact that measurement of subcutaneous body fat at different body sites is becoming increasingly important for the characterization of risk of certain disease states.[55]

When comparing skinfold assessments to body circumference estimates, some data suggests that the latter approach appears to be more sensitive in the determination of subcutaneous body fat,[53] this procedure is in our opinion subjected to clinical variables (bloating syndrome after a meal, premenstrual water retention, etc.) that may affect negatively on the final estimate's results. Also, when comparing SKF to body contour assessments, some data suggest that the pattern of fat thickness body distribution measured over several specific sites by one method of measurement is unlikely to be duplicated by of the other method on the same individual.[40,41]

Adipose tissue patterns show great variability, showing the importance of using skinfold caliper readings from a variety of different anatomic sites including upper limbs, lower limbs and trunk.[30,65]

According to the above conclusions from several authors,[72,13,60, 25,73,62] we would like to suggest that former studies on hCG and obesity lacked of sufficient data to estimate accurately the modifications of adipose tissue distribution in tested volunteers. Consequently we designed the study to assess as many variables as possible .

As far as our study concerns, we subjected each volunteer enrolled in the trial to four bioelectrical impedance, eight anthropometrical plus nine SKF evaluations. Performing this multiple site determinations, our results show that specific SKF are highly responsive to hCG pharmacological intervention (upper and lower umbilical). The greater response was obtained in those regions where the corresponding circumference assessments resulted in nearly significant or significant decreases through the trial period (see waist and abdomen records in Fig. 2 and the above detailed description of statistical results for the effect of the interaction).

II) Oral hCG is an valuable alternative administration route.

No data appear on the scientific literature regarding an oral administration of hCG in humans. But results from this study suggests hCG may be used by the sublingual-enteral route. Despite plasmatic, ß-hCG remained undetectable both in Placebo and hCG groups throughout the study, an oral administration of hCG proved to possess therapeutic activity.

Since commercial preparations of hCG contains ß-endorphin, it may be tempting to hypothesize that this pentapeptide might account for the pharmacological activity observed on mood stability during the Protocol.

III) Volunteers treated with hCG coped better with daily irritating situations.

As can be seen on Figure 5, hCG-treated groups

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handled better their irritability, their mood at home, and were less prone to episodes of extreme nervousness capable of provoking violent discussions. Several reports proposed hCG might be used for the treatment of psychoses or neurosis.[29,61,24] Our study appears to corroborate these proposals.

To conclude, this study poses several still unanswered questions:

1. **hCG absorption.** We have tested all volunteers, screening for the p-hCG in plasma. Concentrations were undetectable in all cases.

   Therefore, which hCG fraction is responsible for the pharmacological activity observed in our study? hCG's molecular size (alpha chain -14,500 KD; beta chain -22,200 KD) makes it highly improbable that the entire molecule has been absorbed. Our hypothesis is that only a fraction of the entire hCG molecule is absorbed through this administration route.

2. **hCG and lipid metabolism.** We do not know precisely how hCG acts on adipose tissue metabolism. However, some reports[32,84,85,83] suggest hCG possesses a metabolic activity on adipose tissue (i.e. decrease lipogenesis). These actions are not directly exerted on adipocytes, since fat cell membranes have no receptors for hCG.[32]

3. **hCG and mood.** A stable mood and lack of attrition characterized the hCG-treated group.

   It is well known that VLCD's are associated with mood changes, particularly attrition[78] during the dieting period. In one study, disinhibition and hunger were significantly related to anxiety and depression while restraint was not.[44] Another study concluded that elevated levels of anxiety persist in female patients throughout a VLCD course of treatment.[45]

Also many patients complain about fatigue during a VLCD.[4]

Conversely, our data suggest that hCG-treated volunteers rather improved their attitude towards their environment, in the sense of an enhanced well-being, less irritability and lack of fatigue. Since commercial preparations of hCG contains 3-endorphin[39] and this neuropeptide has been demonstrated to affect the function of limbic-emotional circuits,[21,58,5,28] we hypothesized that the p-endorphin fraction present in commercial preparations of hCG might account for the activity observed regarding mood control.

Additional studies remain to be performed to test the validity of this hypothesis.

Conclusions

1. Female obese volunteers participating in a double blind study, and submitted to the administration of an oral presentation of hCG plus a VLCD, decreased specific body circumferences and skinfold thickness from conspicuous body areas more efficiently than Placebo+VLCD-treated subjects.

Since a significant fat proportion from total body fat is subcutaneously located (50 to 65 percent, depending on sex and fat distribution), this hCG metabolic activity would result in a reduction of the total body fat mass, the main cause for obesity. We suggested that the combination of a VLCD and oral hCG could not only trigger clinically significant changes in subcutaneous fat stores but simultaneously decrease body weight and modulate body contour.

2. hCG oral administration proved to be a safe and effective procedure on obese treated volunteers. No side effects were observed during the study. There are no reports in the literature regarding this administration route to compare our findings.

3. Compared to placebo treated subjects, volunteers managed with an oral administration of hCG coped more efficiently with daily irritating situations, were in a better mood, and handled home conflicts without stepping up family discussions.

This study appears to contradict former conclusions on the issue of hCG and obesity. We attribute those differences to a different approach, including variables not assessed in former publications.

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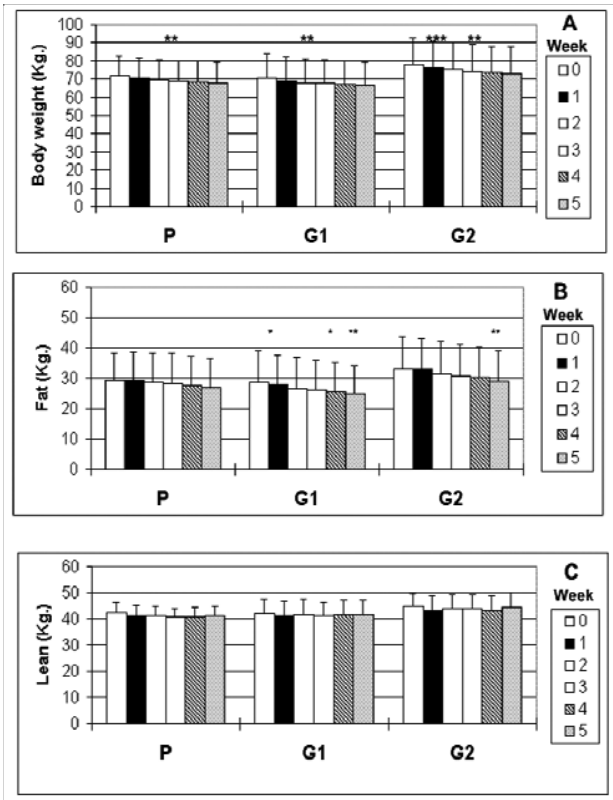

Figure 1: A,B and C. Body weight and bioelectrical impedance records.

During five weeks of hypocaloric diet the subjects enrolled in the clinical trial were simultaneously administered a daily dose of 250 UI hCG (group G1, N=36), or 500 UI (group G2, N=8). A third group (Placebo) received an equivalent volume of saline solution (group P, N=26). Data was obtained at the beginning and weekly during the trial period (records 0 to 5) for Body Weight (panel A) and four bioelectrical impedance assessments (here it is only displayed details from Fat and Lean weights on panels B and C, respectively).

Data are expressed in kg, mean ± SD (bars at top). Results were submitted a priori to MANOVA analysis.

When multivariate and univariate analyses were performed taking exclusively data from weeks 2 to 5, differences between groups were strongly attenuated (see details in the text). The asterisks mark statistically significant differences between weekly records (weeks 1 to 5), and the corresponding basal values determined in week 0 (analyzed a posteriori by Scheffé F test).

* p<0.05, ** p<0.0002, *** p<0.0005

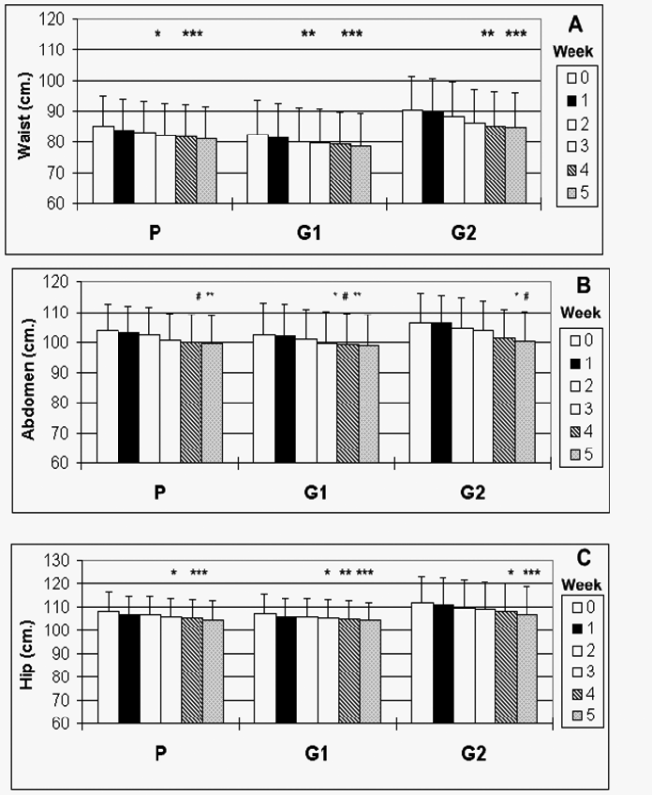

Figure 2. Body circumferences.

Here we display the basal ("0") and subsequent five weekly results (weeks 1 to 5) from three out of eight anthropometrical parameters examined in this work. Panel A=Waist. Panel B=Abdomen. Panel C=Hip. All results are expressed in cm, mean ± SD (bars at top). Regarding all corporal circumferences assessed, only Waist and Abdomen were significantly affected by the interaction of TREATMENT [diet plus pharmacological treatment] and WEEK (trial stage). These differences appeared enhanced when only data from weeks 2 to 5 was gathered to perform a separate MANOVA analysis (other details in legend of Figure 1)

* p<0.05 ** p<0.0005 *** p<10-6 # p<0.005

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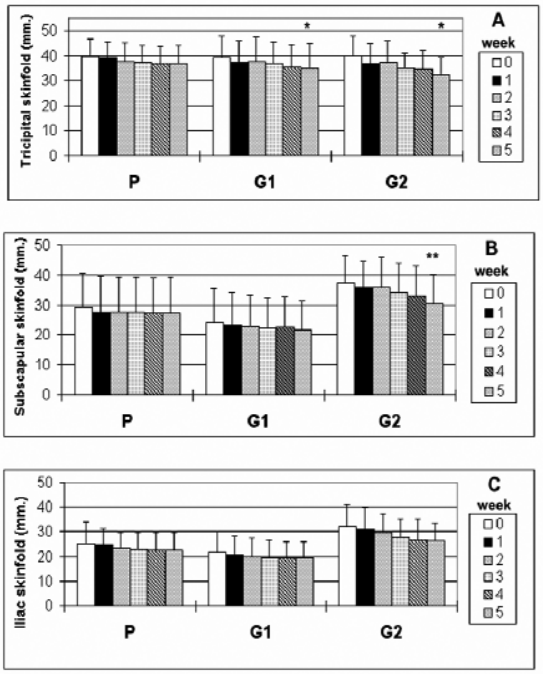


Figure 3 (A,B and C)

Skinfold thickness reduction on three out of five "low-responsive" skinfolds.
Simultaneously with bioelectrical impedance and anthropometrical assessments,
we examined subcutaneous fat stores by plicometries.
Results are expressed in mm, means ± SD (at top). Only Tricipital (see panel A) and
Subscapular (see panel B) skinfold assessments demonstrated significant o nearly significant differences
by comparing group G2 and the control P for the effect of TREATMENT or the INTERACTION
(see statistical analysis details in the text).

It is also shown the data obtained for Suprailiac (see panel C) skinfold. Concerning these series
of low responsive skinfolds, no relevant difference between groups was raised after pairwise
comparisons of each treatment weeks' record with its corresponding basal value: by Scheffé test, * p<0.03, ** p<0.0005

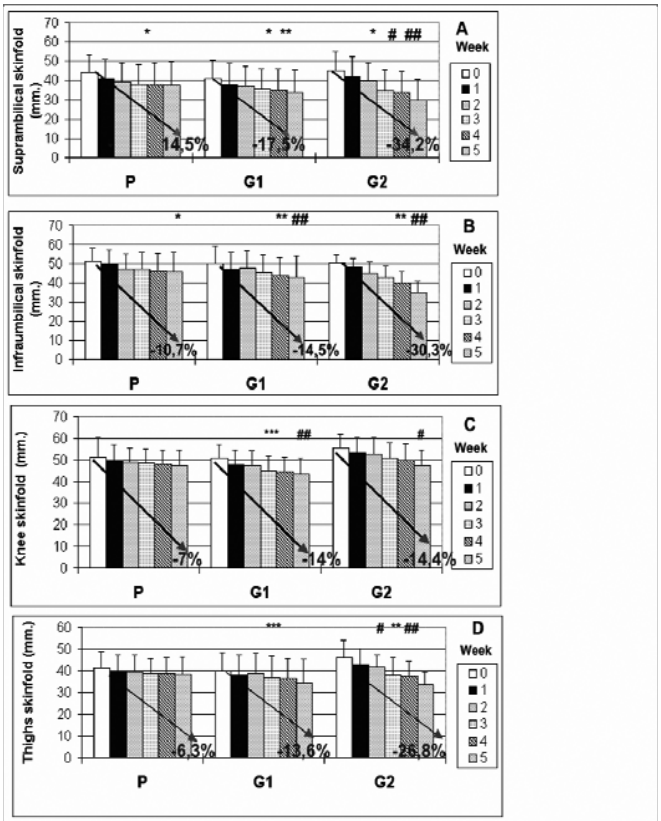
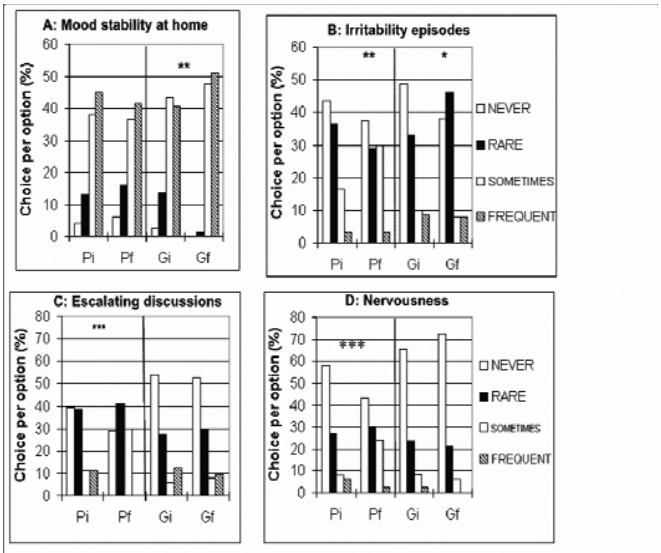


Figure 4: A,B,C and D: Plicometries on four "high-responsive" skinfolds.

Here it is shown a different series of skinfolds displaying a clear treatment-dependent behavior,
most noticeable from the second week of treatment on. When last four treatment' weeks were submitted to study,
MANOVA analysis resulted in nearly significant differences for factor TREATMENT and the INTERACTION.
For each of these skinfolds, highly significant statistical results were found between G2 and P groups
for the effect of the INTERACTION.
In this Figure we can observe the percentages of skinfold thickness reductions, comparing data
obtained at the end of the trial with the corresponding basal values (week zero).

P values resulting from Scheffé test are marked by asterisks as follows: * p<0.05, ** p<0.0005, *** p<10-4, # p<0.01, ## p<10-6.
See other details in the legend of Fig. 3 and the text.

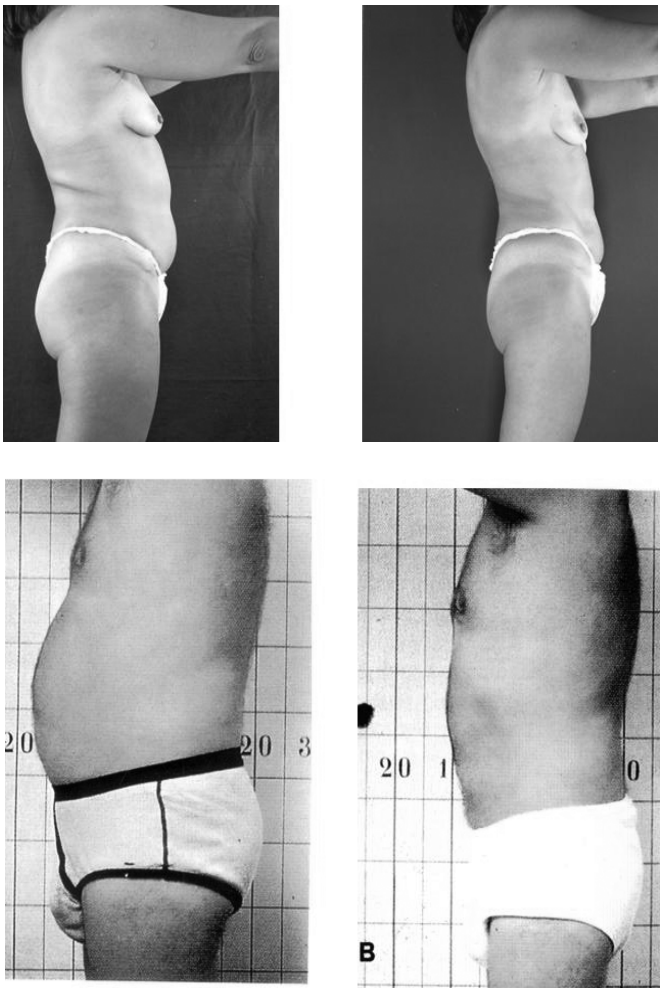


Figures 5 :A,B,C and D.

The figures show responses given by volunteers to four of 28 representative questions .
Volunteers responded to these questions at the end of each week's treatment.
The questionnaire included questions about inter-personal relationships,
well-being, self- control when confronted with conflictive situations, etc.
(see titles of panels A to D).

All data from subjects pertaining to groups G1 and G2 were pooled ("group G") for data
analysis. Initial and final results are indicated by the letters i and frespectively
In the x axis: Pi isPlacebo: initial, Pf is Placebo: final; Gi is initial hCG) and Gf final nCG.

Statistically significant differences in group responses to final and initial questionnaires
were obtained by applying 2c test as follows: for group G, * p<0.05 (panel A)
and ** p<0.002 (panel B); for group P, ** p<0.002 (panel B) and *** p<10-5 (panels C and D)



More photos are available at
http://hcgobesity.org/hcg_obesity_photographs.htm

11. Use of Human Chorionic Gonadotropin (hCG) by Oral-Sublingual or Injectable Route as an Appetite-Suppressant Agent (2009).

Use of Human Chorionic Gonadotropin (hCG) by Oral-Sublingual or Injectable Route as an Appetite-Suppressant Agent.

Apr 28, 2009

Use of Human Chorionic Gonadotropin (hCG) by oral-sublingual or injectable route for the treatment of several food disorders, as an appetite-suppressant agent, food compulsiveness as well as all of those pathologies related to hunger and/or appetite modifications, including overweight, obesity, anorexia, bulimia, emotional hyperphagia, without excluding other pathologies associated to overingestion or reduced ingestion. It also includes its use for the treatment of behavior disorders associated with an increased ingestion, either behavior disorders, neurosis, borderline personality disorders or psychosis, without excluding other psychosomatic disorders.

Skip to: Description Claims Patent History Patent History

Description

This invention is related to the "Use of Human Chorionic Gonadotropin (hCG) by Oral-Sublingual or Injectable Route as an Appetite Suppressant Agent".

SUMMARY

Use of Human Chorionic Gonadotropin (hCG) by oral-sublingual or injectable route for the treatment of several food disorders, as an appetite-suppressant agent, food compulsiveness as well as all of those pathologies related to hunger and/or appetite modifications, including overweight, obesity, anorexia, bulimia, emotional hyperphagia, without excluding other pathologies associated to overingestion or reduced ingestion. It also includes its use for the treatment of behavior disorders associated with an increased ingestion, either behavior disorders, neurosis, borderline personality disorders or psychosis, without excluding other psychosomatic disorders.

APPLICATION FIELD

It is applicable in the treatment of pathologies of hunger and satiety mechanisms. Hunger, satiation and energetic balance are regulated by a redundant neuroendocrine system integrated at the hypothalamus level.

The system consists of a complex web of neurohormonal circuits that include short and long lasting molecular signals of central and peripherical origin as well as other sensory, mechanical and cognitive-type factors.

The system minimizes the impact of fluctuations of ingestion and energetic expense on the fatty mass and the body weight. The short-lasting signals, most of which are gastrointestinal

tract hormones, regulate the amount of food consumed in each meal time. The long-lasting signals reflect the fat reserve size.

Endogenous opioids and hunger: The pro-opiomelanocortine (POMC) contains beta-endorphin, which in turn has met-encephalin and may also produce other shorter encephalins. In the brain, it is mainly located at the hypothalamic area.

The POMC is post-translationally modified thus giving rise to other biologically active peptides including ACTH, Beta-endorphins. These peptides exert their effect through melanocortine receptors (MCR), five of which have been described.

The MC3R and MC4R receptors are the ones involved in the regulation of hunger and satiation. Their stimulation has a central anorexigenic effect. Furthermore, they are thermogenesis mediators in the SNS, as a consequence of which they induce the loss of weight.

The MC4R is exclusively expressed in the neuroendocrine system and it is active in the areas that regulate the food ingestion, such as NPV, the dorsomedial hypothalamus and the lateral hypothalamic area.

The a-MSH is an agonist of MC3R and MC4R and, consequently, it is a very important anorexigenic signal. The expression of a-MSH is increased by the presence of leptine in the POMC neurons of the NAr, while at the same time it inhibits the AgRP neurons.

The role of opioids in the paraphysiology of food disorders would be explained through the self-addiction model. This model proposes that the exacerbated starvation by excessive exercise is itself a kind of body addiction to endogenous opioids.

We demonstrated in a series of studies that the administration of Human Chorionic Gonadotropin (hCG), which contains Beta-endorphin in its molecule, whether by oral-sublingual or intramuscular injectable route, has a remarkable appetite-suppressing action when administered according to the techniques described below. Its mechanism of action lies precisely at the hypothalamus level, wherein the hunger and satiation signals are generated.

PROBLEM TO SOLVE

Food Disorder: Obesity and Overweight: The obesity and overweight are defined as an abnormal or excessive accumulation of fat which may be harmful to health.
Obesity and Overweight Details: The last calculations of the WHO indicate that in 2005 there were worldwide:

-
  - About 1600 million adults (older than 15 years old) suffering from overweight.
  - At least 400 million obese adults.

Furthermore, the WHO estimates that in 2015 there will be about 2300 million adults suffering from overweight and more than 700 million obese adults.

In 2005, there were at least 20 million 5-year-old infants suffering from overweight worldwide.

Although this issue used to be considered as problem exclusive of high-income countries, overweight and obesity are spectacularly increasing in low- and medium-income countries, mainly in the urban areas.

Which are the usual repercussions of overweight and obesity on health?

Overweight and obesity have serious consequences for health. The risk progressively increases as the BMI increases. The high BMI is an important risk factor for chronic diseases, such as the following:

-
  - Cardiovascular diseases (especially cardiopathies and cerebrovascular accidents), which are the main cause of death in the whole world, with 17 million yearly deaths.
  - Diabetes, which has rapidly become a world epidemic. The WHO estimates that the deaths from diabetes will rise by more than 50% in the next 10 years in the world.
  - Locomotive apparatus diseases and, particularly, arthrosis.
  - Some cancers, such as endometrial, breast and colon cancer.
    Food Disorder: Anorexia and Bulimia: Bulimia or nervosa bulimia (excessive hunger) is a mental disorder associated with food. The term "bulimia" comes from the Latin bulimia, which, in turn, comes from the Greek (boulimia) which, in turn, is composed of bous (ox) and limos (hunger).

Its essential characteristic is that an individual suffers from compulsive binge eating events followed by a feeling of guiltiness and control lost. It usually alternates with fast or very little food ingestion events but later on the individual suffers again from compulsive ingestion events.

Binge eating consists in eating in less than two hours an amount of food bigger than that which would be eaten by most individuals.

Despite the fact that the type of food eaten in this binge eating may be varied, generally it is sweets and food with a high caloric content, such as ice-cream, cakes or chocolate.

Another essential characteristic of this disorder relates to inappropriate compensatory behaviors to prevent weight gain. Most individuals use different procedures as an attempt to compensate for the binge eating, the most usual of which is the provocation of vomiting.

Food Disorder: Hyperphagia in other psychological alterations: Excessive ingestion as a reaction to stressing events which results in obesity. Mourning, grief, accidents, surgical procedures and emotionally stressing events may generate a "reactive obesity", especially in diseased individuals predisposed to weight gain.
Inconvenients of appetite-suppressing medicaments: When prescribing it, it is necessary to bear in mind the following characteristics of the appetite-suppressing agents:

- they are modestly effective in the ponderal reduction, thus causing a weight loss ranging from 8 to 10 Kg.
- they have a high abuse, dependence and tolerance potential, and deprivation syndrome.
- their main secondary effects appear at the following levels:
  - CARDIOVASCULAR SYSTEM: palpitations, tachycardia, arterial hypertension, precordial color, arrhythmia.
  - GASTROINTESTINTAL SYSTEM: mouth dryness, nausea, vomits, abdominal aches, diarrhea, constipation.
  - CENTRAL NERVOUS SYSTEM: Overstimulation, excitement, insomnia, anguish, euphoria, depression, migraine, psychotic episodes, convulsions.

(Known) Appetite-Suppressant Medicaments Generic name Noradrenergic agents Benzphetamine Phendimetrazine Diethylpropion Phentermine Mazindol Phenylpropanolamine Serotoninergic agents Phenfluramine Dexphenfluramine Fluoxetine Ephedrine/caffeine

SOLUTION PROVIDED BY THE INVENTION

Human Chorionic Gonadotropin (hCG) Description: The human Chorionic Gonadotropin (hCG) is a glucoprotein and represents the association between an α (alpha) chain and a β (Beta) chain. The hCG is obtained from the urine of pregnant women and it is not homogeneous.

Highly purified medicaments also contain several moieties differing from sialic acid and in the biological action. The amount of hCG is indicated in biological action units.

The hCG hormonal effect is based on its ability to stimulate the biosynthesis of sexual steroids in the gonads (ovaries and testes). The hCG action is qualitatively the same as that of the pituitary gonadotropine (LH). However, the hCG has a considerably longer half-life, which leads to a stronger action in case of a cumulative administration.

In the ovaries, the hCG stimulates the granulosa, theca and stroma or luteal cells in order to keep the progesterone and estradiol production.

In granulosa cells of the small follicles, the estradiol biosynthesis is preferably stimulated by high doses of hCG. As in the granulosa cells of the dominant mature follicles and/or luteinizing granulosa cells, the progesterone biosynthesis is stimulated by high hCG doses. Likewise, the hCG stimulates the production of biologically active peptides in the ovary, said peptides being important for the reproduction regulation (for example, inhibition, relaxation, plasminogen-activator-inhibitor).

In Leydig cells, the hCG stimulates the production of testosterone and other sexual steroids, such as dihydrotestosterone, 17 OH-progesterone and estradiol.

Although the primary prescription of hCG is related to the infertility area, different performed researches that have been carried out conclude that it may be successfully used in a very different diseases without undesired effects since it is a natural-source medicament.

In the traditional Pharmacopoeia, the Chorionic Gonadotropin prescription is applied only through the intramuscular injectable route. The novelty in this invention is that it enables its administration both by intramuscular and oral-sublingual route as an appetite-suppressant agent (a non-foreseen indication before this invention), thus avoiding all of the inconveniences derived from the administration of drugs with potential secondary effects. The presence of Beta endorphine in the hCG molecule would be responsible for the observed clinical phenomena.

ADVANTAGES

Administration of hCG by oral-sublingual or intramuscular injectable route: Unlike the usual appetite-suppressant medicaments, the administration of hCG has no risks for patients since it lacks all of the characteristic side effects of appetite-suppressant medicaments. It does not have side effects or contraindications. The appetite suppression is highly significant.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to achieve the advantages herein briefly commented, to which the users and skilled persons in the art may add many others, there follows a description of the drawings that schematically illustrate the benefits of this invention without a determined scale in the accompanying sheets, wherein:

FIG. 1 is a drawing representing the transgression to the diet during the observation period. Gi: Initial gonadotropin (treatment beginning), Gf: Final Gonadotropin (end of treatment).

FIG. 2 is a drawing related to eating due to anxiety during the observation period. Gi: Initial gonadotropin (treatment beginning), Gf: Final Gonadotropin (end of treatment).

FIG. 3 is drawing related to the tiredness when getting up during the observation period. Gi: Initial gonadotropin (treatment beginning), Gf: Final gonadotropin (end of treatment).

FIG. 4 is a drawing related to the physical hunger during the observation period. Gi (treatment beginning). Gf: Final gonadotropin (end of treatment).

FIG. 5 is a drawing related to irritability during the observation period. Gi: Initial gonadotropin (treatment beginning), Gf: Final gonadotropin (end of treatment).

FIG. 6 is a drawing related to eating when not being hungry during the observation period. Gi: Initial gonadotropin (treatment beginning), Gf: Final gonadotropin (end of treatment).

Clinical Experiences: Ninety patients suffering from varied food disorders were studied, most of them stated to have a daily overingestion with the subsequent overweight development.

The performed study was a double-blind type study for a five-week period. The placebo group (30 patients) received a saline solution, whereas the hCG group received hCG by oral route (from 200 to 500 international units daily, 30 patients) or intramuscular injectable route (from 130 to 200 IU, 30 patients).

In overweight or obesity cases, a very low calorie diet was prescribed to contribute with the body mass reduction.

Results: After revieweing the charts between the patients treated with Gonadotropin, whether by injectable or oral route, and the volunteers to whom the placebo was administered, the following parameters have shown significant differences from the statistical point of view regarding:

1. Physical hunger

2. Transgressions to the diet

3. Eating related to anxiety

4. Tiredness when getting up during the treatment period

5. Irritability during the treatment period

6. Eating without being hungry during the treatment period.

In all of the studied cases, patients have stated to feel clinically well during the research period.

The administration by injectable or oral route of hCG provides, through hypothalamic mechanisms:

1. Appetite reduction, better control over ingestions

2. Reduction of anxiety for food

3. Patient were in very good mood despite the fact of being subjected to a low-calorie diet

4. Overweight or obesity reduction, especially around the waist (central obesity) and abdomen

5. Reduction of cholesterol figures

6. Clinical improvement of diabetes type 2 or resistance to insulin

7. Feeling of wellbeing during the treatment period

8. Improvement in high blood pressure

DESCRIPTION

Under medical supervision, the patient is administered Chorionic Gonadotropin (hCG) by the oral or injectable route. The daily Gonadotropin doses are adjusted between 300 to 500 international (oral-sublingual) units daily or 100 to 300 (injectable) IU during the treatment period.

Since most of these patients resort to appetite-suppressant medicaments because they display some degree of overweight or obesity, in such cases they are also prescribed a very low-calorie (about 500 Kcal/day), low-fat, hypohydrocarbonated, normoproteic diet, providing

200 grams of proteins from animal plus a combination of vegetables and carbohydrates until the indicated amount of calories is reached.

Use: The treatment is carried out for a period not less than a month and it may be extended up to two months. After that, a weight maintenance is indicated for a one month period, after that as of which it may be repeated again.

During the intervals, no treatment with hCG is indicated made and a usual hypohydrocarbonated diet is prescribed.

From the above description and the accompanying drawings, the constructive and functional advantages that characterize the claimed invention are clearly noticed and it is therefore considered as an advantageous technology improvement.

Claims

1. Use of human chorionic gonadotropin (hcg) by oral-sublingual or injectable route as an appetite-suppresant agent, characterized by the daily Human Chorionic Gonadotropin doses between 300 and 500 IU daily (International Units) (oral-sublingual) or 100 to 300 IU (injectable) during the treatment period.

2. Use of human chorionic gonadotropin (hcg) by oral-sublingual or injectable route as an appetite-suppresant agent, as the one claimed in claim 1 characterized by the administration of a very low-calorie (furnishing about 500 Kcal/day), low-fat, hypohydrocarbonated, normoproteic diet, providing 200 grams of animal proteins plus a combination of vegetables and carbohydrates until the indicated amount of calories is reached, for a period not less than a month, which may be extended up to two months, and can be repeated again. During pauses no treatment with hCG is indicated and an usual hypohydrocarbonated diet is prescribed.

3. Use of human chorionic gonadotropin (hcg) by oral-sublingual or injectable route as an appetite-suppresant agent, in accordance with claim 1, characterized by the use of the human Chorionic Gonadotropin (hCG) by oral-sublingual or injectable route for the treatment of different food disorders, as an appetite-suppressant agent, and food compulsiveness.

4. Use of human chorionic gonadotropin (hcg) by oral-sublingual or injectable route as an appetite-suppresant agent, in accordance with claim 1, characterized by the use of hCG for the treatment of all of those pathologies which disorders are hunger and/or appetite alterations, including overweight, obesity, anorexias, bulimias, emotional hyperphagias, without excluding other pathologies associated with overingestion or reduced ingestion.

5. Use of human chorionic gonadotropin (hcg) by oral-sublingual or injectable route as an appetite-suppresant agent, in accordance with claim one, characterized by the use of hCG for the treatment of behavior disorders associated with an increase in ingestion, whether they are behavior disorders, neurosis, borderline personality disorders or psychosis, without excluding other psychosomatic disorders.

Patent History

Application number: 20100081608
Type: Application
Filed: Apr 28, 2009
Issued: Apr 01, 2010
Inventor: DANIEL OSCAR BELLUSCIO (BUENOS AIRES)
Application Serial: 12/430,936

Classifications

Current U.S. Class: **514/8**
International Classification: A61K 38/24 (20060101); A61P 3/04 (20060101);

12. Method to obtain the human Chorionic Gonadotropin (hCG)/cyclodextrin complex for oral administration, product obtained by this method and clinical and therapeutic use of the complex human Chorionic Gonadotropin (hCG)/cyclodextrin (2008).

Method to obtain the human Chorionic Gonadotropin (hCG)/cyclodextrin complex for oral administration, product obtained by this method and clinical and therapeutic use of the complex human Chorionic Gonadotropin (hCG)/cyclodextrin

Dec 22, 2008

To inform about the clinical utility human Chorionic Gonadotropin (hCG) complexed with cyclodextrins for oral administration, its utility in different pathologies and method for obtaining it. The present invention contemplates the use of cyclodextrins as carriers (transporters) and their capacity to form inclusion complexes with bioactive molecules (such as hCG), allowing the clinical activity of the hCG by mouth (oral), facilitating the administration of an originally prescribed medication in injectable form: More specifically, the goal it is the creation of hCG (human Chorionic Gonadotropin)—cyclodextrins complexes, and their clinical use in different disorders from various pathologies, through use of oral pharmaceutical formulations.

Skip to: Description Claims Patent History Patent History

Description

DETAILED DESCRIPTION OF INVENTION

This invention relates to the "Method to obtain the human Chorionic Gonadotropin (hCG)/cyclodextrin complex for oral administration, product obtained by this method and clinical and therapeutic use of the complex human Chorionic Gonadotropin (hCG)/cyclodextrin".

FIELD OF INTEREST

treatment of patients with arterial hypertension, overweight disorders, type 2 diabetes, or reactive hyperglycemia, hypertriglyceridemia and hypercholesterolemia.

CURRENT TECHNIQUE

in traditional Pharmacopoeia the prescription of Chorionic Gonadotropin is indicated via intramuscular injection. The novelty of this invention is that facilitates the oral administration, avoiding all the disadvantages arising from the parenteral administration.

Human Chorionic Gonadotropin (hCG) is a glycoprotein encompassing the association between an α (alpha) and a β (beta) chains. The hCG is obtained from the urine of pregnant women and is not homogeneous.

Highly purified preparations of hCG also contain several fractions that differ in the sialic acid content and biological action. The potency of hCG is indicated in units of biological action.

The hormonal effect of Chorionic Gonadotropin is based on its capacity to stimulate the biosynthesis of sex steroids in the gonads (ovaries and testes). The hCG action is qualitatively the same as the one from the pituitary Gonadotropin (LH). However, hCG has a significantly longer half-life which leads to a stronger action in case of accumulative administration.

HCG stimulates in ovaries the granulosa, theca and stroma or luteal cells to maintain progesterone and estradiol production.

In granulosa cells from small follicles the biosynthesis of estradiol is preferentially stimulated by high doses of hCG. As in the granulosa cells of dominant mature follicles and/or luteinizing granulosa cells, progesterone biosynthesis of is stimulated by high doses of hCG. In addition, hCG stimulates the production of biologically active peptides in the ovary that are important for reproduction regulation (eg.: inhibition, relaxation, plasminogen-activator-inhibitor.

In Leydig cells hCG stimulates testosterone production and other sex steroids such as dihydrotestosterone, 17 OH-progesterone and estradiol.

While the primary indication of the hCG is related to the infertility area, our studies indicate that it can be successfully used in a extensive variety of diseases, without undesirable effects since it is a natural origin product.

DESCRIPTION

Our invention is constituted by the formation of a cyclodextrin+Gonadotropin complex. The cyclodextrins are non-reducing oligosaccharides obtained by the enzymatic hydrolysis of starch.

Cyclodextrins are molecules that contain 6, 7 and 8 units of alpha-D-glucopyranose assembled in position 1-4 giving rise to cyclic structures called: Alpha cyclodextrin, Beta cyclodextrin and Gamma cyclodextrin.

These cyclical structures are constituted by ring-shaped rigid molecules with a central cavity, where primary and secondary hydroxyl groups of the glucopyranose units are oriented towards the outside area of the ring, conferring to the cyclodextrin molecule hydrophilic characteristics, while the central cavity lined up with carbon and ether-oxygen skeletal atoms residues from glucopyranose adopts lipophilic characteristics.

The characteristics of the central cavity allow the cyclodextrins to form inclusion complexes with biologically active molecules, in this case hCG.

The aim of this invention is to communicate a pharmaceutical formulation, whose composition includes hCG (human Chorionic Gonadotropin) stabilized with non-reducing

oligosaccharides, specifically cyclic oligosaccharides known as cyclodextrins, allowing the formation of inclusion complexes, thus facilitating hCG absorption and metabolization through the oral route.

In the formation of these inclusion complexes the cyclical structure of cyclodextrin offers a central cavity with lipophilic characteristics, where molecules with an appropriated size or non-polar fractions of macromolecules can penetrate forming covalent unions and thus stabilizing the complex.

The formation of these inclusion complexes does not alter the characteristics of the molecule, either the complex or the host. Consequently the biologically active molecules retain their intrinsic capacity to permeabilise biologic membranes or interact with specific cell receptors.

In concordance with this concept, we propose the formation of an inclusion complex that we will identify as hCG*CD

hCG+CD′hCG*A/B/G−CD

Where:

hCG: human Chorionic Gonadotropin (glycoproteic hormone), represents the bioactive molecule capable of entering into the central cavity of the cyclodextrin.

(*) Represents the covalent unions between the bioactive molecule and cyclodextrin.

A/B/G−CD represents the cyclodextrin (alpha, beta or gamma cyclodextrins)

Materials and Methods: To prepare the complex the following materials have been used:

-
  - 1. HCG 200 IU (human Chorionic Gonadotropin—lyophilized)
  - 2. TACD-T (alpha cyclodextrin)—Trappsol (USA)
  - 3. KLEPTOSE (beta cyclodextrin)—Roquete Freres (FRANCE)
  - 4. Phosphoric acid 85%—Carlo Erba (ITALY)
  - 5. Sodium Hydroxide (NaOH—Merck)
  - 6. Water injectable quality (Roux Ocefa)
    Preparation of the complex: the cyclodextrin+hCG complex is prepared by dissolving the drug (hCG) in an aqueous solution of cyclodextrin with constant agitation under a specific temperature until an homogeneous solution is obtained.

The pH is adjusted to the desired value and finally the obtained solution is vacuum filtered with a 0.22 micron filter to maintain sterility.

HCG*CD complex solutions were prepared with the procedure described above and under laminar flow conditions and whose concentrations and details are described in tables 1 and 2.

TABLE 1 Alpha cyclodextrin NaCl NaOH 0.1M or hCG (mg/ml) (mg/ml) H_3PO_4 1:5 (IU/ml) 2 9 cs ph 7 200 5 9 cs ph 7 200 8 9 cs ph 7 200 10 9 cs ph 7 200

TABLE 2 Beta cyclodextrin Nacl NaOH or H_3PO_4 hCG (mg/ml) (mg/ml) (mg/ml) (IU/ml) 2 9 cs ph 7 200 5 9 cs ph 7 200 8 9 cs ph 7 200 10 9 cs ph 7 200

All solutions described in Tables 1 and 2 have been analyzed by UV spectrophotometry scanning between 350 nm and 190 nm.

The spectrums were performed in a Beckman spectrophotometer, using quartz buckets with 10 mm thickness and maintaining its temperature at 22 degrees Celsius in thermostatic bath.

The obtained spectrums from the different studied solutions are displayed in the tables below.

As a guide and to facilitate the comparison it has been drawn together the absorption spectrum of a non-complexed hCG solution (200 IU/ml) in the same preparation conditions that the solutions under consideration.

Results: results detailed below were obtained in the formation of the hCG+cyclodextrins complexes, using different concentrations of alpha and beta-cyclodextrins (2 to 10 mg/ml), demonstrating that the formation of hCG/cyclodextrins complexes, such as described below, possess clinical and therapeutic utility.

These results are detailed in the graphics, in which:

GRAPHIC 1: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Alpha cyclodextrin (2 mg/ml).

GRAPHIC 2: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Alpha cyclodextrin (5 mg/ml).

GRAPHIC 3: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Alpha cyclodextrin (8 mg/ml).

GRAPHIC 4: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Alpha cyclodextrin (10 mg/ml).

GRAPHIC 5: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Beta cyclodextrin (2 mg/ml).

GRAPHIC 6: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Beta cyclodextrin (5 mg/ml).

GRAPHIC 7: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Beta cyclodextrin (8 mg/ml).

GRAPHIC 8: shows the absorption spectrum of hCG (200 IU) and hCG (200 IU)+Beta cyclodextrin (10 mg/ml).

GRAPHIC 9: shows in a coordinates chart the clinical case of a female patient, EC, 53 years old, with diagnosed hypercholesterolemia, hyperinsulinemia, arterial hypertension and overweight during a six-week treatment period, using the hCG+cyclodextrin complex by oral administration.

GRAPHIC 10: shows a coordinates chart in the clinical case of the same patient that the graphic above, showing the cholesterol evolution.

GRAPHIC 11: shows a coordinates chart in the clinical case of the same patient that graphic 9, indicating the evolution of insulinemia.

GRAPHIC 12: shows a coordinates chart in the clinical case of the same patient that graphic 9, indicating the evolution of blood pressure.

GRAPHIC 13: shows a chart of the case of a male patient, GB., Aged 30, diagnosed with a insulin resistance syndrome, fatty liver, non-insulin dependent diabetes and overweight, over a treatment period of 6 weeks, using the complex hCG+cyclodextrin by oral administration.

GRAPHIC 14: shows a chart of the case of the same patient in graphic 13, indicating the evolution of the insulin resistance index.

GRAPHIC 15: shows a chart of the case of the same patient in graphic 13, indicating the glycemia evolution.

GRAPHIC 16: shows a chart of the case of the same patient in graphic 13, indicating the evolution of the hepatic transaminases index.

GRAPHIC 17: shows a chart indicating the case of a female patient, AH., 54 years old, diagnosed with insulin resistance syndrome, hyperglycemia, abdominal obesity and fatty liver, for a period of 6 weeks of treatment, using the hCG+cyclodextrin complex by oral administration, indicating the evolution of body weight.

GRAPHIC 18: shows a chart of the case of the same patient in graphic 17, indicating the evolution of the insulin resistance index.

GRAPHIC 19: shows a chart of the case of the same patient in graphic 17, indicating the evolution of the glycemia index.

GRAPHIC 20: shows a chart of the case of the same patient in graphic 17, indicating the evolution of hepatic transaminases index.

GRAPHIC 21: shows the chart of the same patient in graphic 17 indicating the evolution of the abdominal circumference.

Conclusions: from the obtained spectrum results for the different formulations containing alpha and beta cyclodextrins it can be observed that they have different levels of complexes formation.

In the case of prepared solutions with alpha cyclodextrins we observed that the complexes formation degree is lower even with increasing concentration. This phenomenon could be explained bearing in mind that the size or area of the central cavity is small when compared to the size of the hCG (human Chorionic Gonadotropin) molecule.

We noticed that the solutions prepared with beta cyclodextrins have a greater tendency to complexes formation.

This behavior is noticed as long as the concentration of cyclodextrin is increased, but at the same time is limited, implying that there is an optimal concentration for the formation of an inclusion complex, which can be seen between 5 mg/ml and 8 mg/ml cyclodextrin.

The greater formation of complexes degree for the beta cyclodextrins is due to a larger volume or space in its central cavity that allows for greater inclusion of the molecule of hCG (human Chorionic Gonadotropin).

Therefore we concluded that the inclusion complexes hCG+CD′hCG*A/B/G−CD are feasible and that there is an optimal concentration which is in balance with complexed molecules or host, facilitating the stability and therapeutic activity of the formed complex.

The therapeutic activity of the hCG+cyclodextrin complex is evidenced by the modification of clinical parameters after its administration, demonstrated by the pertaining studies (see casuistry).

Problems with known treatments: for arterial hypertension, overweight disorders, type 2 diabetes or reactive hyperglycemias, hypertriglyceridemia or hypercholesterolemia clinical disorders, proposed treatments take into consideration different types of medications depending on the disease.

How this invention solves this problem: in our case the hCG+cyclodextrin complex is a unique medication that is offered as an alternative therapy. Furthermore, if We consider that currently only injectable pharmaceutical presentations of hCG are available, this invention possesses the following advantages:

1. Easy to administer.

2. Simplification of the medication election.

3. Possibility to administer hCG in an outpatient basis, at home, without having to attend a infirmary or health center to receive the intramuscular injection of the medication.

To summarize, the use of human Chorionic Gonadotropin complexed with cyclodextrins by oral administration presents undoubted advantages, providing the patient with the administration of medication by mouth and expanding its spectrum of clinical indications.

APPLICATION: Under medical supervision the patient is indicated to receive human Chorionic Gonadotropin complexed with cyclodextrin by oral route. Depending on the type of clinical indication, the daily doses of Gonadotropin are adjusted between 300 and 600 International Units per day (oral, retaining the solution of Gonadotropin for 1-2 minutes in the oral cavity to facilitate part of its absorption through the rich venous plexus of the oral mucosa, and then swallow) during the treatment period.

In cases of:

-
  - 1. Arterial hypertension.
  - 2. Overweight disorders.
  - 3. Type 2 diabetes or reactive hyperglycemia.

- 4. Hypertriglyceridemia.
- 5. Hypercholesterolemia

Also indicated is a very low calories diet (about 500 calories/day), hypolipidic, hypohydrocarbonated, and proteins provided by 200 grams of animal protein, plus a combination of carbohydrates and vegetables to complete the indicated calories.

Those pathologies that do not require a dietary procedure only contemplate the hCG+cyclodextrin complex administration for their treatment.

The treatments are carried out for a period of not less than one month and can be extended up to three months. After that period a resting period of one month is indicated, after which the procedure can be repeated again.

How it works: the combined treatment of hCG+cyclodextrin and its action in:

- 1. Adipose tissue, inhibiting lipogenesis.
- 2. In the hypothalamic region, improving the concentration of neuropeptides (endorphins).
- 3. In the cardiovascular system, on arterial hypertension.
- 4. In the carbohydrate metabolism, non insulin dependant diabetes.
- 5. In the cortex-diencephalic region, inhibiting the irritative neural circuits, thus acting in behavioral disorders such as anxiety, neurosis, irritative states, stress, chronic fatigue syndrome.
- 6. Intermediary metabolism, lipids metabolism, triglycerides and cholesterol.

Clinical Cases Description:

Case 1. EC (Graphics 9, 10, 11 and 12)

Female patient. 53 years old. Diagnosis: hypercholesterolemia, hyperinsulinemia, arterial hypertension. Overweight.

Treatment period using the hCG+cyclodextrin complex: 5 weeks. Significant reduction of weight and the rest of her clinical and laboratory parameters.

Case 2. GB (Graphics 13, 14, 15 and 16)

Male patient. 30 years old. Diagnosis: insulin resistance syndrome, fatty liver, non-insulin dependent diabetes and overweight.

Significant improvement in his clinical and laboratory parameters after five treatment weeks with the hCG+cyclodextrin complex.

Case 3. AH (Graphics 17, 18, 19, 20 and 21).

1. 54 years old patient. Female. Diagnosis: insulin resistance syndrome. Hyperglycemia. Fatty liver. Abdominal obesity

Significant improvement in her clinical and laboratory parameters after 5 treatment weeks with the oral hCG+cyclodextrin complex.

What is described and represented in the attached graphics and charts clearly highlights the functional and constructive advantages that characterize this invention and is considered an important advance in this technology, to which experts in this area may add many more, asking to include this invention in the pertaining law on this matter, requesting this law for protection according to the claims that follow:

Claims

1) “METHOD FOR OBTAINING THE HUMAN CHORIONIC GONADOTROPIN (HCG)/CYCLODEXTRIN COMPLEX TO BE ORALLY ADMINISTERED” characterized by the preparation of the hCG+cyclodextrin complex in an aqueous solution of cyclodextrin maintaining constant agitation and a given temperature until obtaining an homogeneous solution, subsequently pH is adjusted to the desired value and finally the solution is vacuum-filtered with 0.22 micron filters in order to maintain its sterility; preparing afterwards, under laminar flow conditions, the complexes' solutions.

2) “PRODUCT OBTAINED WITH THE HUMAN CHORIONIC GONADOTROPIN (HCG)/CYCLODEXTRIN METHOD” 1), characterized by a solution of hCG*CD complex whose concentrations and details are indicated in the subsequent tables 1 and 2: TABLE 1 Alfa cyclodextrin NaCl NaOH 0.1M or hCG (mg/ml) (mg/ml) H3PO4 1:5 (IU/ml) 2 9 cs ph 7 200 5 9 cs ph 7 200 8 9 cs ph 7 200 10 9 cs ph 7 200 TABLE 2 Beta cyclodextrin NaCl NaOH or H3PO4 hCG (mg/ml) (mg/ml) (mg/ml) (IU/ml) 2 9 cs ph 7 200 5 9 cs ph 7 200 8 9 cs ph 7 200 10 9 cs ph 7 200

3) “METHOD FOR OBTAINING THE HUMAN CHORIONIC GONADOTROPIN/CYCLODEXTRIN COMPLEX TO ADMINISTER BY ORAL ROUTE, PRODUCT OBTAINED BY THIS METHOD AND CLINICAL AND THERAPEUTICAL USE OF THE HUMAN CHORIONIC GONADOTROPIN (HCG)/CYCLODEXTRIN COMPLEX” as claimed in any of the previous claims characterized by being implemented under medical supervision, indicating the patient human Chorionic Gonadotropin (hCG) by oral administration, complexed with cyclodextrin, depending on the type of clinical indication the daily doses of Gonadotropin are adjusted from 300 to 600 International Units, oral, retaining the solution of gonadotropin for 1-2 minutes in the mouth before swallowing, to be administered during the treatment period.

FIG. 1

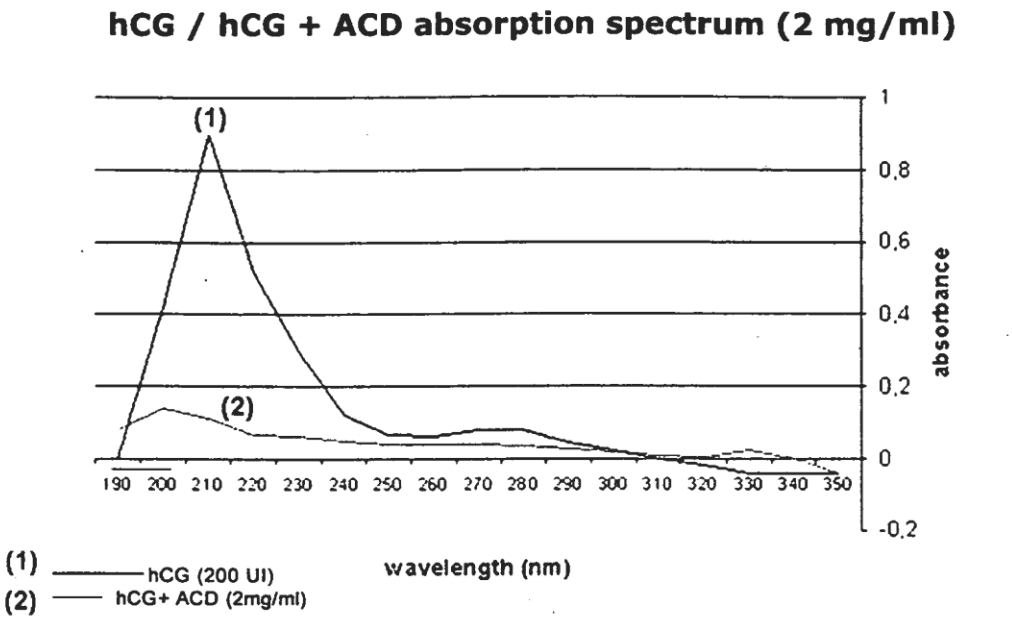

hCG / hCG + ACD absorption spectrum (2 mg/ml)
(1)
(2)
1
0,8
0,6
0,4
0,2
0
-0,2
absorbance
190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
wavelength (nm)
(1) hCG (200 UI)
(2) hCG+ ACD (2mg/ml)

FIG. 2

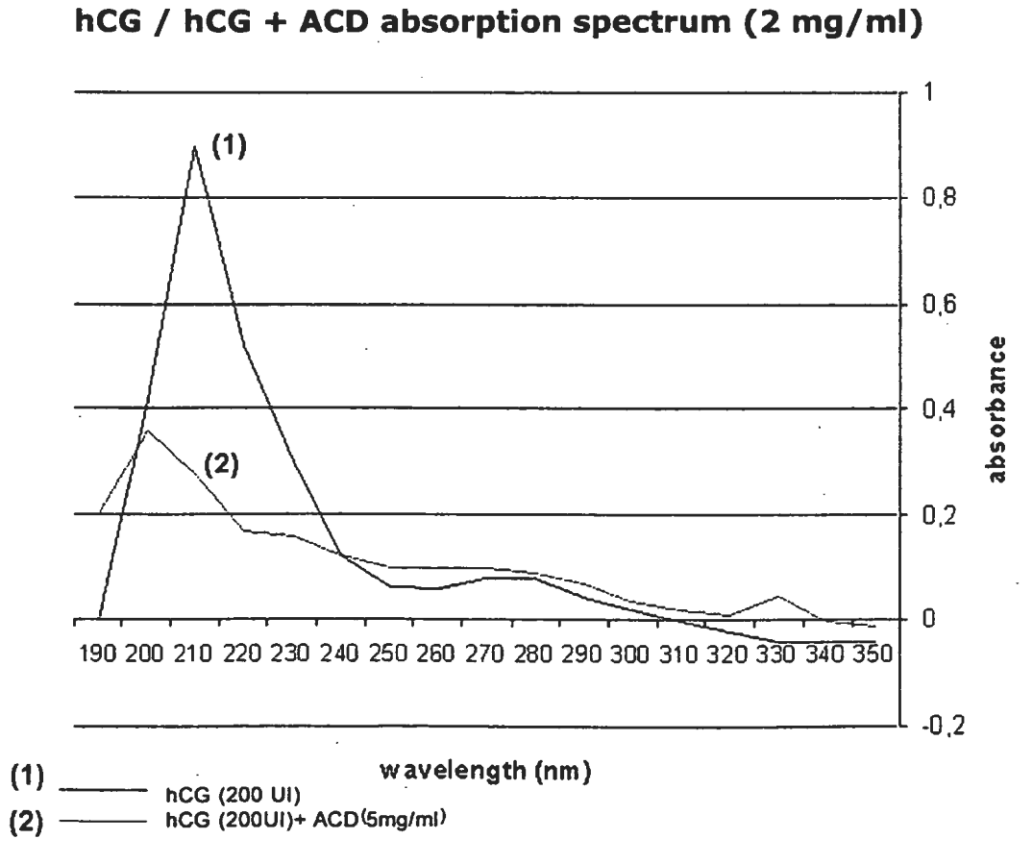
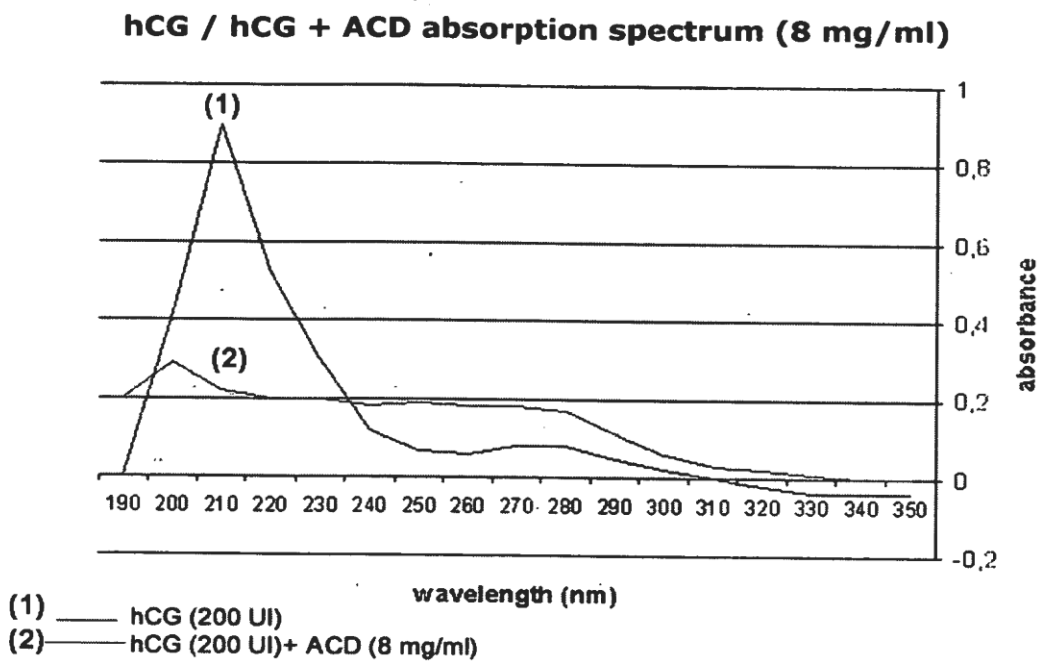
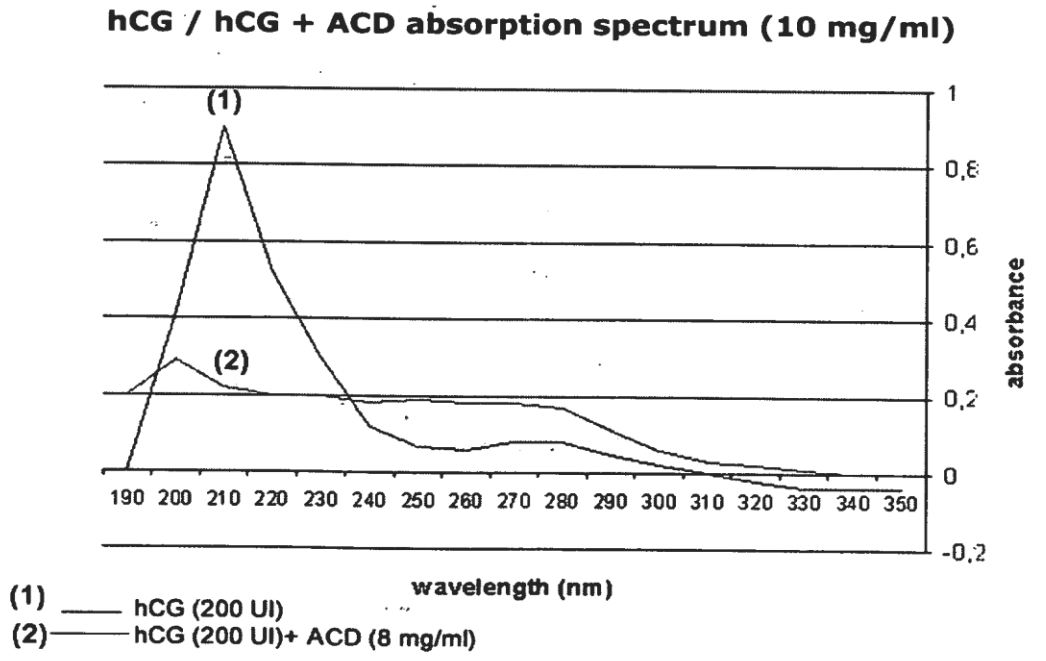

hCG / hCG + ACD absorption spectrum (2 mg/ml)
(1)
(2)
1
0,8
0,6
0,4
0,2
0
-0,2
absorbance
190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
wavelength (nm)
(1) hCG (200 UI)
(2) hCG (200UI)+ ACD(5mg/ml)

FIG. 3



(1) —— hCG (200 UI)
(2) —— hCG (200 UI)+ ACD (8 mg/ml)

FIG. 4



(1) —— hCG (200 UI)
(2) —— hCG (200 UI)+ ACD (8 mg/ml)

FIG. 5

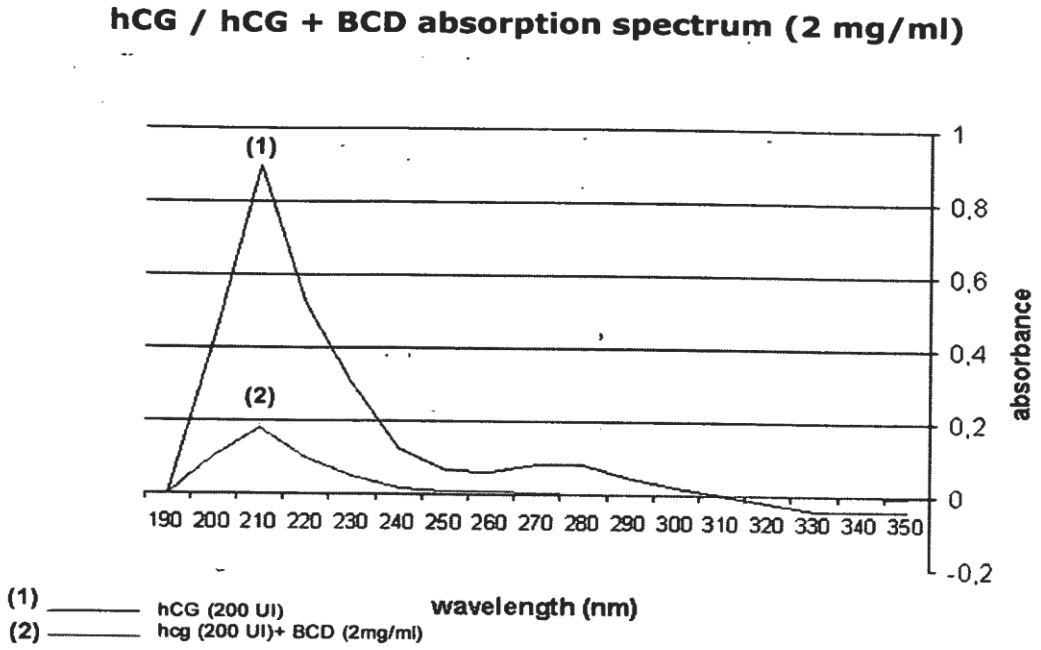

hCG / hCG + BCD absorption spectrum (2 mg/ml)
(1)
(2)
1
0,8
0,6
0,4
0,2
0
-0,2
absorbance
190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
wavelength (nm)
(1) hCG (200 UI)
(2) hcg (200 UI)+ BCD (2mg/ml)

FIG. 6

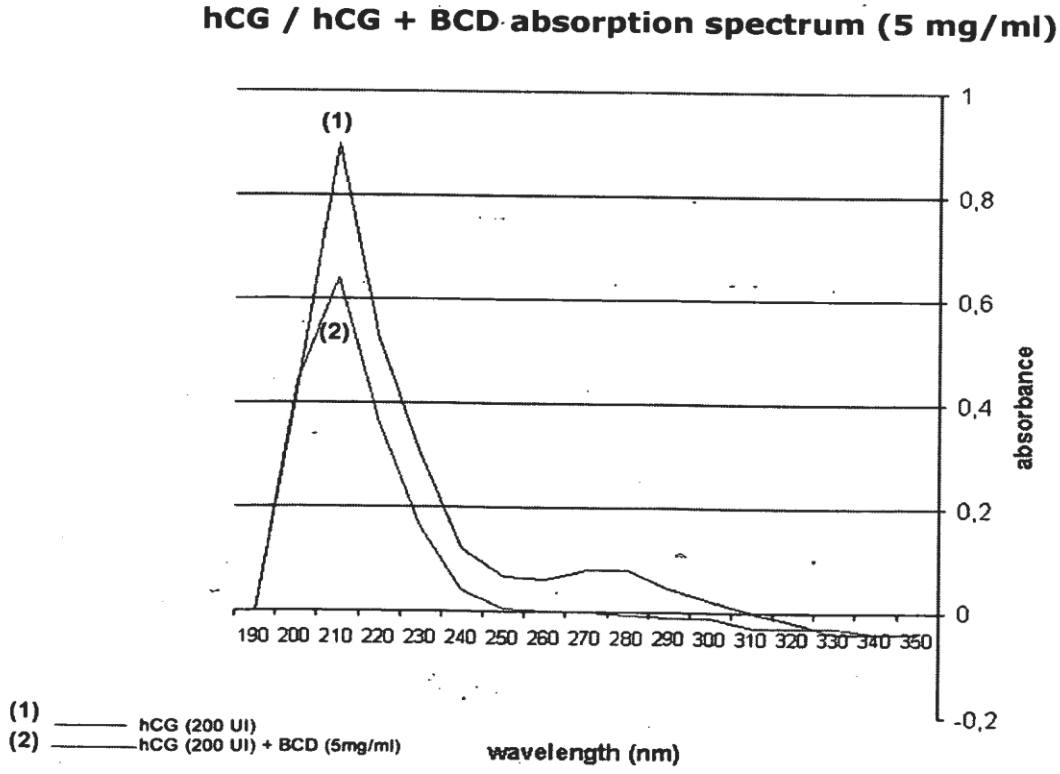

hCG / hCG + BCD absorption spectrum (5 mg/ml)
(1)
(2)
1
0,8
0,6
0,4
0,2
0
-0,2
absorbance
190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
wavelength (nm)
(1) hCG (200 UI)
(2) hCG (200 UI) + BCD (5mg/ml)

FIG. 7

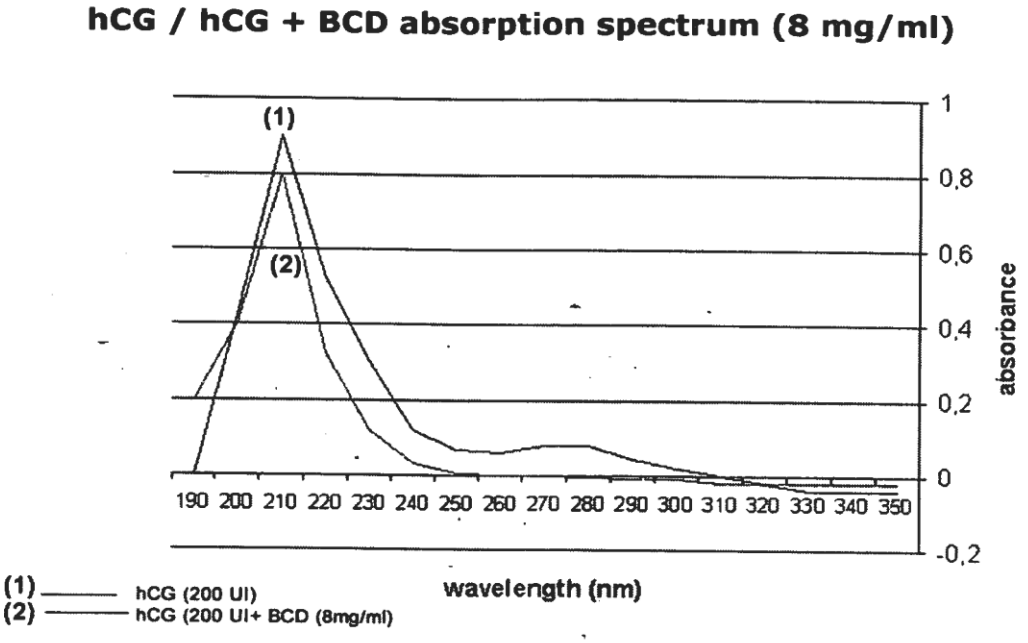

hCG / hCG + BCD absorption spectrum (8 mg/ml)
(1)
(2)
1
0,8
0,6
0,4
0,2
0
-0,2
absorbance
190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
wavelength (nm)
(1) hCG (200 UI)
(2) hCG (200 UI+ BCD (8mg/ml)

FIG. 8

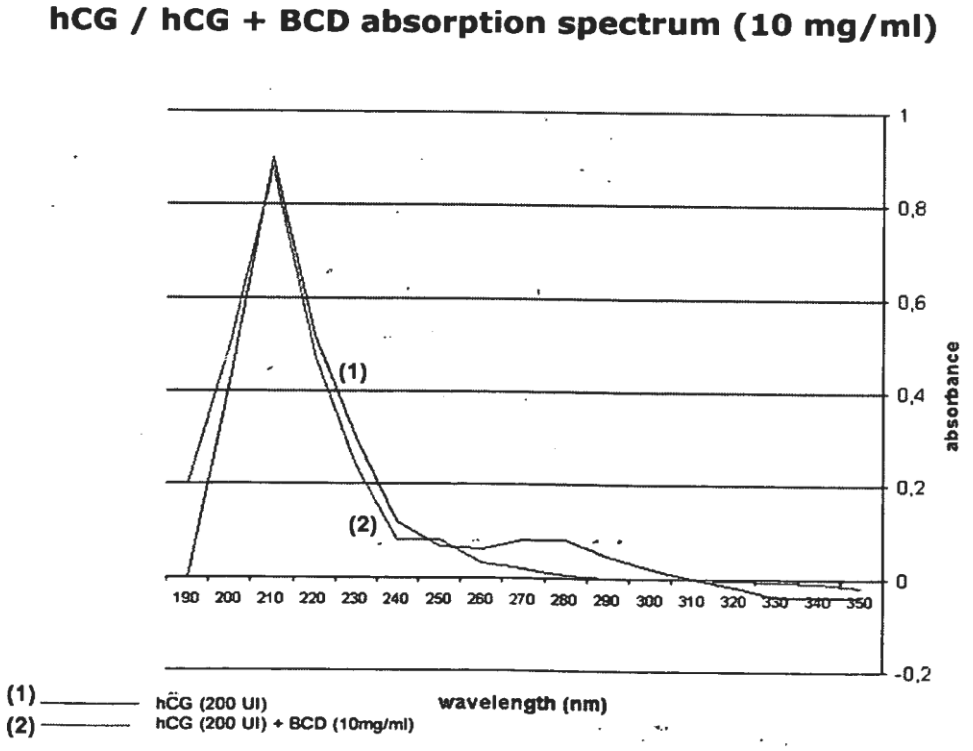

hCG / hCG + BCD absorption spectrum (10 mg/ml)
(1)
(2)
1
0,8
0,6
0,4
0,2
0
-0,2
absorbance
190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
wavelength (nm)
(1) hCG (200 UI)
(2) hCG (200 UI) + BCD (10mg/ml)

FIG. 9

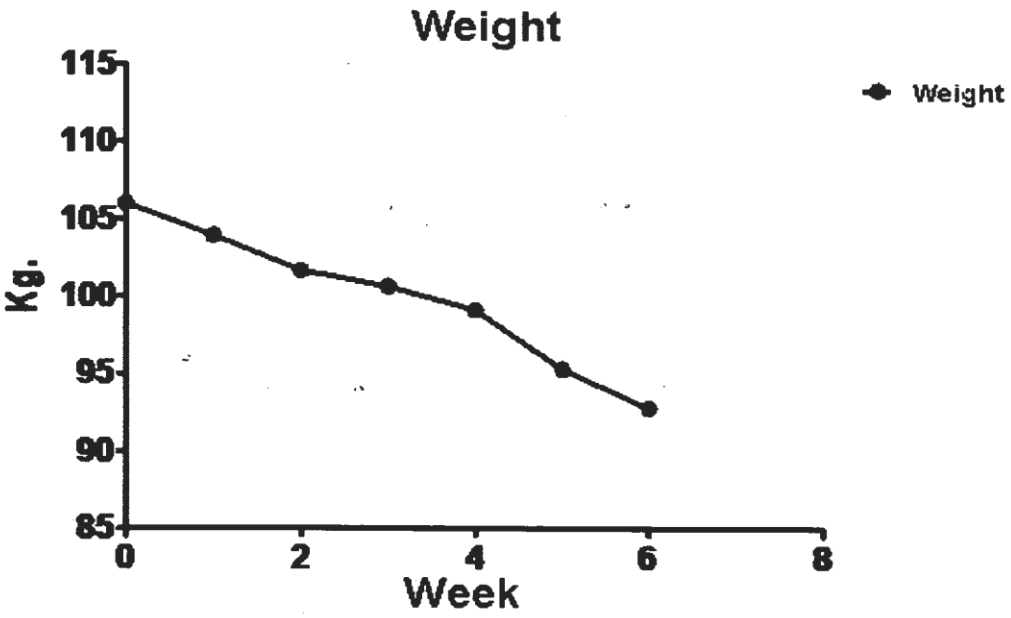

Weight
Weight
115
110
105
100
95
90
85
Kg.
0
2
4
6
8
Week

FIG. 10

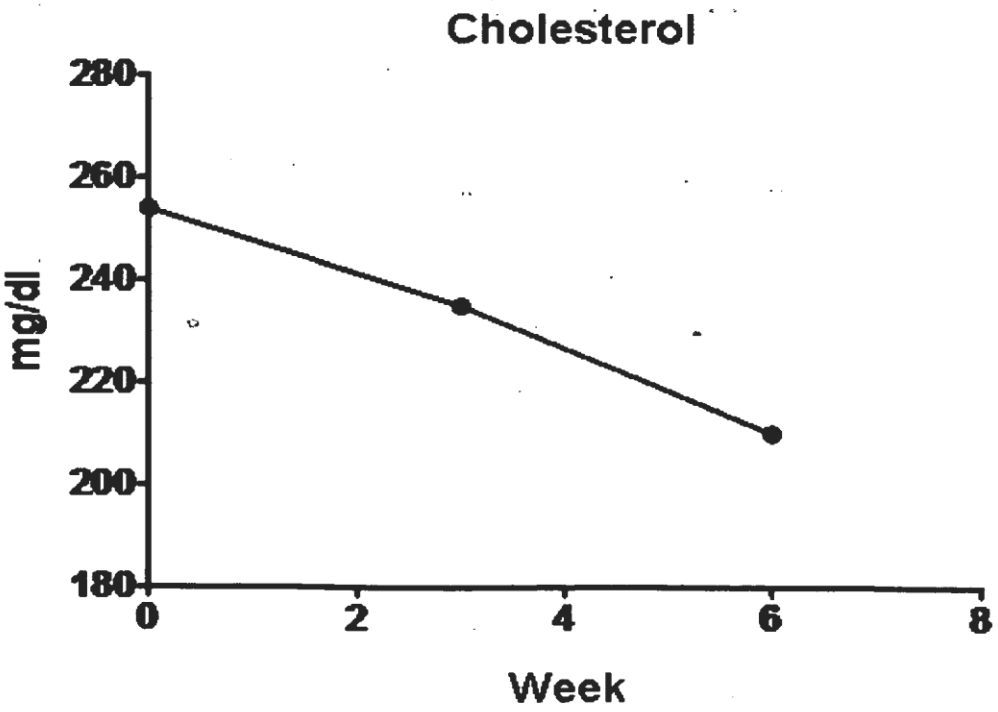

Cholesterol
280
260
240
220
200
180
mg/dl
0
2
4
6
8
Week

FIG. 11

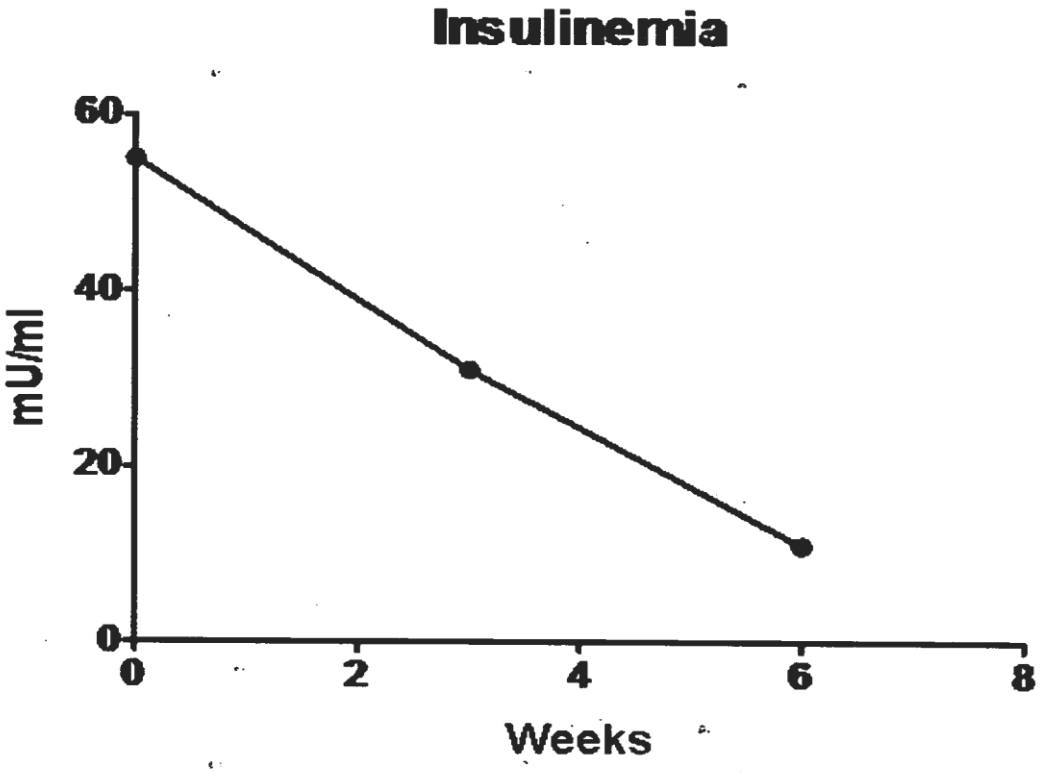

Insulinemia
60
40
20
0
mU/ml
0
2
4
6
8
Weeks

FIG. 12

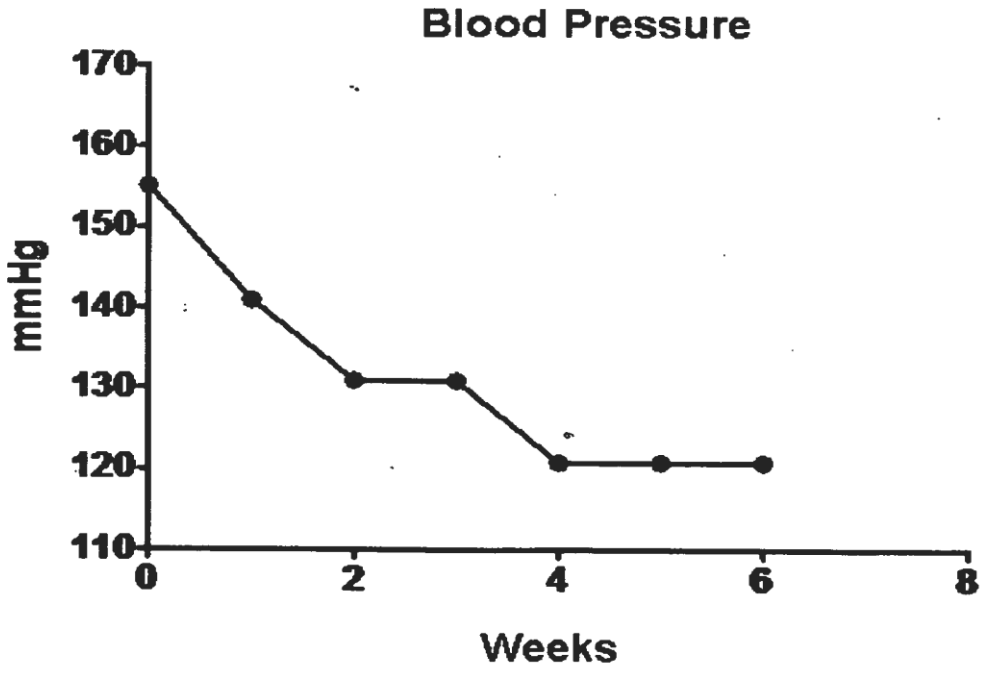

Blood Pressure
170
160
150
140
130
120
110
mmHg
0
2
4
6
8
Weeks

FIG. 13

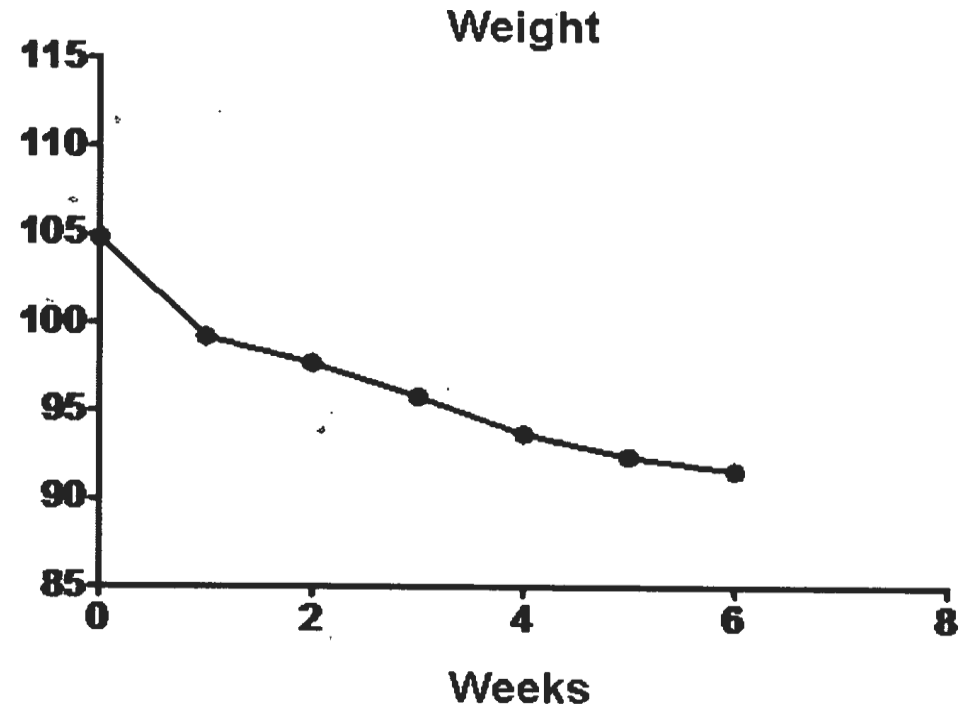

Weight
115
110
105
100
95
90
85
0
2
4
6
8
Weeks

FIG. 14

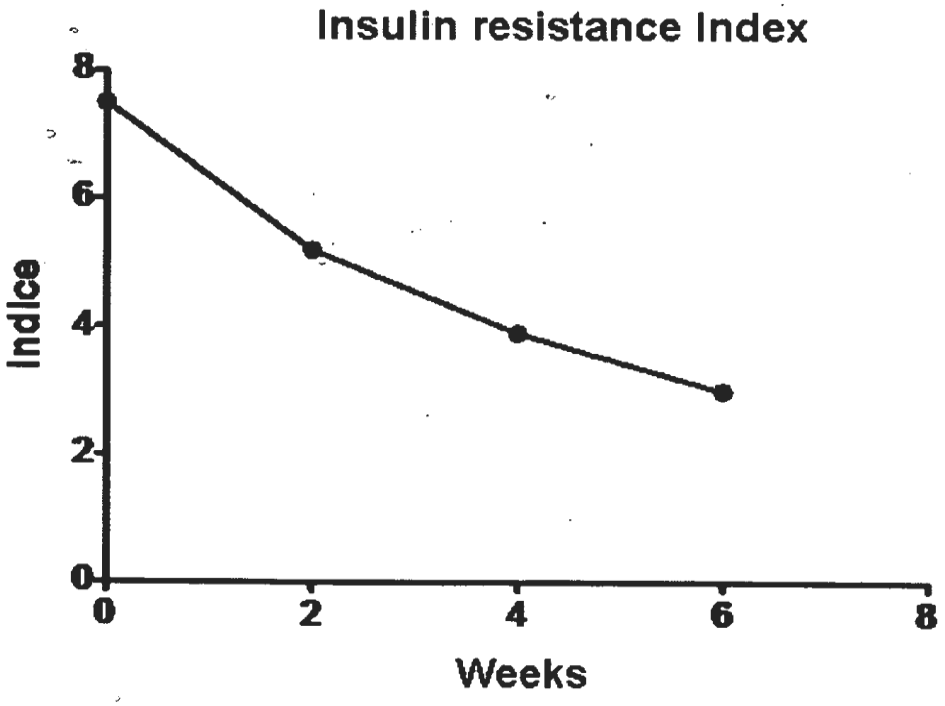

Insulin resistance Index
8
6
4
2
0
Indice
0
2
4
6
8
Weeks

FIG. 15

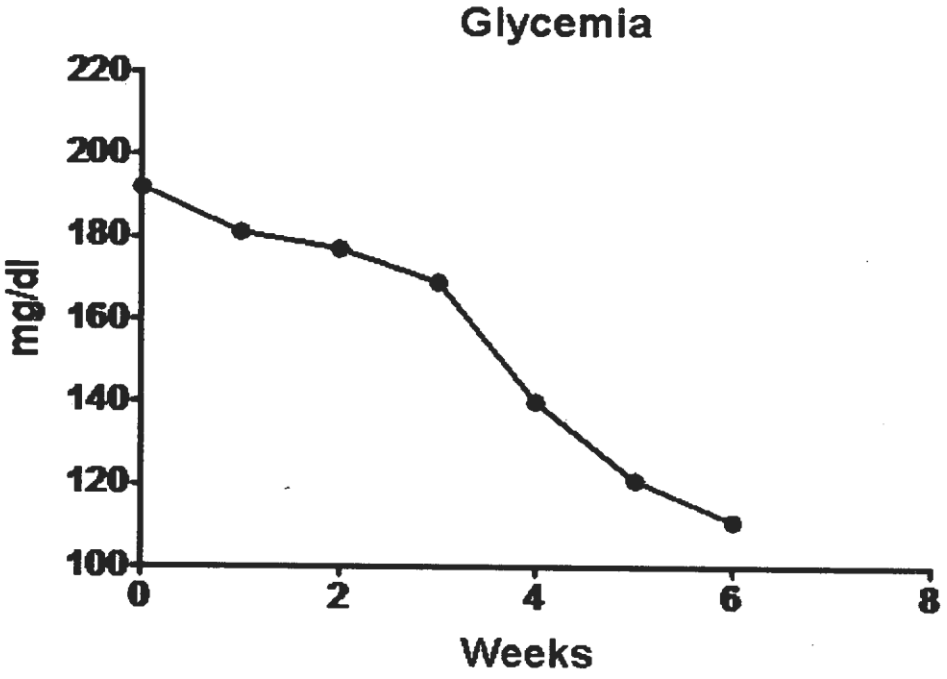

Glycemia
220
200
180
160
140
120
100
mg/dl
0
2
4
6
8
Weeks

FIG. 16

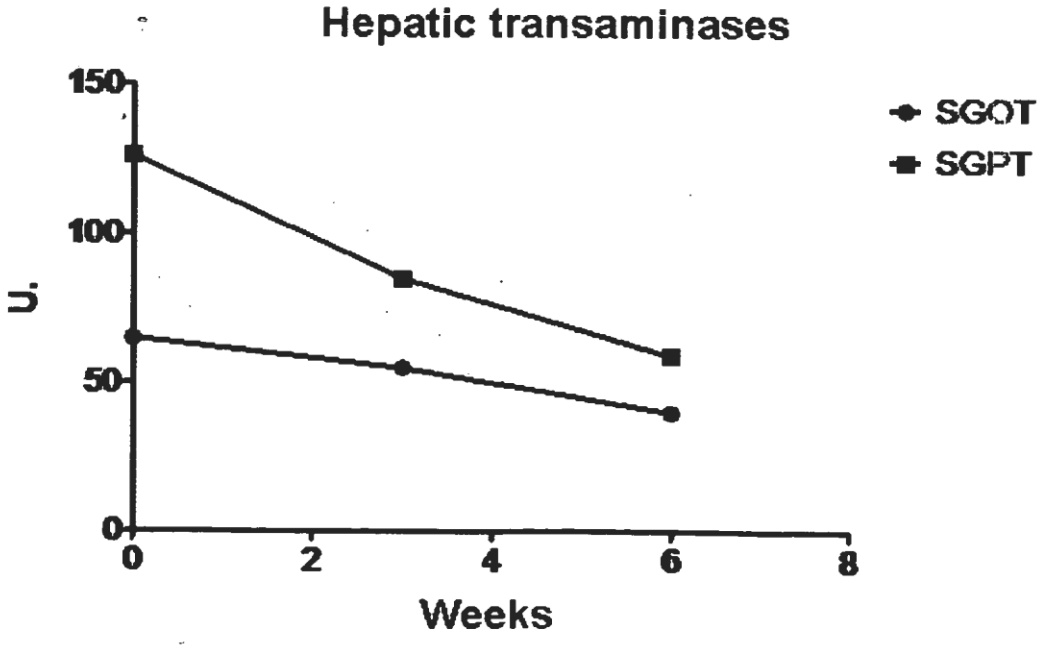

Hepatic transaminases
SGOT
SGPT
150
100
50
0
U.
0
2
4
6
8
Weeks

FIG. 17

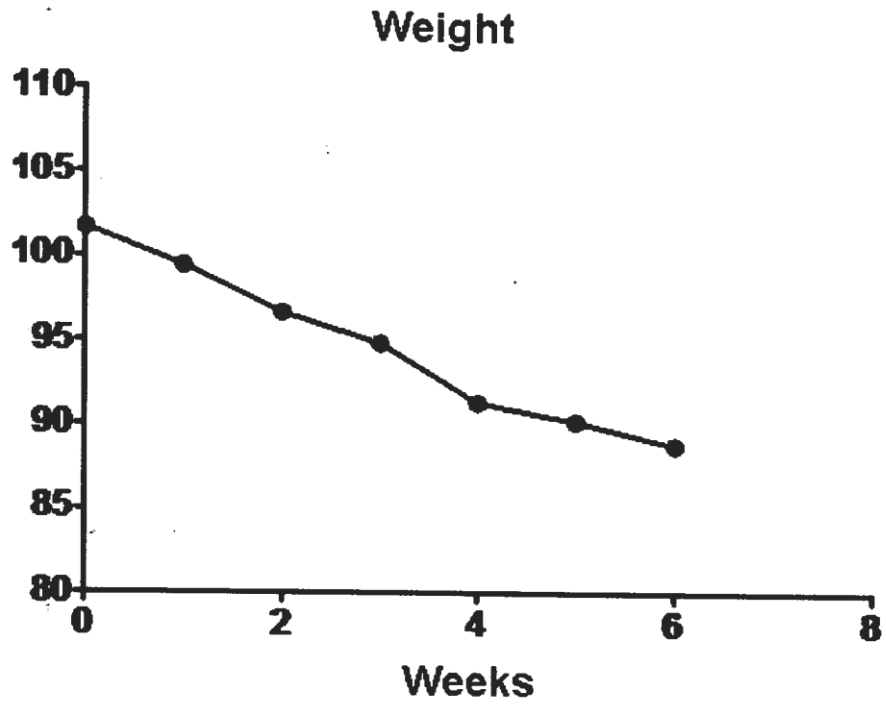

Weight
110
105
100
95
90
85
80
0
2
4
6
8
Weeks

FIG. 18

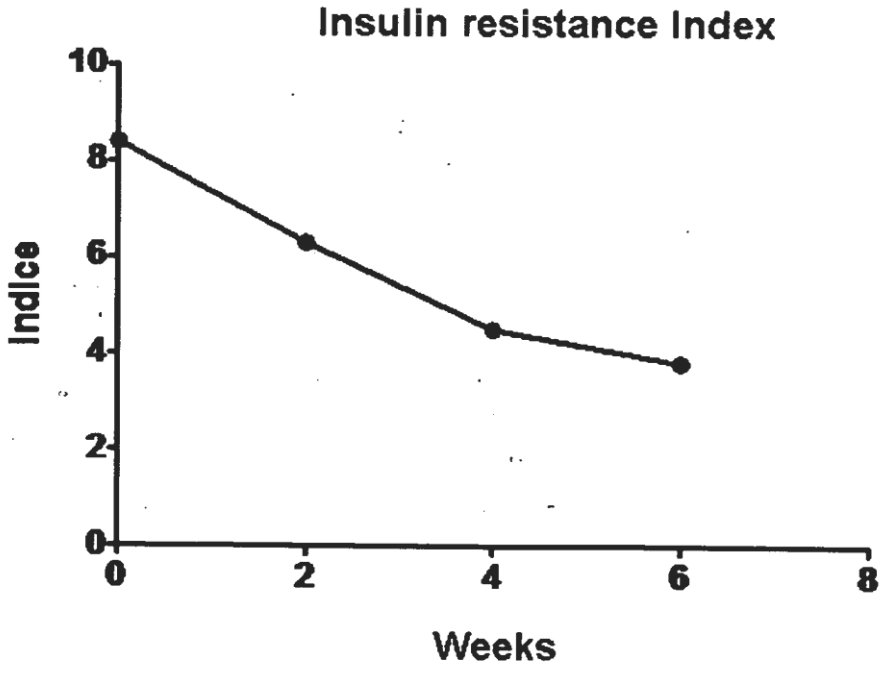

Insulin resistance Index
10
8
6
4
2
0
Indice
0
2
4
6
8
Weeks

FIG. 19

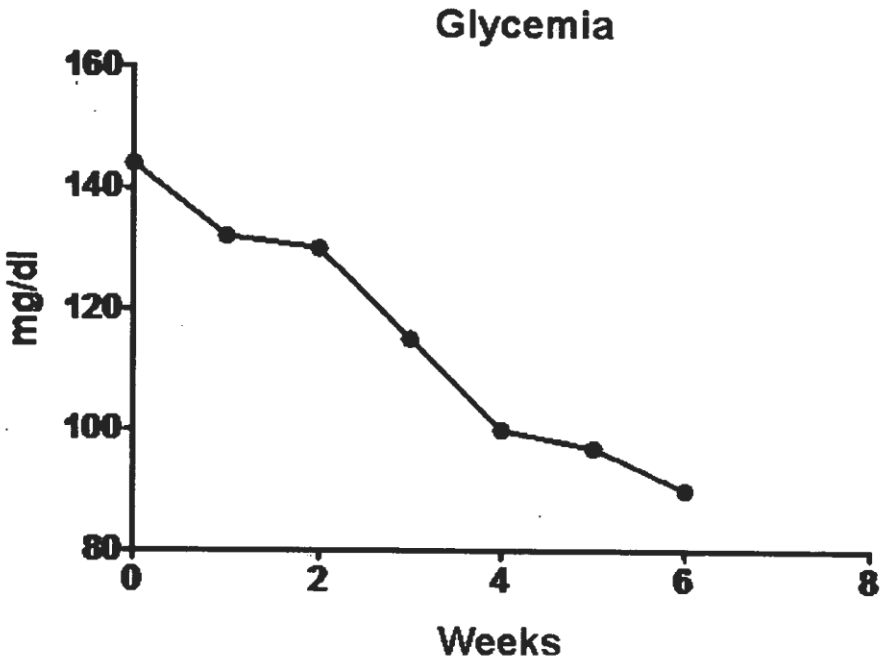

Glycemia
160
140
120
100
80
mg/dl
0
2
4
6
8
Weeks

FIG. 20

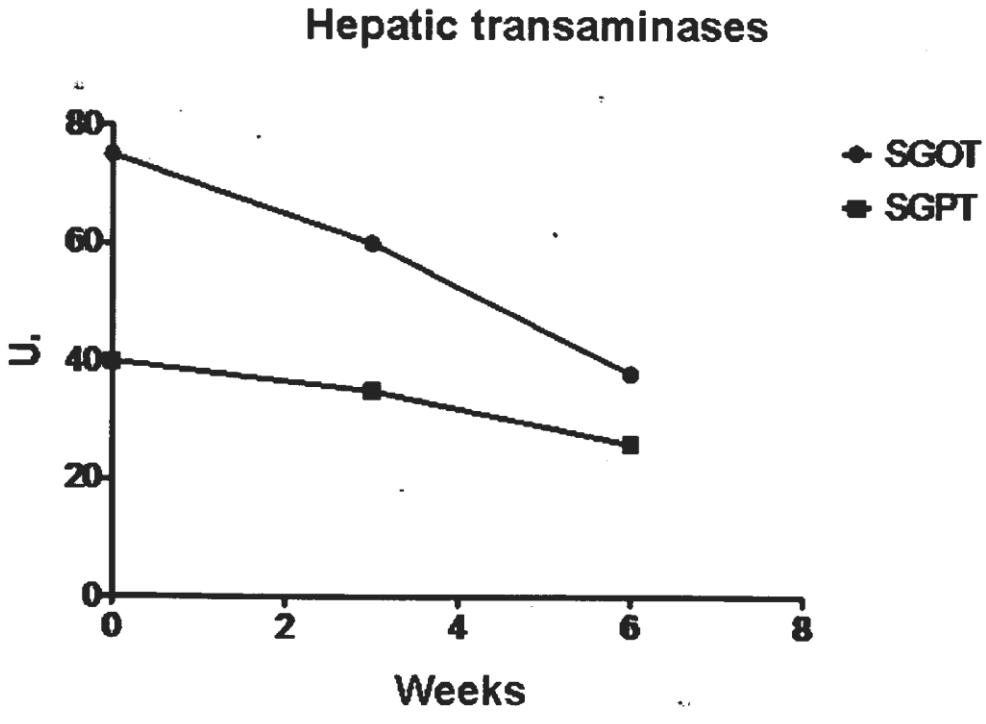
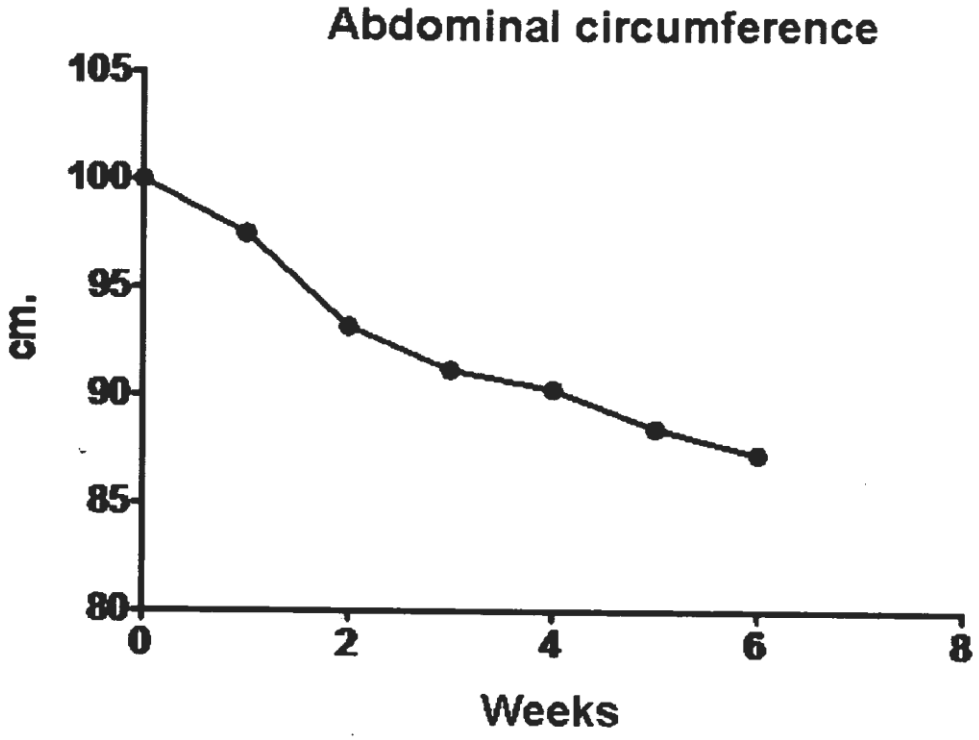

Hepatic transaminases
80
60
40
20
0
U.
0
2
4
6
8
Weeks
SGOT
SGPT

FIG. 21



Patent History

Application number: 20090176697
Type: Application
Filed: Dec 22, 2008
Issued: Jul 09, 2009
Assignees: (Capital Federal), (Capital Federal)
Inventors: Daniel Oscar Belluscio (Capital Federal), Sergio Ariel Vaney (Capital Federal)
Application Serial: 12/318,073

Classifications

Current U.S. Class: **514/8**
International Classification: A61K 38/24 (20060101); A61P 3/04 (20060101); A61P 3/10 (20060101);
http://patents.justia.com/patent/20090176697

13. Use of human chorionic gonadotropin oral or injectable for metabolic syndrome treatment (2008).

Use of human chorionic gonadotropin oral or injectable for metabolic syndrome treatment

Belluscio, Daniel Oscar. "Use of human chorionic gonadotropin oral or injectable for metabolic syndrome treatment." U.S. Patent Application 12/314,719, filed December 16, 2008.

Dec 16, 2008

To be used as a therapy for patients with one or more of the following clinical symptoms or laboratory findings: high blood pressure, diabetes type 2, reactive hyperglycemia, plasmatic hypertriglyceridemia, hypercholesterolemia and gout as part of the metabolic syndrome.

Skip to: Description Claims Patent History Patent History

Description

DETAILED DESCRIPTION OF INVENTION

This invention relates to “THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME”. The use of Human Chorionic Gonadotropin oral or injectable for the treatment of metabolic syndrome.

SCOPE

To be used as a therapy for patients with one or more of the following clinical symptoms or laboratory findings: high blood pressure, diabetes type 2, reactive hyperglycemia, plasmatic hypertriglyceridemia, hypercholesterolemia, and gout as part of the metabolic syndrome.

CURRENT TECHNIQUE

Metabolic Syndrome (MS), also known as plurimetabolic syndrome, insulin-resistant syndrome or syndrome X, is a clinical entity which, with broad phenotypic variations, is suffered by individuals with endogenous predisposition. to it as genetically determined and conditioned by environmental factors.

Typically, it shows insulin resistance and compensatory hyperinsulinemia associated with hydrocarbonated metabolic disorders, high blood pressure, lipid alterations (hypertriglyceridemia, decreased HDLC, the presence of LDL type-B, increased free fatty acids and postprandial lipemia) and obesity, resulting in an increase in morbidity and mortality due to atherosclerosis.

There are other factors associated with MS:

- hyperuricemia or gout;
- Thrombophilia and fibrinolysis defects;
- Hyperleptinemia or leptin resistance; and also: homocysteine (controversial role in IR), leukocytosis, increased GSR, increased PAI-1, hyperandrogenism,

fatty liver, gallstones, osteoporosis, Acanthosis Nigricans, and polycystic ovary syndrome.

Many cases evidence that diabetes mellitus (DM) is potentially more frequent in MS patients (A).

MS is the aggregate of the most dangerous heart-risk factors, i.e., diabetes and pre-diabetes, abdominal obesity, changes in cholesterol rate and high blood pressure.

Although 80% of the nearly 200 million diabetic adults worldwide will die due to heart disease, MS subjects are also in a greater-risk sage and are twice as potential sufferers of heart arrest or heart attack as the rest of the persons who do not suffer this syndrome.

Due to this fact, MS and diabetes are ranked above AIDS/HIV with relation to mortality and morbidity, even though it has not the same level of recognition as the latter.

MS persons have five times more probabilities to develop diabetes 2 (unless they have it already).

This the real aggregate of the additional risk factors expected from each of the components (ex., the appearance of high levels of triglycerides on cholesterol test).

From a practical and essentially medical perspective, the parameters proposed above are the most extended for MS identification, as shown in the following table in a simple way:

Men Women Abdominal obesity (waist >102 cm >88 cm circumference) Triglycerides ≧150 mg/dl ≧150 mg/dl Hypercholesterolemia <40 mg/dl <50 mg/dl Blood pressure ≧130/≧85 mmHg ≧130/≧85 mmHg Fast glycemia ≧110 mg/dl ≧110 mg/dl

Diagnosis is established where three or more of the risk determinants above are present.

Forty percent of population at large may be prone to IR.

MS affects 42% of women and 64% of men who are glucose-intolerant, and 78% of women and 84% of men with DM2.

MS triples the risk for heart disease (up to 80% MS patients die because of complications of heart disease).

MS is also associated with global increase in mortality for any cause.

RELEVANCE IN ARGENTINA

According to studies performed, MS relevance is high, with percentages of about 30% of population at large.

With relation to the different definition criteria mentioned above, MS prevalence was 34.9%, 27.2% and 25.6%, respectively, and more frequent in men than women—39.2% vs. 29.0%—respectively.

MS prevalence increased with age, but there were no significant differences between men and women from 60 to 65 years old (39.2% increase in men and 39.1% in women).

Once adjustments were made according to age, sex, physical activities, history of diabetes and menopausia, low-education level subjects had 54% higher risk for MS and 44% higher risk for "hypertriglyceridemic waist" (defined as simultaneous presence of central obesity [in this paper determined under IDF criterion] and triglycerides >150 mg/dl) compared to high-education level subjects.

MS high prevalence levels show the importance of detection and treatment. Low education level was an independent predictor, and this social class should have a priority concerning heart disease and diabetes prevention.

PREDICTION OF MS EVOLUTION

Average follow up for 8.9 years showed that mortality due to heart disease increased separately in 45% of men and 73% of women with MS. MS total mortality relative risk was 27% in men and 25% in women. Therefore, there is an urgent need to use medical treatment to improve life quality in these patients.

PROBLEM TO BE SOLVED

Regarding treatment, currently there are no alternatives providing for the management of MS patients with a single medicine.

THIS INVENTION CAN SOLVE THE PROBLEM

The new application of Human Chorionic Gonadotropin as established on this invention is highly relevant since it enables the improvement of several clinical parameters through a single therapeutic alternative.

ADVANTAGES

The use of Human Chorionic Gonadotropin oral or for injectable together with a very low-calorie diet for a short period for the treatment of MS under a precise control and follow-up protocol allows simultaneous treatment of the following symptoms:

- 1) Hyperglycemia
- 2) Hypertension
- 3) Hypertriglyceridemia
- 4) Abdominal obesity
- 5) Sleep apnea that is frequently found as part of the MS

DESCRIPTION OF INVENTION

"THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME" under clinical control, wherein patients are administered Chorionic Gonadotropin (hCG) orally or by injection.

Daily doses of Gonadotropin are adjusted depending on the type of overweight to 300-600 International Units per day (for oral administration, patients maintain Gonadotropin solution

for 1-2 minutes in their mouth for an easier absorption by the rich venous plexus of the mouth, and then swallow it) or 100-300 IU (by IM injection) during the whole treatment period.

Moreover, patients have to follow a very low-calorie diet (about 500 Kcal/day) that is also low-fat, hypohydrocarbonate and normoproteic and provides 200 gr of animal protein plus a combination of vegetables and carbohydrates up to completion of the necessary calories.

The treatment takes at least one month and can be extended up to two months. Then there follows a one-month period to maintain weight, after which the treatment can be repeated.

No hCG treatment is followed at intervals, but a usual hypohydrocarbonate diet is prescribed.

A combined therapy of hCG+very low-calorie diet, due to its action on fatty tissue inhibiting its synthesis, and due to its action on the hypothalamus, results in:

1. Constant hyperglycemia during the treatment period.

2. Fast improvement of hypertriglyceridemia.

3. Reduction of cholesterol high levels.

4. Stabilization of blood pressure to normal or acceptable levels.

5. Marked reduction of total fat mass.

6. A feeling of well being during the treatment period.

7. Reduction of abdominal diameter.

The advantages of this invention, which should not be limited to the brief description above, will become more apparent and the invention itself better understood by reference to the following cases of patients treated using the method described above, a conclusion of the treatment, and the figures of comparative tables showing body weight evolution, abdomen measurement and glycemia tests.

(FIGS. 1, **2**, **3**, **4**, **5**, **6**, **7**, **8** and **9**).

⊙Patient AB (FIGS. 1, **2** and **3**)

Male aged 38 years, with the following MS parameters:

- Weight: 115.700 Kg
- Height: 1.74 cm
- Abdominal obesity (waist circumference): 122 cm
- Triglycerides: 250 mg/dl
- HDLC: 38 mg/dl
- Blood pressure: 140-90 mmHg (administered with antihypertensive medication)
- Fast glycemia: 184 mg/dl (administered with oral antidiabetic medication)

⊙Patient AF (FIGS. 4, **5** and **6**)

Male aged 59 years, with the following MS parameters:

- Weight: 114.800 Kg
- Height: 1.86 cm
- Abdominal obesity (waist circumference): 132 cm
- Triglycerides: 313 mg/dl
- HDLC: 32 mg/dl
- Blood pressure: 160-100 mmHg (administered with antihypertensive medication)
- Fast glycemia: 255 mg/dl (administered with oral antidiabetic medication)

⊙Patient LVM (FIGS. 7, **8** and **9**)

Female aged 60 years, with the following MS parameters:

- Weight: 93 Kg
- Height: 1.61 cm
- Abdominal obesity (waist circumference): 101 cm
- Triglycerides: 290 mg/dl
- HDLC: 43 mg/dl
- Blood pressure: 170-100 mmHg (administered with antihypertensive medication)
- Fast glycemia: 194 mg/dl (administered with oral antidiabetic medication)

The evolution of these patients during the treatment period with THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME is detailed below together with the Figures attached.

First patient:

Patient AB: male

Male aged 38 years, with the following MS parameters:

- Weight: 115.700 kg
- Height: 1.74 cm
- Abdominal obesity (waist circumference): 122 cm
- Triglycerides: 250 mg/dl
- HDLC: 38 mg/dl
- Blood pressure: 140-9 0 mmHg (administered with antihypertensive medication)
- Fast glycemia: 184 mg/dl (administered with oral antidiabetic medication)

Evolution of the different parameters:

-
  - 1. Body weight in Kg. (FIG. 1)
  - 2. Abdominal circumference in cm. (FIG. 2)
  - 3. Glycemia in mg/dl (FIG. 3)

Second patient:

Patient AF: Male aged 59 years

- Weight: 114.800 kg Height: 1.86 cm
- Abdominal obesity (waist circumference): 132 cm
- Triglycerides: 313 mg/dl
- HDLC: 32 mg/dl
- Blood pressure: 160-100 mmHg (administered with antihypertensive medication)
- Fast glycemia: 255 mg/dl (administered with oral antidiabetic medication)

Evolution of the different parameters:

-
  - 1. Body weight in Kg (FIG. 4)
  - 2. Abdominal circumference in cm (FIG. 5)
  - 3. Glycemia in mg/dl (FIG. 6)

Third patient:

Patient LVM: Female aged 60 years

- Weight: 93 Kg
- Height: 1.61 cm
- Abdominal obesity (waist circumference): 101 cm
- Triglycerides: 290 mg/dl
- HDLC: 43 mg/dl
- Blood pressure: 170-100 mmHg (administered with antihypertensive medication)

Fast glycemia: 194 mg/dl (administered with oral antidiabetic medication)

Evolution of the different parameters:

-
  - 1. Abdominal circumference in cm (FIG. 7)
  - 2. Body weight in Kg. (FIG. 8)
  - 3. Glycemia in mg/dl (FIG. 9)

The advantages of this invention are plain from the description above as well as the images included, showing clear functional advantages of the product, characterizing the invention and representing a beneficial technological improvement that warrants the inclusion of the invention in the law with the pertinent legal protection as per the appended claims.

Claims

1. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME characterized by administration of Human Chorionic Gonadotropin (hCG) in patients with Metabolic Syndrome, in a range of 300-600 International Units daily by oral route, or 100-300 International Units daily by injection during the treatment period.

2. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME of claim 1, characterized by administration of Human Chorionic Gonadotropin (hCG) for the treatment of high blood pressure.

3. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME of claim 1, characterized by administration of Human Chorionic Gonadotropin (hCG) for the improvement of clinical and laboratory findings of diabetes type 2 or of reactive hyperglycemias.

4. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME of claim 1, characterized by administration of Human Chorionic Gonadotropin (hCG) as a hypolipemic agent and hypotriglyceride activity inducer.

5. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME of claim 1, characterized by administration of Human Chorionic Gonadotropin (hCG) as a hypocholesterolemic agent.

6. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME of claim 1, characterized by administration of Human Chorionic Gonadotropin (hCG) as a coadyuvant therapeutic agent for the treatment of gout clinical symptoms.

7. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME of claim 1, characterized by administration of Human Chorionic Gonadotropin (hCG) as a therapeutic agent for the treatment of overweight.

8. THE USE OF HUMAN CHORIONIC GONADOTROPIN ORAL OR INJECTABLE FOR THE TREATMENT OF METABOLIC SYNDROME of claim 1, characterized by administration of Human Chorionic Gonadotropin (hCG) as a therapeutic agent for patients' general condition and for the achievement of a feeling of well being during the treatment period.

Patent History

Application number: 20090156468
Type: Application
Filed: Dec 16, 2008
Issued: Jun 18, 2009
Assignee: (Capital Federal)
Inventor: Daniel Oscar Belluscio (Capital Federal)
Application Serial: 12/314,719

Classifications

Current U.S. Class: **514/8**
International Classification: A61K 38/16 (20060101);

14. Human chorionic gonadotropin (HCG) orally or for injection for the treatment of mood disorders and alcoholism (2008).

Use of human chorionic gonadotropin (HCG) orally or for injection for the treatment of mood disorders and alcoholism

Jan 14, 2008

A new use of Human Chorionic Gonadotropin (HCG) diluted as previously established for the treatment of mood disorders and alcoholism. The substance Human Chorionic Gonadotropin (HCG) to be used as medical therapy for effective treatment of mood disorders as well as highly effective treatment of alcoholism.

Skip to: Description Claims Patent History Patent History

Description

DETAILED DESCRIPTION OF INVENTION

This invention relates to "THE USE OF HUMAN CHORIONIC GONADOTROPIN (HCG) ORALLY OR FOR INJECTION FOR THE TREATMENT OF MOOD DISORDERS AND ALCOHOLISM."

SCOPE

The substance Human Chorionic Gonadotropin (HCG) to be used as medical therapy for effective treatment of mood disorders as well as highly effective treatment of alcoholism.

PREVIOUS ART

Current Technique

Human Chorionic Gonadotropin (HCG) was found and described for the first time in pregnant women's urine by Ascheim and Zondek, about 1927. It was later found that this substance is produced in human placenta. Since it was discovered in 1927, it was recommended for countless uses. At present, it is mostly prescribed for fertility problems and cryptorchidism (failure of both testicles to descend in children). HCG is currently supplied as a lyophilized substance for injection. Material is drawn from pregnant women's urine. It is available from several international pharmaceutical laboratories.

PROBLEM TO BE SOLVED

About 1954 an English investigator published a paper containing his own experience with this substance in the treatment of obesity. The paper was welcomed and accepted by scientists generally until 1974-75, when the method became obsolete.

The method provided by the investigator abovementioned had several problems: it was for injection, caused immunity after treatments longer than six weeks, had some secondary effects, such as fluid retention, and so on.

THIS INVENTION CAN SOLVE THE PROBLEM

This invention aims to demonstrate that an HCG preparation for oral administration or for injection used either as a simple dilution or coupled to albumin or a cyclodextrin can be therapeutically effective in the treatment of mood disorders including (but not limited to) neurosis, irritability, depressive states, borderline states, and so on.

HCG preparation as above described is also effective in the treatment of all types of alcoholism.

ADVANTAGES

HCG oral preparation provides the same therapeutic effects as the psychotropics commonly used in the treatment of the disorders as described above, but does not have the same technical and pharmacologic problems as such drugs.

Moreover, it is an alternative to be considered in the cases of alcoholism since there is no effective treatment for this condition yet.

The preparation can be used for longer periods without secondary effects.

DESCRIPTION OF INVENTION

The standard lyophilised preparation supplied by pharmaceutical laboratories is used for HCG preparations. Originally, HCG is supplied as a lyophilised powder containing 2,000 to 10,000 International Units (IU) of HCG per vial. IU concept stands for an agreement whereby each IU represents the quantity that is adequate to cause maturity of an egg in experimental animals.

For the purposes of this invention, HCG is dissolved in 1% physiological saline with or without addition of human albumin or different buffers, to be administered as an injection or orally, placing it under the tongue and maintaining it there for an easier absorption by the rich sublingual venous plexus.

Dilutions are prepared in such a way that each cubic centimeter of diluted HCG corresponds to a certain quantity expressed as IU.

Once solution has been prepared in sterile conditions, it can be stored in the refrigerator for periods of 4 to 7 days. This period of time can be extended (7-10 days) if the solution is stored under cold chain conditions.

Once the solution has been absorbed by the sublingual mucosa, a fraction of HCG is absorbed and carried into the circulation until it reaches the regulation centers of hypothalamic region, which contain appetite and satiation centers and fatty tissue metabolism.

APPLICATION EXAMPLES

Oral administration is more advantageous than injections one since it is easier to administer and equally effective. Since treatment is innocuous, it can be used for several months without problems and with equally effective results.

The Following Study was Conducted in Order to Validate 105 Obtained Clinical Results:

Seventy (70) women were screened (double blind study was conducted at site Gynecology Section). After signing the required consent, they were divided into two groups: Group A received saline alone, whereas Group B received two different concentrations of HCG. The study was designed based on double blind study methods: neither the volunteers nor the staff knew who received placebo and who belonged to the HCG-administered group.

The numbers assigned to each volunteer showed the type of substance (placebo or HCG) to be administered. The envelopes containing the codes were opened at the end of the study.

Determinations

The following tests were carried out during the study:

A—Laboratory studies (Day 0), and after the study.
B—Irritability test during treatment, which was evaluated through a questionnaire to be completed by patients once a week, including Hamilton test for depression and questionnaire for mood disorder evaluation.

All evaluations were performed by the same observer throughout the treatment period in order to avoid observation differences due to different observers performing evaluations.

Study Period

Study period was five weeks, at the end of which the envelope containing the codes for each patient was opened, and the data obtained were used for statistical studies (regression and variance studies).

Data Analysis

The following studies were performed:

Data were entered in a database and compiled in ASCII format.

Frequency, media, standard deviation and standard error analyses were conducted. Variance, co-variance and multiple regression analyses were conducted.

Results

Volunteers completed a questionnaire concerning their mood during treatment.

The following statistical differences between both Groups were found:

HCG-administered patients felt better during study period ($p<0.03$ on the third week of treatment, and $p<0.01$ by the fifth week of treatment.) They had better and deeper sleep periods ($p<0.06$ on the third week of treatment.) They showed greater acceptance of points of view that were different from their own ($p<0.01$ on the fifth week of treatment.)

They were less irritable ($p<0.001$ from the fourth week of treatment.) They got less upset every time things were not as expected ($p<0.05$.)

They were less willing to argue for trifles ($p<0.05$.)

They were less inclined to argue loudly ($p<0.005$ on the fourth week of treatment.)

Results:

After four weeks' treatment 65% of the treated patients reported that they were in a better mood, less irritable, had longer and better sleep periods, had a tendency to avoid arguing for trifles, and their familiar relationships were more friendly.

On the other hand, the volunteers who had problems with excess of alcoholic drinks reported that they “did not feel like drinking”, even when they kept away from liquor and even when social pressure was usually very strong. Approximately 10% of the patients completely quit alcoholic drinks spontaneously during treatment.

Conclusions:

Mood disorders are a very common pathology in society nowadays, and the several treatments recommended are not always properly used for moderate to severe secondary effects.

The use of HCG has demonstrated efficacy in the treatment of mood disorders without revealing undesirable effects, as well as the capacity to be administered for long periods.

On the other hand, alcoholism is a serious social health problem for which there are no available therapeutic solutions. Since oral HCG has no secondary effects, its administration for the treatment of chronic alcoholism is an excellent and innocuous therapeutic aid.

The advantages of this invention, which are briefly described above, should not be limited to such description but added with additional contributions from users and experts in the art, and will become more apparent and better understood through the images of the tests performed, which are schematically shown below without references to scales, in the attached image wherein:

FIG. 1 is a chart of the tests performed showing patient's mood during treatment.

FIG. 2 is a chart of the tests performed showing irritability episodes.

FIG. 3 is a chart of the tests performed showing the arguments held during treatment.

The advantages of this invention are plain from the description above as well as the images included, showing clear functional advantages of the product, characterizing the invention and representing a beneficial technological improvement that warrants the inclusion of the invention in the law with the pertinent legal protection as per the appended claims.

Claims

1. “THE USE OF HUMAN CHORIONIC GONADOTROPIN (HCG) ORALLY OR FOR INJECTION FOR THE TREATMENT OF MOOD DISORDERS AND ALCOHOLISM” characterized by HUMAN CHORIONIC GONADOTROPIN (HCG) being diluted in physiological saline, with or without the addition of human albumin, or a cyclodextrin or different buffers, in a proportion of 1%, to be administered either by injecting it or orally, as a sublingual form, maintaining it there for an easier absorption by the sublingual venous plexus.

2. “THE USE OF HUMAN CHORIONIC GONADOTROPIN (HCG) ORALLY OR FOR INJECTION FOR THE TREATMENT OF MOOD DISORDERS AND ALCOHOLISM” of claim 1, characterized by the solution being prepared in such a way that each cubic centimeter of diluted HCG corresponds to a certain quantity expressed as international units.

3. “THE USE OF HUMAN CHORIONIC GONADOTROPIN (HCG) ORALLY OR FOR INJECTION FOR THE TREATMENT OF MOOD DISORDERS AND ALCOHOLISM” of any of the previous claims, characterized by preparation of the solution under sterile conditions and at cold temperature, and future distribution under cold conditions.

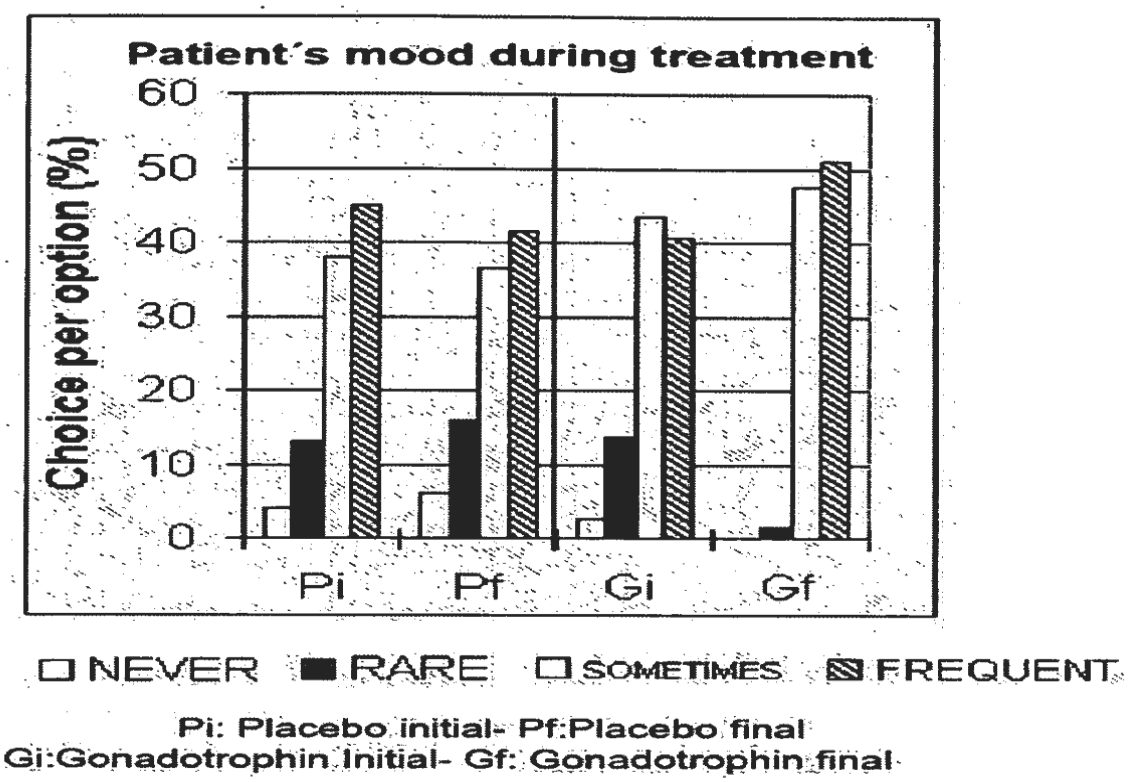
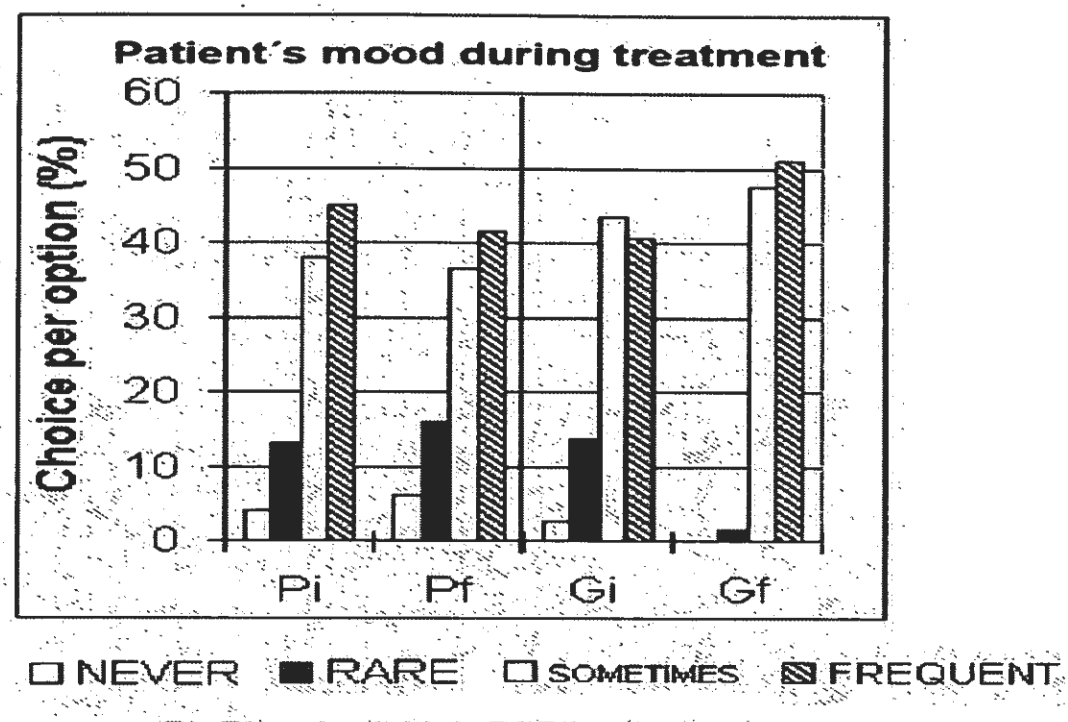
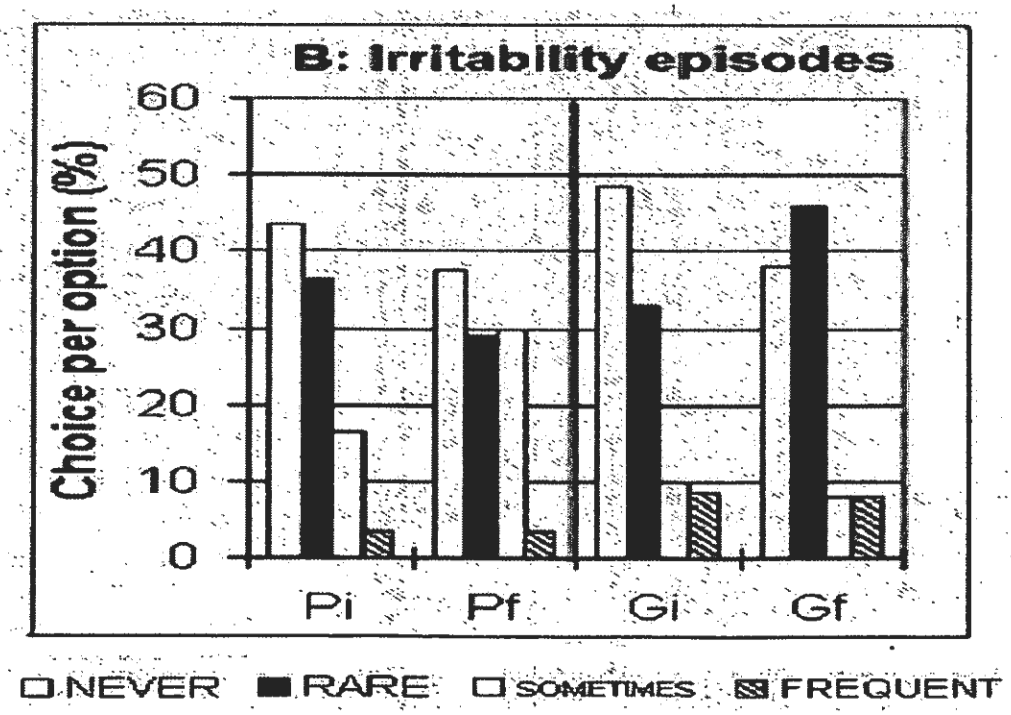


FIG. 1



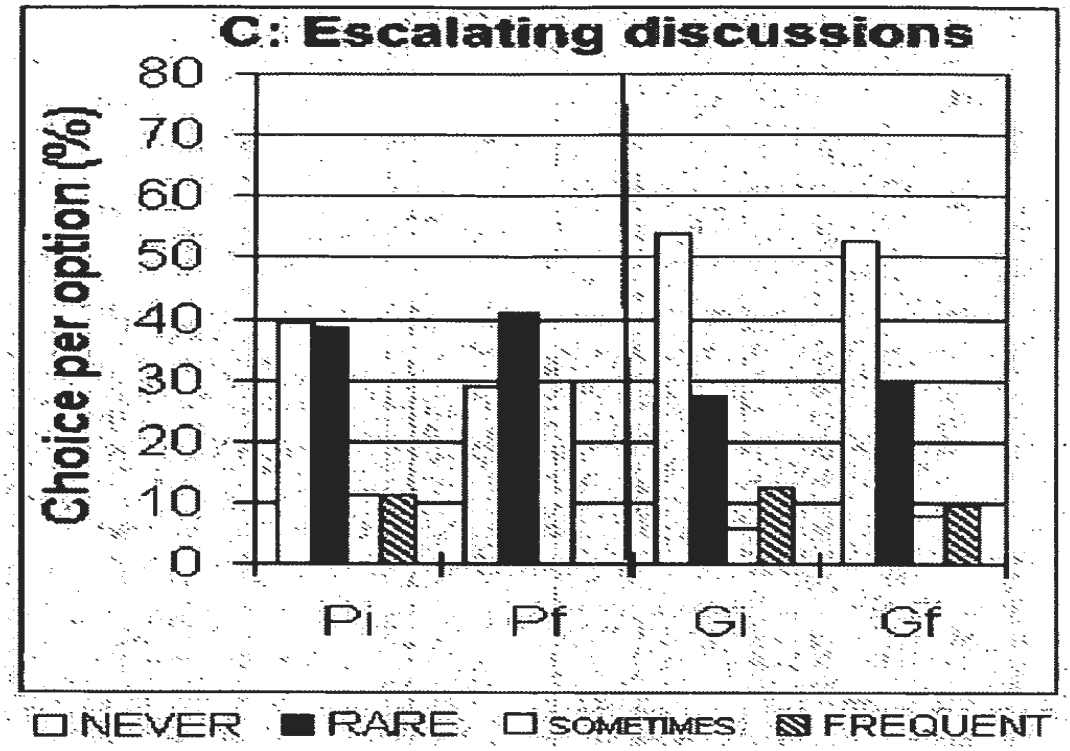
Pi: Placebo initial- Pf:Placebo final
Gi:Gonadotrophin Initial- Gf: Gonadotrophin final

FIG. 2



Pi: Placebo initial- Pf:Placebo final
Gi:Gonadotrophin Initial- Gf: Gonadotrophin final

FIG. 3



Pi: Placebo initial- Pf:Placebo final
Gi:Gonadotrophin Initial- Gf: Gonadotrophin final

Patent History

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Type: Application
Filed: Jan 14, 2008
Issued: Oct 23, 2008
Assignee: (Capital Federal)
Inventor: Daniel Oscar Belluscio (Capital Federal)
Application Serial: 12/007,596

Classifications

Current U.S. Class: **514/12**
International Classification: A61K 38/24 (20060101); A61P 25/32 (20060101); A61P 25/00 (20060101);

15. Controversies in plastic surgery: suction-assisted lipectomy (SAL) and the hCG (human chorionic gonadotropin) protocol for obesity treatment (1987).

Aesth. Plast. Surg. 11:131–156, 1987

Aesthetic Plastic Surgery

Controversies in Plastic Surgery: Suction-Assisted Lipectomy (SAL) and the hCG (Human Chorionic Gonadotropin) Protocol for Obesity Treatment

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Zürich, Switzerland

Abstract. The advent of SAL (suction-assisted lipectomy) has dramatically increased the number of obese patients coming to our consultation offices. Despite several articles suggesting a conservative approach to fat suction, some reports insinuate that SAL might be a useful tool for obesity treatment. This hypothesis is refuted by a vast body of evidence that concludes that the adipose tissue may regenerate in adult humans. Therefore, surgical procedures are not advised as the method of choice to manage the disease. On the other hand, the terms obesity and being overweight may not be interchangeable. Obesity may be a disease whereas being overweight is a *sign* of the disease. Consequently, proper preoperative selection of candidates for SAL becomes mandatory. The hCG (human chorionic gonadotropin) method for obesity treatment appears to be a complete program for the management of obesity. It contains pharmacologic, dietetic, and behavior modification aspects in a 40-day course of treatment. Some data suggest hCG to be lipolytic, thus explaining former clinical observations regarding body fat redistribution in treated patients. hCG commercial preparations contain β-endorphin, an opioid peptide linked to mood behavior. This article speculates on the possible actions of the complex hCG β-endorphin in the neuromodulation of mood and energy metabolism. The method comprises a behavior modification that helps in handling the patient better. There are some correlations between a current behavior modification program and the basic guidelines contained in the hCG protocol. Thus, the hCG method appears to be a reasonable alternative in the management of a long-standing, unsolved problem of human metabolism.

Key words: Adipose tissue — Metabolism — Endorphins — physiology — Obesity, treatment — Gonadotropin(s), chorionic, pharmacodynamics — Gonadotropin(s), chorionic, therapeutic use

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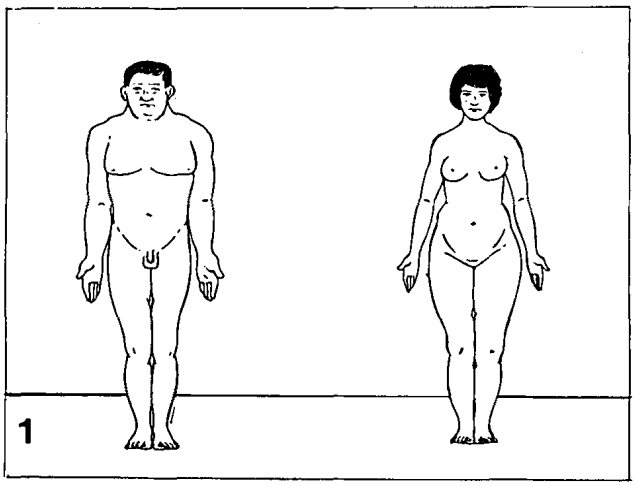
Introduction

SAL (Suction-Assisted Lipectomy) and Obesity

Few surgical procedures aroused as much interest from plastic surgeons and the lay press as SAL did. Pioneered by the early reports of Fischer and Fischer [103] and Schrudde [273], SAL reached its heyday after the publications of Illouz [159–162] and Kesselring [186–189]. Actually, SAL has become the "prima donna" in the surgical armamentarium of plastic surgeons, and nearly no part of the human anatomy is spared, including the thighs, knees, neck, buttocks, calves, arms, breasts, flaps, back, and abdomen. Patients under and over the age of 50 have, therefore, experienced the back-and-forth movement of a cannula connected to a suction pump [72–73b, 107, 128, 145–146, 186–189, 250, 308a–b, 326]. Cautious words about SAL are scarce [69, 124, 322] compared with the myriad of enthusiastic reports. The number of SAL performed surpasses any other aesthetic surgical procedure and this tendency is growing [4].

Nevertheless, because SAL is a novel surgical technique, its precise indications remain the center of dispute. Articles have been published that propose a conservative approach to fat suction, whereas diverse publications suggest SAL may be an useful tool in the therapy of obesity [241]. The differences between the criteria are not of mere academic interest. If SAL is the appropriate maneuver



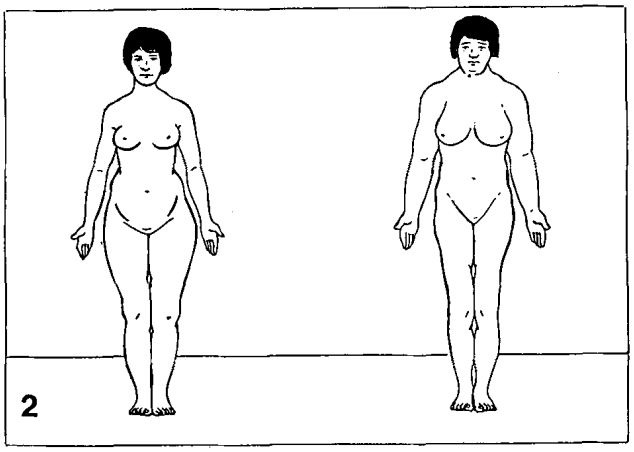


Fig. 1. Android **(left)** and gynoid **(right)** types of obesity

Fig. 2. The hypothetic long-term result from an overzealous SAL. Patient with a classical gynoid-type of obesity **(left)** showing waviness in thighs region and an android redistribution of fat after a SAL **(right)**. This "new" body fat distribution forewarns a higher incidence of metabolic complications

for the management of the obesity, then plastic surgeons would receive the merit of having developed an easy procedure that solves a disease that has been present for thousands of years. But if SAL *is not* the adequate method for obesity therapy, then preoperative patient *selection* becomes of utmost importance.

Body Fat Distribution and SAL

Fat suction might have adverse effects in obese patients: it is well known from Vague's report that there exist two types of obesity, depending on body fat distribution: a gynoid type and an android type [312, 314] (Fig. 1). The gynoid type of obesity tends to accumulate fat in the hips, buttocks, thighs, and lower abdomen. In the android type, adipose tissue largely localizes in the back, shoulders, and upper abdomen. Gynoid fatness is more resistant to dieting. The android type is easier to treat but shows an increased incidence of clinical complications, such as hyperlipemia, hypercolesterolemia, diabetes, hypertension, diabetes, and gout [313, 316].

Excessive fat removal by SAL may stimulate, in the long run, counterregulatory balances resulting in adipocyte hypertrophy and/or hyperplasia from the adipocytary pool. Faust and Kral concluded: ". . . rapid weight gain after a lipectomy cannot involve tissue that is no longer present, so it may require hypertrophy of the remaining tissues." [96]. In the case of gynoid obesity, this compensatory growth after a lipectomy (or an overzealous SAL) may occur in the upper part of the body. Thus, by force of surgical treatment a "cosmetic" obesity may evolve into a "medical" one [Fig. 2]. This modification of body fat distribution certainly does not benefit the patient. When compared with gynoid fatness, the android type of obesity shows an increased cardiovascular risk [313, 316].

Alternatively, counterregulatory mechanisms may generate adipocytary hypertrophy and/or hyperplasia in the liposuctioned area. Figure 3 shows an obese patient twice liposuctioned elsewhere, showing recurrence both of obesity and body contour deformity.

In our opinion, SAL has a definite place in body contour surgery provided that it is performed in small quantities, in conspicuous fat accumulations, and for an aesthetic improvement of the body contour (Fig. 4) [325]. Therefore, today's plastic surgeons should bear the responsibility for selecting those patients who would benefit from a preoperative weight reduction program. During the past seven years we have insisted that candidates for a body contour surgical procedure should correct their obese condition prior to the operation itself [319–325]. This is imperative, because of the increased numbers of moderately obese patients coming to our consultation offices.

In our experience, a most difficult issue is the selection of an adequate obesity therapy suitable to our plastic surgical requirements as well. Weight reduction programs offering an acceptable weight loss but poor skin tone are fairly common (Fig. 5).

After many trials, we concluded that the hCG (human chorionic gonadotropin) program suited our

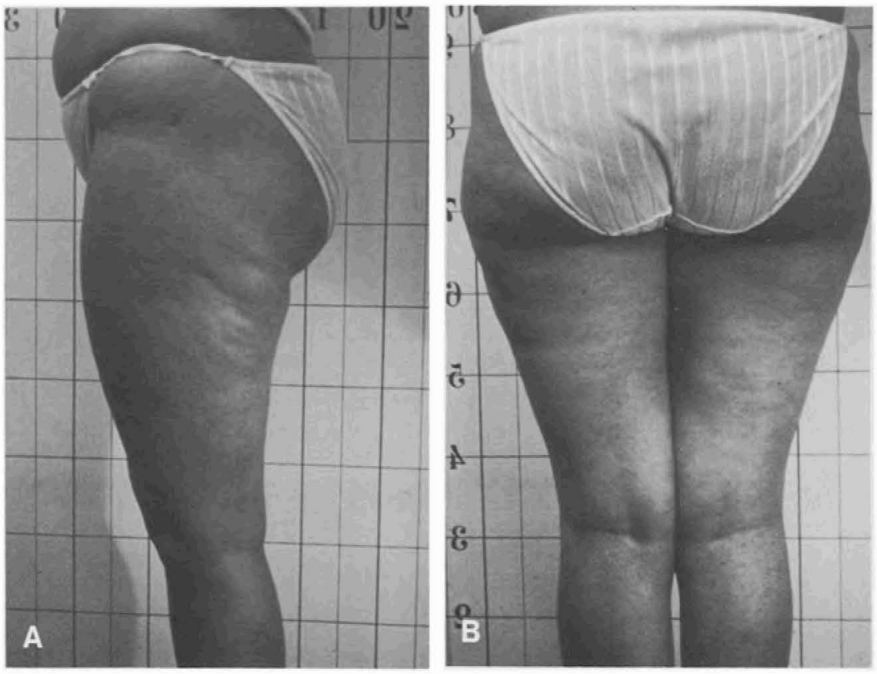


Fig. 3. Obese patient twice liposuctioned elsewhere showing recurrence of obesity and body contour deformity

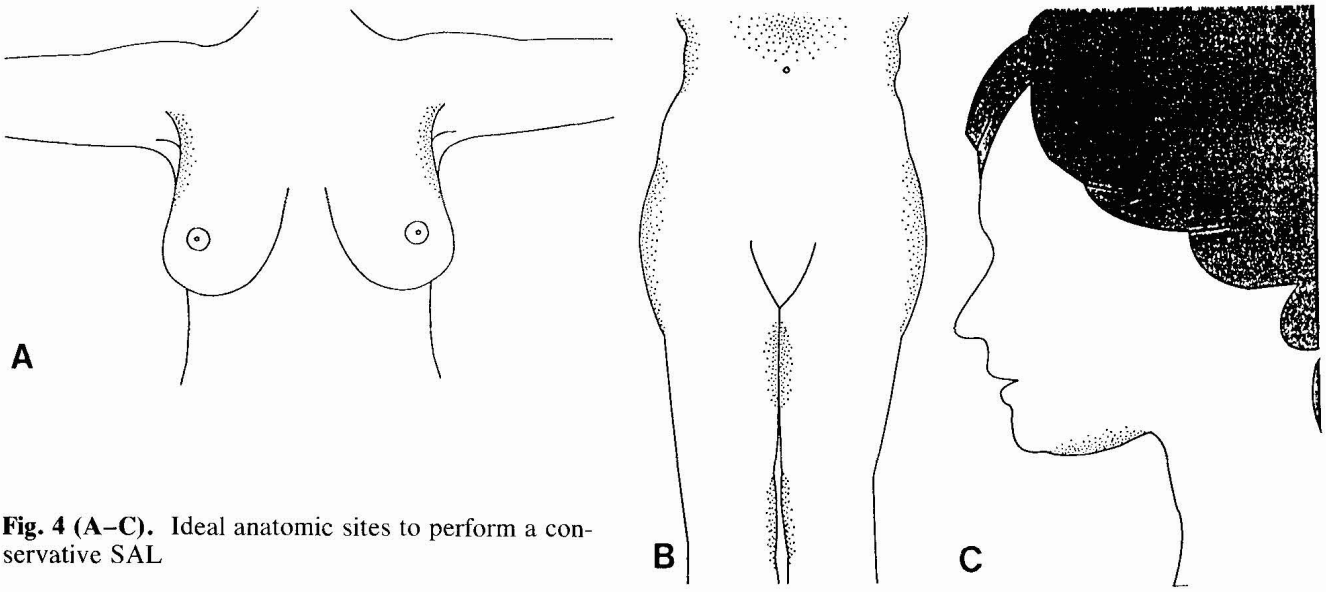


Fig. 4 (A–C). Ideal anatomic sites to perform a conservative SAL

needs and goals: rapid weight loss, excellent body contour, and good skin tone after treatment (Fig. 6). As is well known, this striking approach to obesity provoked several years ago a growing wave of criticism [6, 14, 19, 28, 42, 60, 61, 74, 108, 130, 140, 224, 247, 256, 276, 294, 337]. Nevertheless, because of recent data suggesting hCG might be lipolytic *in vivo*, we believe the whole subject deserves a new evaluation. For this objective we have mapped out a working hypothesis on the subject. Consequently, the purposes of this article are (1) briefly review some new trends on obesity classifications and summarize current concepts on obesity and adipose tissue metabolism and (2) discuss several lines of evidence that suggest that the hCG method is a complete pharmacologic, dietetic, and behavioral modification program for obesity treatment.

Part I: Overview of Obesity and Adipose Tissue

"Observe that the things which are considered to be right today are those which were considered to be impossible yesterday. The things which are thought wrong today are those which will be esteemed right tomorrow." *Hudhaifa*

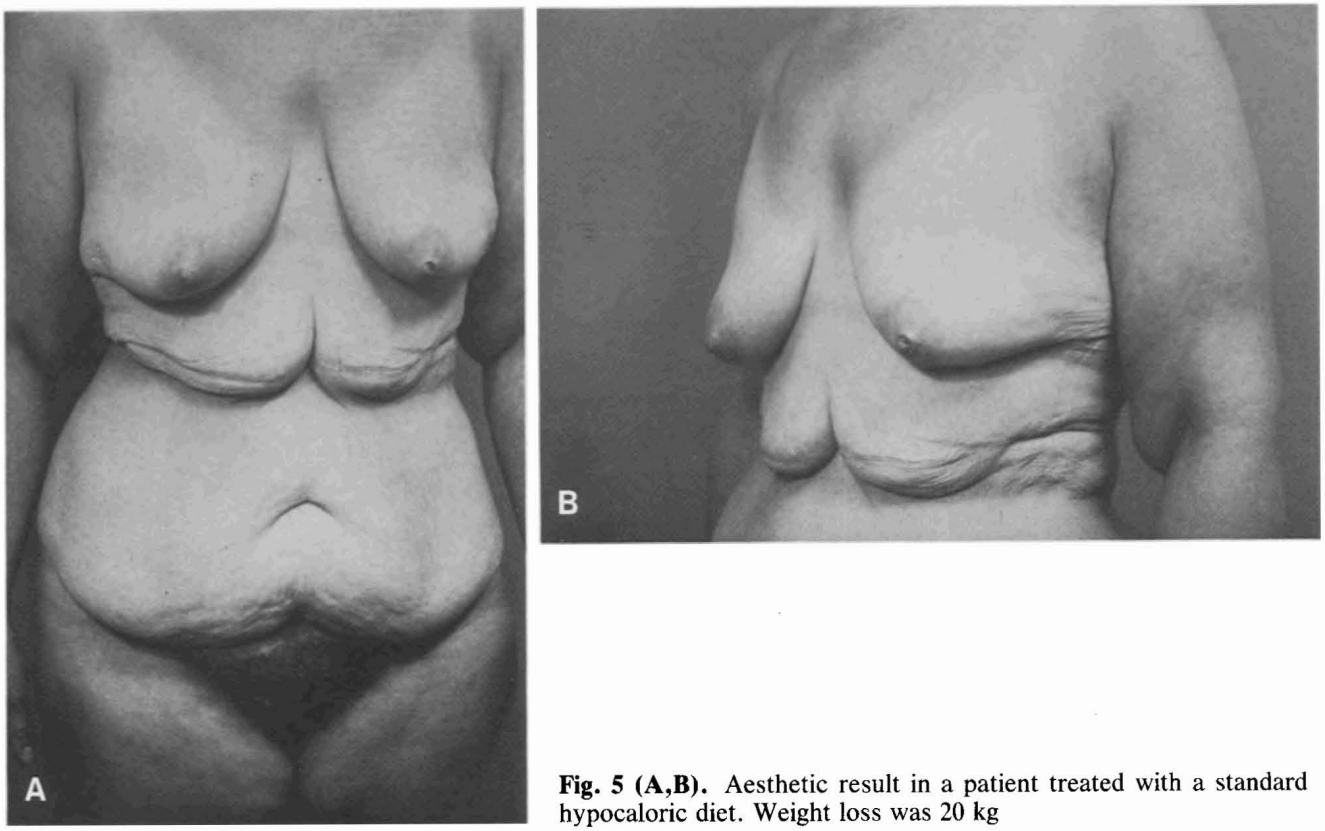


Fig. 5 (A,B). Aesthetic result in a patient treated with a standard hypocaloric diet. Weight loss was 20 kg

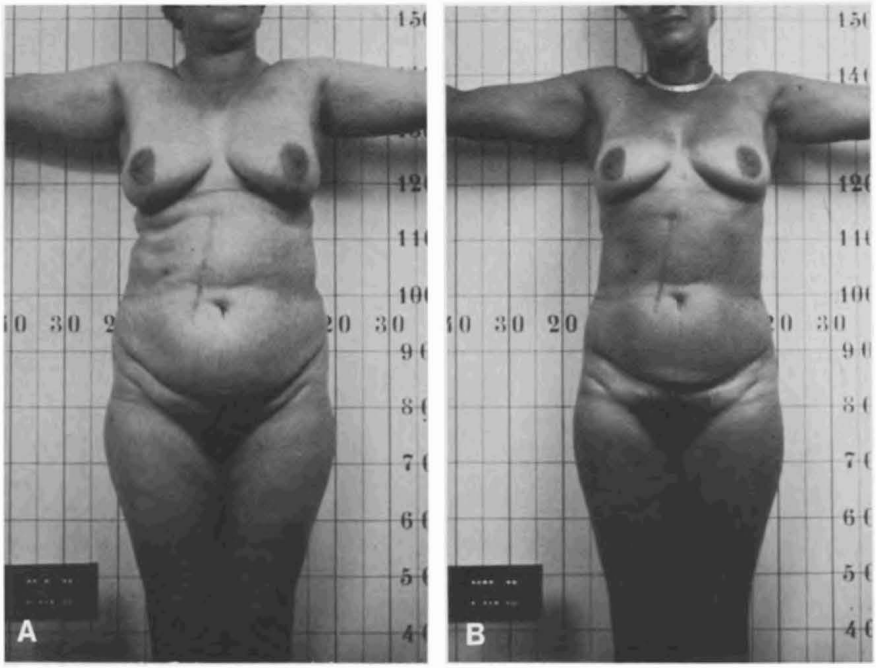


Fig. 6. Patient before **(A)** and after **(B)** a full course of treatment (40 days) under the hCG program. Weight loss was 16.3 kg

OBESITY

Classification of Obesity

Clinical signs other than weight and height are currently relevant in the assessment of the obese patient. A considerable body of evidence suggests that fat distribution plays a prognostic role in the evaluation of the disorder of obesity. As mentioned before, Vague's report was a major advance on the subject. Similar conclusions regarding the clinical importance of body fat topography were put forward by several authors. Kissebah's laboratory

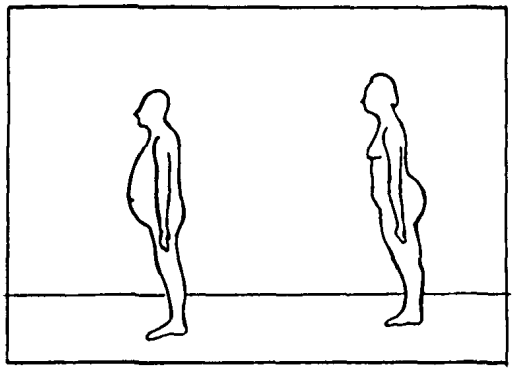


Fig. 7. Abdominal **(A)** and gluteofemora, **(B)** types of obesity. (Redrawn from [11])

classified the obesities in UBSO (upper body segmental obesity) and LBSO (lower body segmental obesity) [92]: UBSO is characterized by a WHR (waist to hip ratio, the relationship between waist and hip circumference) close to or above 1. LBSO shows a WHR below 1. A WHR close to or above 1 forewarns of clinical complications such as atherosclerosis, heart strokes, and infarcts. The Swedish school categorized obesity in abdominal and gluteofemoral types (Fig. 7) [31a–b, 201, 204]. The former is more prone to metabolic complications (diabetes, hypertension, heart strokes), but it is easier to treat than the latter.

The NHANES survey designed a classification based on the relationship between the BMI (body mass index) and the sum of skinfold thickness (166a–b). Thus, individuals may be classified as obese–overweight, obese–lean, overweight not obese, and lean not obese. The incidence of hypertension and hypercholesterolemia was higher in the obese-not-overweight group.

Recently, the National Institutes of Health proposed a major breakthrough on this subject. The panel concluded that a treatment for obesity was advisable even in discretely overweight patients, provided that a family history of obesity, obesity-related diseases, or personal antecedents of obesity-related diseases was present [235]. Consequently, obesity was declared a disease. Being overweight was not the single diagnostic tool used to characterize the disorder [231, 235].

"Not by Food Alone"

The overall state of obesity treatment remains a disappointing subject [22, 34, 58, 83, 84, 121, 123, 129, 163, 184, 212, 239, 292, 300]. Notwithstanding the social pressures to keep pounds off, statistics show success in the opposite direction [1, 53, 191, 235]. Interest in the disease and research on the topic are relatively new. Until the early 1940s, the adipose tissue was a neglected subject [119], and obese patients were generally blamed for gluttony, cheating, lack of will power, and greed [123, 127, 173, 184]. Many students of obesity adhered to the nihilistic attitude that obesity is caused simply by overeating, and that it can be cured only by undereating. Despite the patients' efforts, however, for many the disease remained "incurable" [121].

Fortunately, not everyone shared this gloomy opinion of the disease. A group of researchers felt obesity might be characterized by a basic disorder of energy metabolism. Direct and indirect data contributed to the researcher's conclusions.

Indirect Data

Neumann [232] conducted a study on himself. During a prolonged control period he varied his daily food intake significantly. His weight, however, remained stable. He concluded that somehow his body managed to get rid of the surplus caloric intake.

Similar conclusions were advanced by Gulick [138] and Passmore [244]. The term "luxusconsumption" was coined to describe these clinical observations. The next step in the research was to investigate the mechanisms whereby the organism maintained a relative constancy in body weight. Miller and Mumford [222] proposed that the extra ingested calories were dissipated by heat loss during exercise, a conclusion not unanimously agreed to by other investigators [48]. Despite contradictory evidence, it soon became apparent that there was no direct relationship between daily food intake and body weight.

Sims published a classic report on this topic. In his study, normal healthy individuals fed with a high caloric diet (up to 4000 kcal/day) maintained a fairly stable weight during the test period. In those cases where weight was increased, normalization was attained by restoring subjects to a normal daily food intake. Sims concluded: "A primary disturbance of the mechanisms which monitor energy balance of the body, and which regulate food intake, could secondarily lead to metabolic and endocrine changes; these in turn could contribute to perpetuate obesity [280, 281]." Interestingly, not all the volunteers for the study showed the same response to a hypercaloric diet.

Edholm [89], after a series of clinical experiments measuring caloric intake and energy consumption in soldiers, concluded that there were no significant

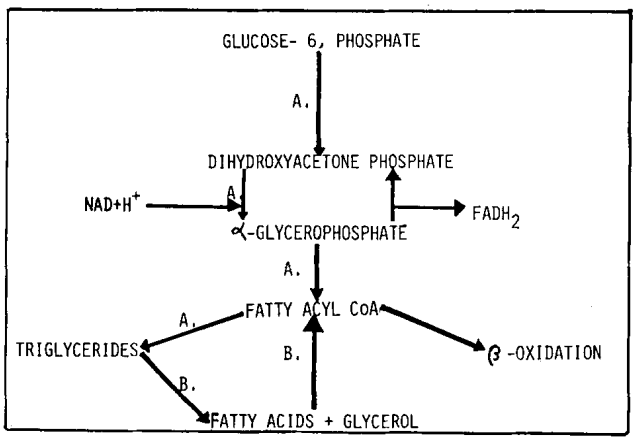


Fig. 8. Possible "wasteful" or "futiless cycles" in lipid metabolism. Letter "A" points to the diversion of carbohydrates into the fatty acid synthesis cycle; letter "B" to the hydrolysis–esterification cycle. Both metabolic pathways are less conservative from the bioenergetic viewpoint

correlations between body weight and daily food consumption.

Direct Data

Direct evidence from studies of obese patients were reported by several authors. Miller [223] demonstrated that under well-controlled conditions, a percentage of dieting obese patients failed to lose weight when compared with their counterparts. Since the study was performed on an in-patient basis, the failures could not be ascribed to a poor adherence to the diet. The reasons why these obese individuals were resistant to change remained unexplained.

Different reports reached the same conclusions: Obese subjects did not always overeat in the expected quantities. Some of them were, in fact, eating the same amount or less than their lean counterparts [17, 44, 170, 171a–b, 246, 293].

Theories on Obesity Genesis

Several theories have been proposed to explain the process whereby obese individuals maintain an abnormal high regulation of body weight. Keesey et al. suggested the concept of a "set point" for body weight regulation [179–181]. Consistent with his reports, the organism regulates a stable body weight by means of a precise system tuned to a fixed "set point". Keesey et al. proposed that obese patients possess an abnormally elevated set point. Thus, their organisms adjust energy metabolism to an increased level of body weight.

Some data contend that obese patients may show an altered activity of "futiless" metabolic cycles [167, 298]. This implies the continual cycling of substrates through a series of synthetic and degradative reactions which have the same initial and final energy status. This type of reaction is energy demanding and results in loss of the energetic efficiency of the system, dissipating a great amount of heat. The following "futiless cycles" have been suggested bear some relevance in obesity (Fig. 8): (a) the fatty acid synthesis–oxidation cycle and (b) the triglyceride hydrolisis–reesterification cycle. Both cycles involve the HSL (hormone-sensitive lipase). This is activated by adrenaline, thus explaining their lipolytic and probably their calorigenic affects on adipose tissue [298].

The issue of whether obese patients show an increased metabolic efficiency, or a thermogenic defect, still remains an open question [23, 88, 117, 142, 176, 277, 283]. More recently, it has been suggested that obese patients may show an impairment of FFA (free fatty acid) mobilization from adipose tissue [210].

Conclusions

Obviously much work remains to be done in this fascinating field of energy metabolism. However, from our perspective the following conclusions may be drawn:

1. Nonobese individuals preserve a stable body weight regardless of wide fluctuations in daily caloric intake [66, 70].
2. Similar regulatory mechanisms seem to operate in obese patients. Unfortunately for them, this regulatory system maintains an increased level of body weight despite periods of forced dieting [206].

With respect to the processes involved in this bioenergetic cycle, Hirsch has elegantly concluded: "The persistence of obesity in the face of well-publicized information on the health hazard of obesity . . . . suggests to me that there is a more subtle problem of obesity that many of us have been lead to believe" [151].

Obesity: A Multifactor Disorder

Evidence suggests that obesity is a multifactor disorder. A huge body of data concludes that genetics [9, 39, 41, 52, 54, 125, 167, 297, 304, 329], the environment [24, 43, 81, 82, 87, 156, 193, 245, 261, 301a], psychological traits [75, 122, 252, 258], socioeconomic level [5, 12, 259, 301a], development [90, 172, 182, 183, 205, 328], and a CNS (central nervous system) disturbance [7, 21, 49, 116, 175, 197, 253] contribute to the genesis or the maintenance of the disorder. Thus "nature" and "nurture", in variable

Table 1A. Site differences in subcutaneous fat metabolism after one week of therapeutic fasting of obese subjects (from [11])

Metabolic event	Abdominal fat	Femoral fat
Basal metabolism	Profound changes	Less profound changes
Catecholamine action	No change	Increased α-adrenergic effect Inhibition at post receptor level
Antilipolytic effect of insulin	No change	Increased sensitivity
Fat cell size	Decrease	No change

Table 1B. Site differences in subcutaneous fat metabolism after one week of therapeutic fasting of obese subjects (from [11])

Fat cell size	F > A[a]
Basal lipolysis rate	F < A
Basal lipoprotein lipase activity	F > A
Insulin action	F > A
Catecholamine action	F < A

[a] F = femoral fat cells; A = abdominal fat cells

proportions, are equally important in the consideration of obesity [17, 37, 51a, 56, 77, 135, 152, 168, 339].

Adipose Tissue

Heterogeneity and Multiple Physiological Aspects of the Adipose Tissue

The adipose tissue is not a uniform mass randomly distributed throughout the human body. Depending on topographic localization, adipocytes possess different sensitivities to hormones, enzymes, drugs, and fasting periods [10, 11, 38, 91, 177, 203, 287, 288, 306, 315]. The processes of lipolysis and lipogenesis in adipocytes are subject to the action of several hormones and drugs (for review see [78]). It has been observed that during fasting catecholamines inhibit femoral fat lipolysis in women [10, 11]. According to Arner [10, 11] these findings may be explained by the recent observation that the β-adrenergic receptor number is decreased in femoral fat pads during therapeutic fasting [10, 11, 240]. Insulin binding to adipocytes is modified in different fat deposits during therapeutic fasting (Tables 1a and 1b) [91]. On the other hand, some evidence concludes that the adipose tissue is quite an active mass as far as the metabolism of FFA [78], steroid hormones [97a,b], and amino acids [310] is concerned.

Lipoprotein Lipase (LPL)

Lipoprotein lipase (LPL) is an enzyme that hydrolyzes plasmatic VLDL (very-low-density lipoproteins) and chylomichrons, thus releasing FFA from the intravascular lumen. The adipocyte takes up these FFA and reesterifies them to triglycerides (TG) in the interior of the fat cell (Fig. 9). Several reports suggest that a high LPL adipose tissue activity, as seen in some obese subjects, predisposes them to increased fat storage [131, 238, 257, 274].

LPL activity was found to be higher in the femoral than in abdominal regions in women, except during lactation. During lactation, however, LPL activity is decreased in women's femoral fat pads. These findings suggest that femoral adipose tissue possesses a particular metabolic specialization during lactation [254].

Steroid Hormones

There exists an extremely large pool of steroid hormones in adipose tissue, several times that observed in plasma [97a,b]. Consequently, the adipose mass may be an important variable of steroid hormone metabolism in humans.

Adipocyte Regeneration in Adult Individuals?

Earlier reports suggested that the adipose cell does not multiply in adults [29, 30, 47, 149, 268, 269]. Based on this preliminary data, it was speculated that SAL could be the appropriate tool for the treatment of obesity [162]. Nevertheless, this enthusiastic surgical approach to a longstanding problem of human metabolism soon was over shadowed by a series of reports that concluded that the adipocyte may, indeed, multiply in adult individuals. Evidence of this came from experiments in animals and the long-term followup of obese patients.

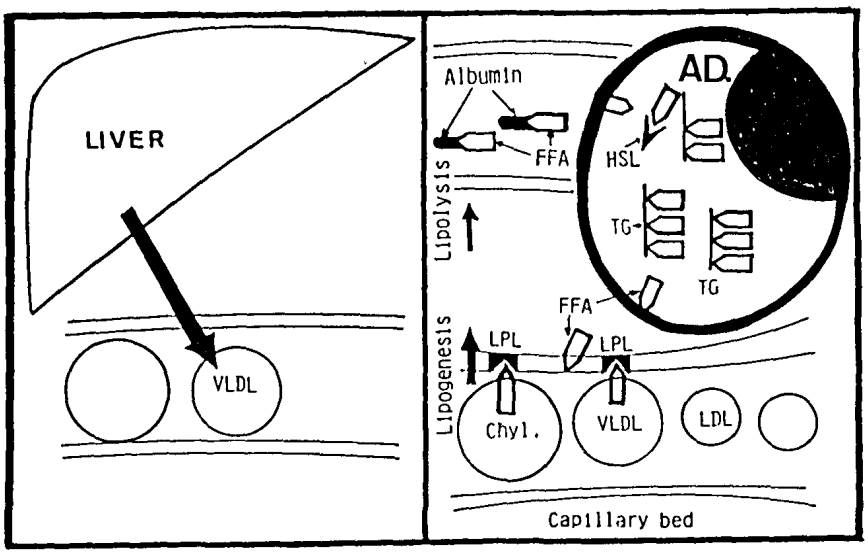


Fig. 9. The mechanism of action of LPL (lipoprotein lipase). The enzyme hydrolyzes VLDL (very low density lipoproteins) and Chyl. (chylomicrons) from plasma, releasing FFA (free fatty acids) in the extracellular space. The adipocyte (Ad.) uptakes these FFA and reesterifies them back to TG (triglycerides). When needed, these TG are hydrolyzed back to FFA by the HSL (hormone-sensitive lipase) and released in the circulation coupled to the albumin (Alb.) fraction.

Adipocyte Regeneration in Rodents

Roth [264] demonstrated that after a lipectomy, the remaining fat cells multiply in rats. Miller [226] showed evidence concerning a *de novo* production of adipocytes in adult rats. Faust showed that under certain conditions, specific rat adipose tissue pads may regenerate [93, 96].

Adipocyte Regeneration in Humans

Foley [105] concluded that overeating leads to recruitment of new adipose cells in moderately obese patients. Sjöstrom et al. suggested that the adipose cells multiply in adult subjects [282a,b]. One of his reports was a long-term followup of obese women [282a]. Kral [199a,b], in a followup of three lipectomized women, observed that one had regained the weight she had before the operation, a second patient had to keep a rigorous diet to maintain her weight, and there is no data concerning the third patient. Kral concludes: "Surgical reduction of fat mass does not seem to prevent a future weight gain." Taken together, these data suggest that the total adipose mass is under the control of some type of regulatory mechanism. This "homeostatic" system might compensate for eventual losses of fatty tissue through hypertrophy and/or hyperplasia from the adipocytary pool.

Regulation of the Adipose Tissue Mass

Maintenance of a fairly stable weight throughout life or the recovery of the adipose mass after surgical interventions strongly suggests that there exists a CNS (central nervous system) mechanism that controls fat deposition and release in adipose tissue (for review see [332]). The proposal of the hypothalamic region as the regulatory organ appears plausible [209, 332]. The hypothalamus has been reported to play a regulatory role in the menstrual cycle [20, 100], cardiac frequency [227], and immunity [76]. Thus, it is reasonable to assume that body energy homeostasis is modulated in the hypotalamic region as well [251, 332] (Fig. 10). However, a major drawback to this hypothesis lies in the difficulty to extrapolate some clinical conditions as observed in humans (e.g., obesity) with the results of experiments in animals.

Part II: The hCG Method for Obesity Treatment

"There are, it may be, so many kinds of voices in the world, and none of them is without significance"

I Corinthians

Introduction

As is well known, the first protocol for the management of obesity with hCG was reported in *Lancet* [278] by the late Dr. A.T.W. Simeons. However, previous publications concluded that hCG was a useful drug for the treatment of certain clinical presentations of adolescent obesity, except Fröhlich's syndrome [65, 116].

Since 1966 this clinic has managed obese patients with the hCG method. As experience was gained by treating 12,000 obese subjects, modifications to the original protocol were introduced. Uniform results, excellent body contour after treatment, and absence of clinical complications are the main characteristics of this outstanding form of obesity therapy. The

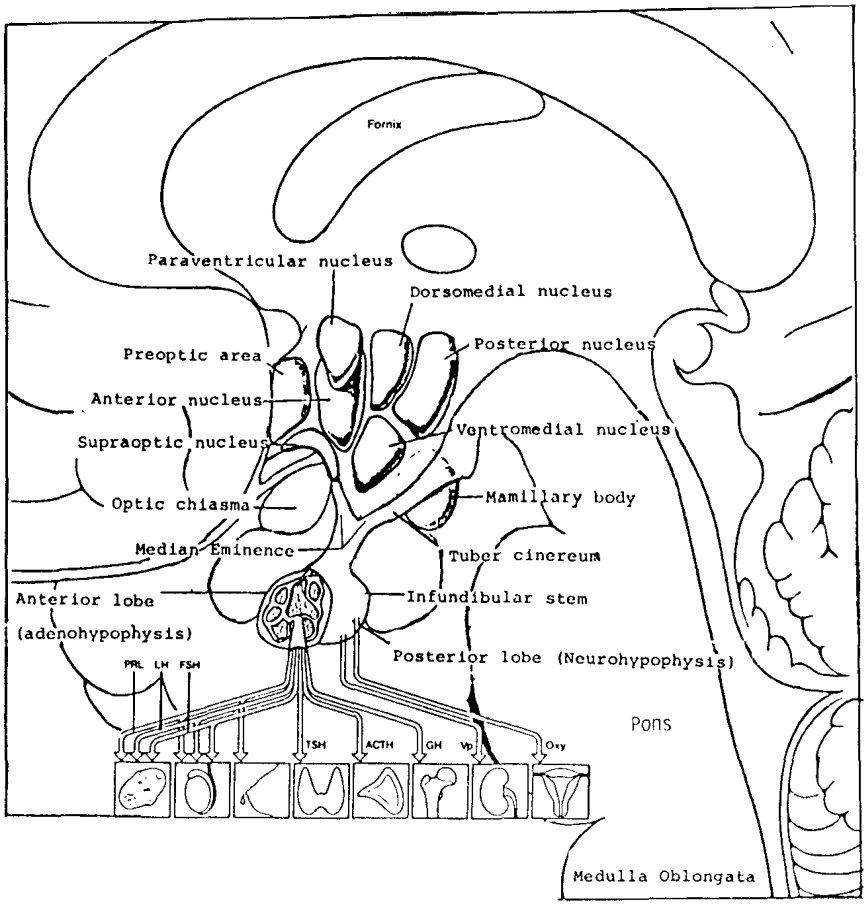


Fig. 10. The hypothalamic region. Different hypothalamic nuclei and their relationships to pituitary gland can be seen. PRL: prolactin; LH: luteinising hormone; FSH: follicle stimulating hormone; ACTH: adrenocorticotrophic hormone; TSH: thyroid stimulating hormone; GH: growth hormone. Hormones from the posterior part of pituitary: Vp: vasopresine; Oxy: oxitocyne

procedure was accepted [80] until the mid-1970s when, for several reasons, it fell from credibility:

1. An excessive proliferation of the so-called "fat clinics." These institutions injected hCG under totally uncontrolled conditions [19]. Unproper management of the hCG protocol resulted in an increased rate of clinical complications [86].
2. An overestimation of the real therapeutic possibilities of hCG. Publicity lead the people to believe that hCG was the "magic wand" that would cure their disease.
3. A series of clinical tests, which nearly all [61, 74, 108, 130, 140, 224, 276, 289, 294, 337] but one well-controlled one [14] concluded that the method was of no use for obesity treatment.

We have postulated elsewhere [320a–325] that hCG is *not* the magic solution to cure obesity. A daily injection of hCG gives optimum results *only when used in a rational weight reduction program. Therefore, strict observation to the complete protocol is mandatory.*

A Hypothetical Framework

This clinic is engaged in a study program on the subject. We have developed a working hypothesis based on the results of our clinical experience, on recent evidence from the field of obesity research, and on some speculative hypotheses. The latter were introduced when experimental data were not available. The model is incomplete and much work remains to be done to test the validity of these hypotheses.

A Working Hypothesis in Obesity Therapy. The basic postulates of our model are (1) obesity is not the same as being overweight, (2) obesity has physical signs, (3) human obesity might be characterized by a hypothalamic disorder, (4) the hCG method comprises pharmacologic, behavior modification, and dietetic aspects. The pharmacologic aspects are (a) hCG is lipolytic *in vivo*, (b) hCG may act at the hypothalamic level, (c) hCG affects mood behavior.

1. Obesity is not the same as being overweight. As we have seen before, recent data indicates that obesity is a different clinical entity than being overweight. Several lines of evidence contribute to this hypothesis:

Gynoid type of obesity is preserved from the clinical complications appearing in android obesity. When compared with similar weights, the latter appears more "malignant" than the former [313, 316].

Recent laboratory tests have reported abnormalities suggesting metabolic complications of obesity in normal or near-normal weight subjects

[267]. Therefore, current classifications of obesity in terms of body weight may not correlate with clinical severity of the disorder.

According to the NHANES survey conclusions, incidence of hypertension is higher in obese but not overweight individuals [166a,b].

The National Institutes of Health consensus panel concluded that appropriate timing to treat obesity may depend on clinical variables other than height and weight [235].

Taken together, these data indicate that obesity and being overweight are not interchangeable terms: the former may be a clinical disease, whereas the latter could be a sign of disease, not a disease itself [50]. Should this be true, then the assessment of obese subjects should include variables other than height and weight alone.

2. Does obesity have physical signs? As far as we know, it was Dr. A.T.W. Simeons who described for the first time physical signs that he considered typical of obesity [279]: (1) one or two folds of skin around both sides of the back or the chest, (2) the presence of a fat pad on the nape of the neck in an otherwise moderately obese patient, (3) a noticeable valgum of the knees, (4) a fat pad inside the knees. These physical signs could be "clinical markers" used to separate obese individuals from those who are simply overweight. Obese patients should be treated with a more energic weight reduction program because they show a higher incidence of clinical complications.

3. Obesity might be characterized by a hypothalamic disorder. Notwithstanding recent data that suggest that the adipocyte might be the main cause of obesity [94, 95, 132, 262], there is much evidence that the total body fat mass is regulated by a central nervous system modulatory system [209, 214, 332]. Therefore, despite genetic influences may predispose adipose cells to accumulate lipids [41, 79, 132, 147], the overall activity of fat deposition and release must depend on an integratory circuit, which should control the metabolic activity of diverse fat cells all over the organism.

A well-studied topic is the relationship between hypothalamic experimental lesions and the development of obesity in rats. In 1939, Hetherington and Ranson [143, 144] reported that small electrolytic lesions in the VMN (ventral hypothalamus) resulted in hyperphagia and obesity. Though the first publications focused on the metabolic and endocrine disorders accompanying hypothalamic lesions, later on several reports insisted that a basic modification in eating behavior (hyperphagia) heralded the onset of metabolic abnormalities (hyperinsulinemia) [8a,b, 185, 286, 295, 296]. However, recent investigations suggest this interpretation may be incorrect. A current formulation for these syndromes proposes that neurally mediated hyperinsulinemia is the primary factor contributing to excessive fat accumulation [164, 165]. This concept is not shared by all investigators [134, 295, 296].

Despite the controversy on the subject, it is generally agreed the hypothalamus somehow plays a regulatory role in the mechanism of energy metabolism regulation [67, 112, 120, 158, 169, 209, 214, 215, 225, 243, 251, 272, 332]. Nevertheless, a major problem lies in the extrapolation of the results obtained in animal experiment to the clinical condition of obesity as observed in humans. Except for a handful of cases [49, 64] no demonstrable hypothalamic lesions have been reported in common obesities. Thus, it appears that experimental animal models of obesity are of limited value when considering human obesity (for a review on experimental and genetic models of animal obesity see [51b, 101]).

A reasonable alternative to this problem may be that human obesity might be characterized by a subtle hypothalamic disorder, still not accessible to current diagnostic methods [112, 272]. Indirect evidence that supports this hypothesis is seen in several experiences in humans. Amatruda et al. [7] demonstrated that a group of obese males showed an abnormal response to 100 μg of GnRH (gonadotropin releasing hormone). Jung et al. [174] concluded that women with familial obesity have a hypothalamic function disorder which was not totally corrected after weight loss. Kopelman et al. [195, 196], after studying the prolactin (PRL) response to insulin-induced hypoglycemia, concluded that hypothalamic function is disturbed in massive obesity. The causes for this regulatory disorder are presently unknown.

A Hypothalamic Opioid Disorder in Human Obesity?

Recent data from the opioid research field opened a new perspective in the consideration of human obesity: Obesity might result from an opioid regulatory derangement in the diencephalic region [220]. Several data suggest that CNS opioids regulate energy metabolism [192, 216–218, 335] and ingestion of nutrients [126, 178, 207, 228–230, 270, 285, 335]. One of the best studied neuropeptides is β-endorphin. It has been suggested that this opioid acts upon the mechanism that elicits eating through a "food-rewarding" system. This cycle might function as follows: Food ingestion may increase CNS opioid levels [216]. This creates a "self-gratifying" sensation [62]. Therefore, obese subjects should be compelled to elevate their food intake to maintain an elevated CNS opioid concentration [62].

From this perspective, gluttony observed in obese patients could be explained on a biochemical basis: Addiction to food would be a recognizable

CNS opioid disorder. Following this line of reasoning, food restriction in obese subjects would decrease the content of CNS endorphins, creating a "withdrawal syndrome" similar to that observed in drug addicts. This hypothesis finds partial support in the Gambert et al. report [115] that concludes that fasting decreases the content of hypothalamic β-endorphin in rats.

We hypothesize that modification of the content of hypothalamic opioids may be related to energy metabolism as follows:

1. Hypothalamic neuropeptide hypersecretion in obese patients may create a dependence on food because food intake would increase CNS opioid concentration [and thus self-gratification]. In this case, obesity would be maintained by an elevated energy input. A persistent high food intake level could lead to metabolic changes which may in turn perpetuate obesity [280, 281].
2. The hypothalamus might be part of the diffuse neuroendocrine system, as proposed by Margules [217, 218]. He suggested that opioids are the neuromodulators of this system. Any stressful situation—a diet, for example—could disrupt the homeostasis of the system. In the case of a diet, the period of decreased energy input would be compensated by physiological adjustments in energy metabolism. This counterregulatory phenomenon could result in the maintenance of the body weight "set-point."

Finally, some evidence seems to suggest that the diencephalic region plays a regulatory function in the metabolism of fat deposition and release. Research on hypothalamic neuropeptides may shed new light on the interpretation of obesity. Subtle modification of the diencephalic opioid concentration may be the cause or an indication of an underlying neuromodulatory disturbance. This would, in turn, initiate the metabolic changes that lead to obesity.

4. Multiple Aspects of the hCG Protocol

Pharmacologic Aspect: hCG is lipolytic in vivo. According to Simeons [278], obesity was characterized by the presence of an "abnormal" adipose tissue. These fat pads were localized in specific body areas. Simeons suggested that hCG showed an affinity for these fat masses. As far as we know, there are no reports proposing that hCG mobilizes this "abnormal" fat. However, some data demonstrate that hCG can mobilize lipids from adipose tissue.

Fleigelman [104] concluded that the administration of hCG in rats decreased the activity of α-glycerophosphate dehydrogenase and glucose-6-phosphate dehydrogenase from the liver and adipose tissue. This could mean a diminished lipogenic activity in both tissues under hCG (Fig. 11).

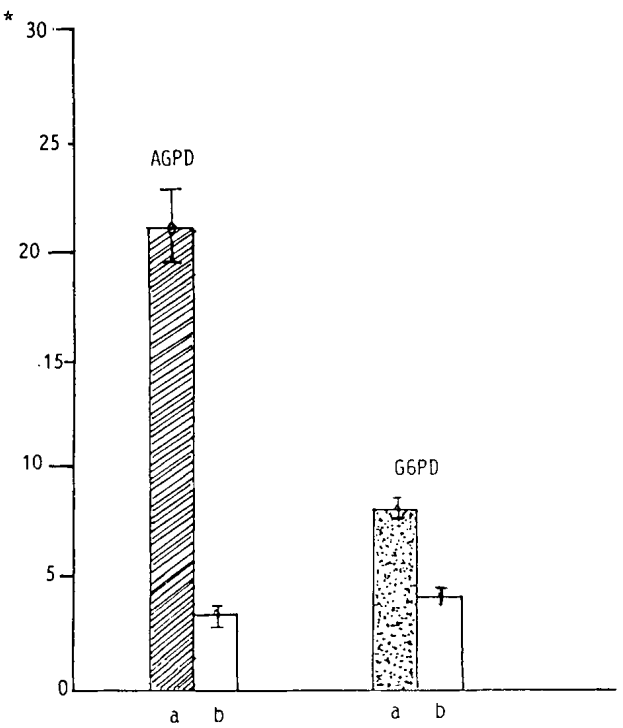


Fig. 11. The activity of two enzymes from rat adipose tissue before **(A)** and after **(B)** hCG administration. AGPD: soluble α-glycerophosphate dehydrogenase; G6PD: glucose-6-phosphate dehydrogenase. (All enzymatic activities are expressed as micrograms formazan/μg nitrogen) (Drawn from [104])

Yanagihara [334] reported that hCG accelerates "not only mobilization of fat from fat deposits, but also its utilization in peripheral tissues. hCG increased the metabolism of injected fat emulsions, suggesting not only the acceleration of not only oxidation of fat, but increased ketone production in the liver and its utilization in peripheral tissues." Romer [260] reported that hCG intensifies the metabolism of rat brown adipose tissue.

Administration of hCG in humans appears to increase the release of free fatty acids that varies with the age of the subjects. Melichar et al. [221] demonstrated that hCG causes a marked FFA release in newborn infants. In adults, a single injection of hCG stimulated the release of FFA by $P > 0.05$ when compared with placebo-treated individuals. This lipolytic action of hCG appears to be mediated. Tell [309] reported that adipocytes do not possess receptors for hCG. Therefore, the lipolytic action of hCG is mediated through an organ or system, which may release a lipid-mobilizing substance in response to hCG stimulation.

Alternatively, chCG (crude, commercial hCG) may exert an *in vitro* lipolytic activity: commercial preparations of hCG contains β-endorphin [139], an opioid peptide with a suggested *in vitro* lipolytic activity [255].

hCG might act at hypothalamic level. At this point, it seems relevant to discuss some data regarding hCG. hCG is a glycoproteic hormone, normally secreted by trophoblastic cells of the placenta during pregnancy [275]. It consists of two dissimilar, separately but coordinatedly translated chains called the alpha and beta subunits [27, 59, 102, 249, 317, 318]. The three pituitary hormones LH (lutenizing hormone), FSH (follicle stimulating hormone), and TSH (thyroid stimulating hormone) are closely related to hCG in that all four are glycosylated and have a dimeric structure comprising Alpha and Beta chains as well. The amino acid sequences of the alpha chain of all four human glycoprotein hormones are nearly identical. the amino acid sequences of the beta subunits differ because of the unique immunological and biological activities of each glycoproteic hormone [263]. β-hCG contains a carboxilic residue of 30 amino acids that are characteristic of hCG [25–27].

Its name, human chorionic gonadotropin originated when it was found that hCG matured the infantile sex glands (gonadotropin) and that it was secreted by the placenta (chorionic) [13, 338]. Recent data suggest, however, that both terms can be quite misleading: normal human tissues [45, 305, 336], plasma from nonpregnant subjects [40, 242], trophoblastic and nontrophoblastic tumors [55, 68, 71, 153, 236, 265, 266, 291, 317], bacteria [3, 16, 213, 219, 284], and plants [85, 109, 110] express hCG or a hCG-like material (for review see [157]). Recently, it has been suggested that this hCG-like material may act as a local growth modulatory factor (D. Belluscio, unpublished).

As far as the scope of this article is concerned, we see that the hypothalamic region is a target organ for the extragonadal actions of hCG. Yaginuma [333] showed that in rats peripherally injected ^{125}I-hCG crosses the blood–brain barrier and accumulates in the hypothalamic region. Hirono [148] reported that hCG has a direct effect on hypothalamic median eminence (ME), inhibiting the synthesis and release of FSH and the release of LH from the anterior pituitary through the hypothalamus. Board [36] demonstrated that hCG administration increases the secretion of the growth hormone in humans. hGH (human growth hormone) may perform lipolytic [98] and calorigenic [46] functions in humans. Thus, hCG could stimulate hGH secretion. This would, in turn, stimulate lipolysis from adipose tissue. Alternatively, and from a purely speculative viewpoint, hCG could stimulate, through the hypothalamus, the secretion of a pituitary lipid-mobilizing factor [57].

hCG and mood behavior. A most intriguing clinical aspect of the hCG program is the sense of well-being observed in treated patients [14, 278, 279, 319–325]. However, these findings were refuted by several publications [130, 224, 294, 337]. Nevertheless, recent data may shed some light on the subject: Hashimoto and Sawai reported that commercial preparations of hCG contain β-endorphin [139], a neuropeptide related to changes in mood behavior [136, 271]. Pure hCG contains β-endorphin as well [2]. Consequently, we hypothesized that the content of β-endorphin in hCG might be responsible for the slight "euphoria" observed in our patients. This opioid might act in the hypothalamic region, an area of major synthesis of β-endorphin [113, 133, 136, 198, 271]. But a major drawback to this supposition lies in the fact that except for a few reports [35, 63, 192], several studies conclude that peripherally injected β-endorphin does not cross the blood–brain barrier, or, if it does, it is either taken up by the brain or broken down with extreme rapidity [137, 154, 200, 208]. Only direct administration to the central nervous system seems to show clinical effects [248].

It occurred to us, from a pure hypothetic viewpoint, that hCG might be the "carrier" for β-endorphin into the brain, delaying its catabolism and facilitating its penetration into the brain: hCG crosses the CNS blood–brain barrier [18], and it accumulates in the hypothalamus [333]. Extremely low concentrations of the complex hCG/β-endorphin at the hypothalamic level should be sufficient to exert a therapeutic effect: β-endorphin is one of the most potent of the tested neuropeptides [136]. Alternatively, β-endorphin could enter the brain at the spinal cord level [118].

The complex hCG/β-endorphin may act in obese patients as follows: (1) The hypothalamic content of β-endorphin decreases during starvation [115]. If the same observation was seen in humans, then exogenous β-endorphin may prevent the withdrawal syndrome that accompanies a dieting period. (2) It could stimulate the secretion of the hypothalamic GHRH (growth hormone releasing hormone) factor and hence lipolysis [98].

Since the above are speculations, they should be read with caution: much work remains to be done to test the validity of these hypotheses.

Behavior Modification Aspect. After Stuart's report [299], data on the utility of a behavior modification program for obesity treatment became available [99, 301b, 302, 303, 327, 330, 331]. The idea behind these programs is that the primary behavior to be changed is eating, and a number of exercises are designed to slow the rate of eating. Former behavioral programs based on only behavior modification had little success [106, 330]. Recently, however, satisfactory long-term results have been reported with a combination of behavior modification and the administration of a very low calorie diet [32, 33, 211].

In our opinion, the protocol hCG contains behav-

Table 2. A comparison between the basic behavior modification techniques comprised in the hCG protocol **(left)** and those from a current behavior modification program **(right)**

(A) Daily visits to the doctor	(A,B) Reinforcement of prescribed behaviors
(B) Daily weighing of the patient	
(C) Extreme sensitivity of the method to daily dietary errors	(C) Self-monitoring of the patients
(D) Modification of daily eating habits	(D) Development of techniques to control the act of eating
(E) A programmed maintenance period	(E) Maintenance period after treatment

ior modification procedures that are similar to the basic guidelines of a standard behavior modification protocol (Table 2).

Dietetic Aspect. Diet plays a specific role in obesity therapy: It decreases energy input thus stimulating energy consumption from fat deposits. No study that we know of has reported complications with the 500-kcal diet. Recently it has been shown conclusively that the use of the very-low-calorie diet for managing of obese patients is safe [114, 155, 190, 237, 290].

Results

First we want to ask: Does a new classification of obesity require a new clinical test? In our opinion, the value of a standard double-blind test to evaluate the hCG program seems questionable. There is no doubt that a 500-kcal diet will render an acceptable weight loss in patients who receive a daily injection of hCG, a placebo, or simply dietary advice [150, 278]. On the other hand, if obesity and being overweight are medical terms that define different clinical conditions, hCG should be tested against a placebo only in obese patients [278, 279]. Such a clinical study has never been done before and would require the close cooperation between a research laboratory and a department of internists. The latter should be fully acquainted with the minimal details of the hCG complete protocol. The research lab should be willing to initiate a research program on this poorly investigated relationship between hCG and obesity.

The following results are from our clinical experience. We prepared a random selection of 450 patients treated with the hCG method between 1971 and 1979. Results can be seen in Tables 3a and 3b. It became clear that weight loss under the hCG protocol is most substantial when compared with standard weight reduction programs. Figures 12–17 show some of our obtained results.

At the total dose indicated for a complete course of treatment with hCG (5000 IU), no complications have been reported. Gonadal hyperstimulation syndrome [15] and acute Meigs syndrome [111] are always related to a higher dose of hCG (20,000 IU or more), generally used in combination with hMG (human menopausal gonadotropin) [233, 307]. Minor complications have been reported: loss of telogen effluvium hair [202, 311] observed in patients subjected to a dieting period and pain at the injection site of a commercially prepared hCG, but not with a different one [141, 234].

In our experience the following minor complications were observed: (1) menstrual cycles disturbances in 0.1% of patients. Several of our obese patients who presented amenorrheic disorders prior to treatment reverted to normal cycles when weight was decreased; (2) hair loss in less than 0.01% of the treated subjects. The hair was of the Telogen effluvium (mature hair) type. Normal regrowth was observed after treatment in all cases. There were no cases of permanent alopecia reported in well over 12,000 treated subject.

Conclusions

The advent of SAL has dramatically increased the number of obese patients coming to our consultation offices. Therefore, a cooperation with a physician who specializes in obesity is of utmost importance. This team work will help in the proper selection of patients and to decide whether a medical weight reduction program should be performed in the first place.

Obesity is a multifaceted disorder. Present classifications include the assessment of height, weight, adipose tissue distribution, and familial antecedents of obesity or obesity-related diseases. Current decisions on the appropriate timing of obesity treatment are based on a careful analysis of the variables listed earlier. Patients who are five or ten pounds overweight should be treated with a weight reduction program when personal or familial antecedents advise it.

The adipose tissue reacts differently to hormones and drugs, depending its topographical localization. Conspicuous body areas seem to be more resistant to fasting because of the particular metabolic char-

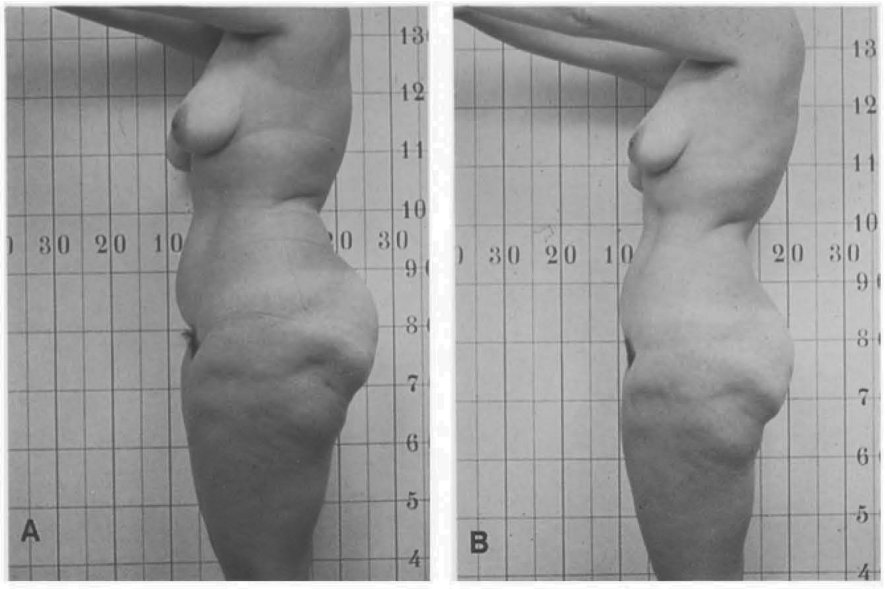


Fig. 12. A 45-year-old patient before **(A)** and after **(B)** a weight loss of 13.5 kg in a 35 day course with the hCG program. Note absence of skin sagging despite the significative weight reduction

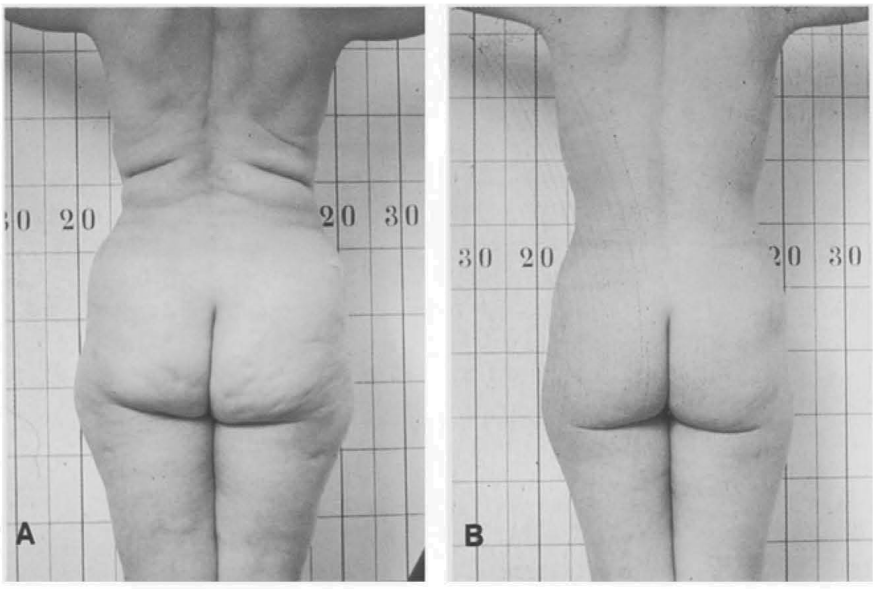


Fig. 13. Harmonious 12 kg weight loss in a 39-year-old patient treated with our protocol (40 days). Physical signs characteristic to obesity have dissappeared **(A)** before; **(B)** after

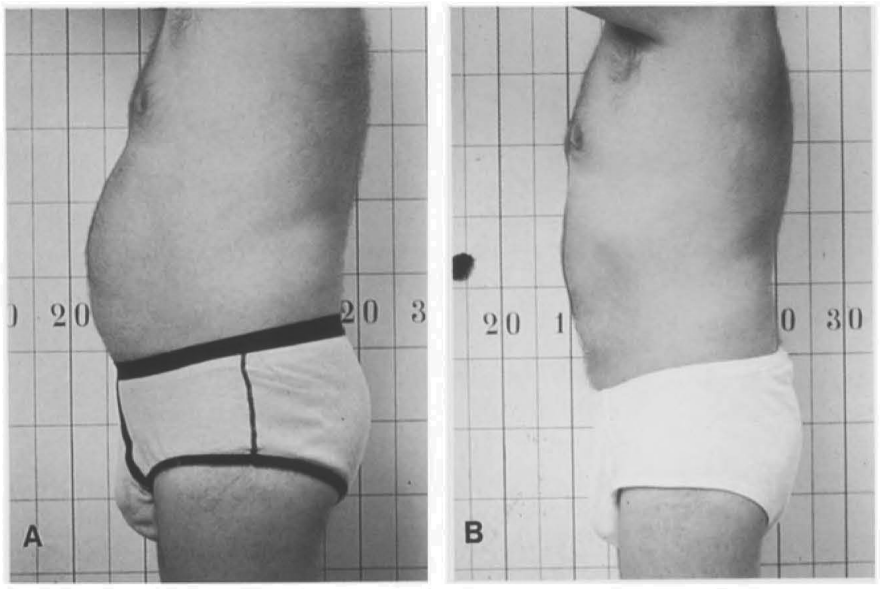


Fig. 14. A 30-year-old male before **(A)** and after **(B)** a weight loss of 17.3 kg, managed with the hCG method. It can be noticed the net improvement of his abdominal type of obesity

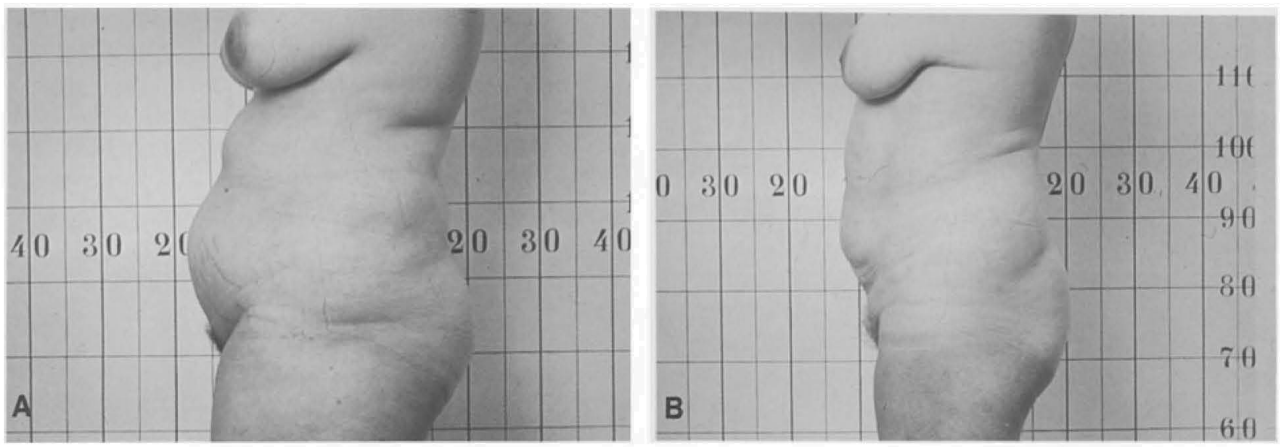


Fig. 15. Obese 51-year-old patient before **(A)** and after **(B)** a weight reduction of 16.2 kg in the course of a hCG treatment (42 days). Observe the dissappearance of striae cutanea from the lower abdomen

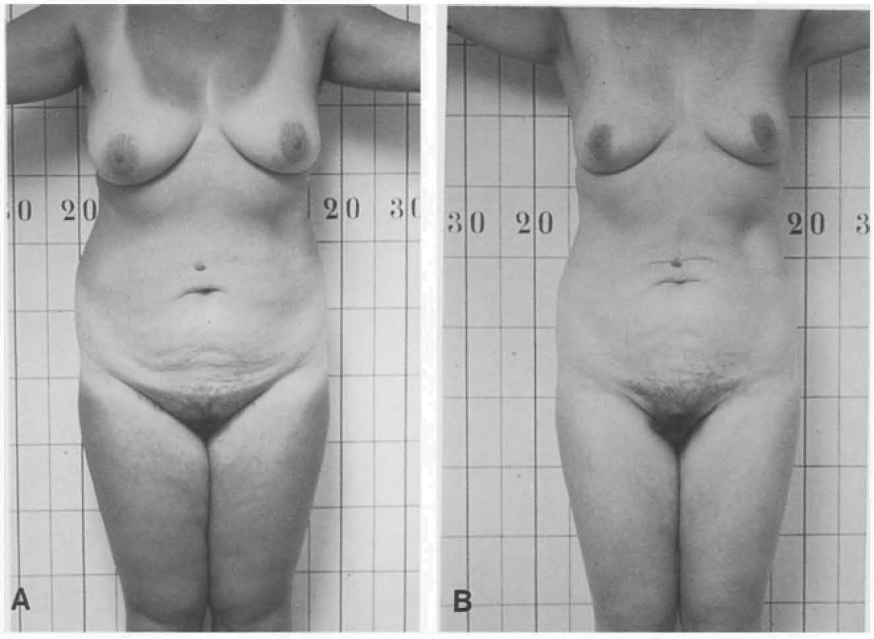


Fig. 16. Obese patient before **(A)** and after **(B)** a weight loss of 12.4 kg after a course of 40 days of treatment with our hCG protocol. Symmetric body fat reduction. Minimal sagginess of skin

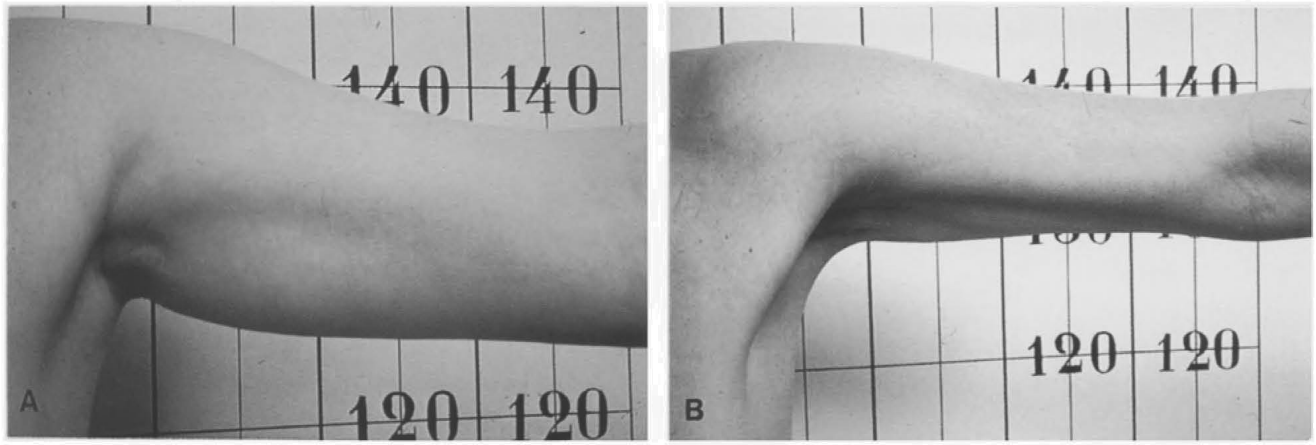


Fig. 17. This photograph shows that proper aesthetic results can be obtained with the hCG method without any surgical procedure: arm from an obese patient before **(A)** and after **(B)** the hCG treatment

acteristics of regional adipocytes. It seems that some cases of "resistant" obesity might be explained by the decrease of the release of free fatty acid from adipose tissue, or a relative decrease in the number of beta-receptors from adipose tissue during therapeutic fasting. This relative decrease in beta-receptor number may favor the alpha action (accumulation of lipids) of hormones.

Individuals tend to maintain a fairly stable weight throughout their life. For the obese, this "set point" of body weight regulation appears abnormally elevated. This hypothesis indirectly proposes that there exist a mechanism that controls fat deposition and release. Some evidence points to the hypothalamic region as the control organ.

Counterregulatory mechanisms tend to compensate for the loss of fat mass. This compensatory growth may occur in body areas where adipocyte hypertrophy and/or hyperplasia could result in increased morbidity. On the other hand, regrowth of adipose tissue in lipectomized areas may result in the recurrence of both obesity and body contour deformity. Thus, surgical intervention on adipose tissue (SAL or lipectomies) is not advised as the method of choice for obesity therapy. Nevertheless, SAL has a definite place in body contour surgery for the management of small, localized fat accumulations.

The hCG protocol is a safe, appropriate approach to obesity. It combines pharmacological, behavior modification, and dietetic aspects. When properly managed, it results in a rapid weight loss and excellent body contour. Clinical complications and unfavorable results are related to hazardous modifications of the original protocol.

There is some evidence that suggests that hCG possesses lipolytic activity. Therefore, the basis of use of hCG for obesity treatment might be biochemical. Because hCG does not mobilize lipids *in vitro*, the hypothalamic region might be the intermediate organ in hCG lipolytic action. On the other hand, hCG stimulates hGH secretion. Thus, it was hypothesized that hGH might be the lipolytic hormone secreted to hCG stimulation.

Commercial preparations of hCG contain β-endorphin, and opioid peptide that may affect mood behavior. We speculated that this neuropeptide may be responsible for the sense of well-being observed in our hCG-treated patients.

Since it has been reported that β-endorphin does not cross the blood–brain barrier, it was suggested that hCG might act as a "carrier" for β-endorphin in the brain. Alternatively, β-endorphin may account for an *in vitro* lipolytic activity.

The hCG method comprises a behavior modification program that helps to a better handle obese patients. There is some correlation between the behavioral program included in the hCG protocol and a current behavior modification program for obesity treatment.

The 500-kcal diet as prescribed in the original method proved to be safe and effective.

Obesity is a widespread condition afflicting millions of individuals all over the world. It is a slow killer disease, causing disability, morbidity, and diminution of the quality of life.

Table 3A. Randomized study of 450 patients treated between 1977 and 1979 in our clinic with the hCG protocol

Total patients: 450		
Females: 351		
Males: 99		
Age: females: 15–71 years		
males: 16–75 years		
Degree of overweight (%)[a]:	females:	54.23% (±25.28)
	males:	74.03% (±41.06)
Average treatment (days):	females:	41.24
	males:	41.68

[a] Degree of overweight is expressed according to the indications of the table published by the Metropolitan Life Insurance Company, 1959

Table 3B. Randomized study of 450 patients treated between 1977 and 1979 in our clinic with the hCG protocol

	Before	After	Reduction
Females			
Weight (kg)	81.60(±14.25)	70.61(±10.04)	10.99
Circumference (cm)			
Breast	105.23	98.10	7.13
Waist	89.40	79.10	10.30
Hip	111.64	101.54	10.10
Males			
Weight (kg)	101.60(±16.3)	88.46(±8.04)	13.13
Circumference (cm)			
Waist	107.72	97.05	10.67
Hip	108.97	98.57	10.40

The hCG method of treatment might be a reasonable therapeutic alternative aimed at offering relief to a longstanding unresolved problem of human metabolism.

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16. Combined medico-surgical torsoplasty (1980).

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Aesthetic Plastic Surgery

Combined Medico-surgical Torsoplasty

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Abstract. A combined medico-surgical treatment of obesity illustrates the possibility of achieving harmony of body contours with minimal scarring, risks to the patient, and effort on his or her part. Daily injections of 125 IU of human chorionic gonadotrophin, combined with a special 500-calorie diet, has proven to be a successful medical treatment in more than 6,000 patients treated over a period of 12 years. It had a rapid effect in reducing body contour circumferences over the full course of treatment, and offered the patient a sense of well-being and satisfaction. Mildly overweight responded to this treatment without surgery, a "knifeless torsoplasty." High-risk obese patients were prepared for subsequent surgery. Hypertrophic deformities in a single body area were corrected into a well-proportioned silhouette.

Key words: Obesity — Body contour surgery — Preoperative weight loss therapy — Human chorionic gonadotrophin

Daily, and more than we realize, we deal with patients suffering from sheer obesity. Prior to coming to us, they have been through all sorts of treatments; secluded away in clinics, they may have spent their yearly vacations submitting to drastic hypocaloric diets, fitness programs, spa regimes, psychologic help, or a combination of these. Different types of weight loss are observed in various situations:

1. A normal weight loss in an expected period of time. These patients with a good body contour are usually healthy overeaters who are masters of their own losses and gains in weight and were not a concern of this study.

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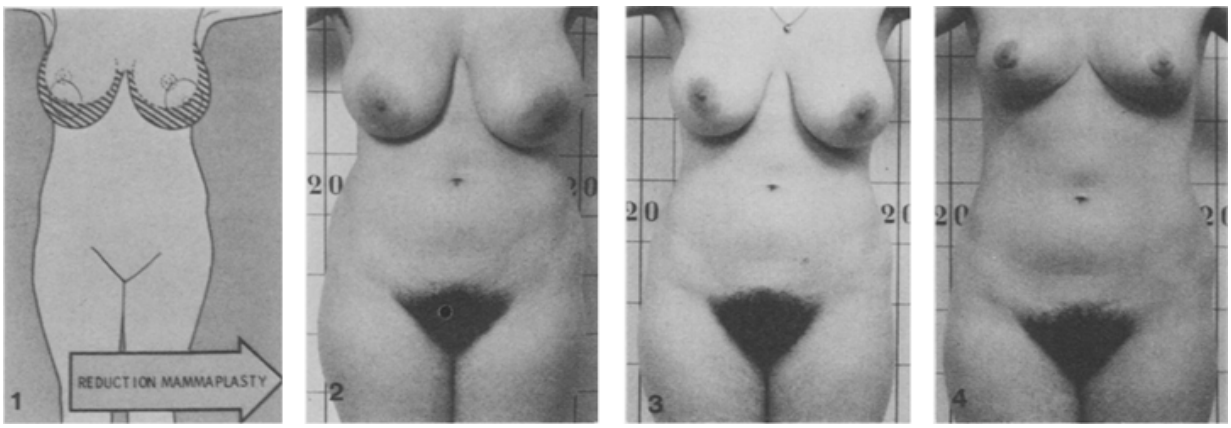
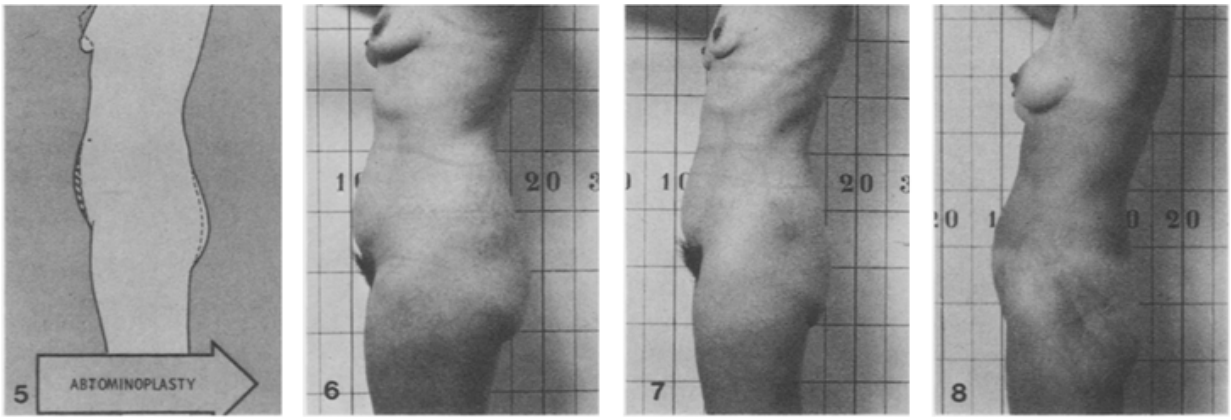


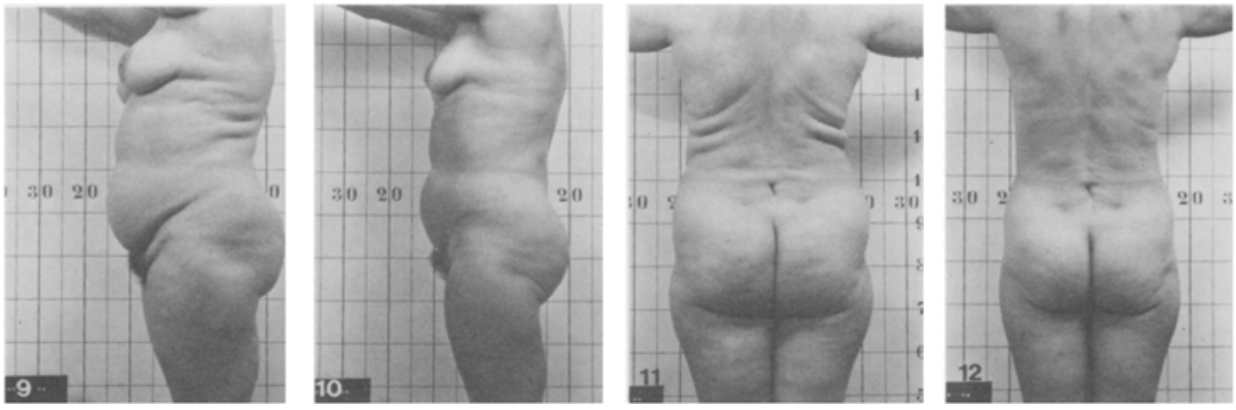
Figs. 1–4. A 20-year-old female with asymmetrical gigantomastia. She underwent 40 days of therapy with gonadotrophin and a 500-calorie diet, losing 13.6 kg (30 lb), followed by a reduction mammoplasty. Size reductions in the largest body circumferences were: 14 cm; waist, 7 cm; hips, 16 cm; and thighs, 9 cm.



Figs. 5–8. A 24-year-old female with "crumpled tummy" as a result of 2 pregnancies. She underwent gonadotrophin therapy with a 500-calorie diet for 30 days and lost 6.4 kg (14 lb). A combined torsoplasty—an abdominoplasty and augmentation mammoplasy—and thigh lift were then performed. Size reductions in the largest body circumferences were: chest, 2 cm; waist, 6 cm; hips, 10 cm; and thighs, 7 cm.

2. A slow, insufficient weight loss, mainly in the less noticeable parts of the body with a Biafran look in the upper torso and a Hottentot look over the hip and lower limb regions.
3. A massive weight loss over an extended period of time resulting in redundant skin in several body areas, especially in the hip and lower limb regions.
4. An impossibility to lose weight.

Patients in groups 2, 3, and 4 above are overweight and suffer from different degrees of obesity, with all the dangers inherent in this widespread condition of the wealthier parts of the world, such as heart and circulatory diseases, high blood pressure, fatty livers, gall- and kidney stones, gout, thromboses, and degenerative arthropathies. Putting the blame on overeating does an injustice to the truly obese individual; he often starves. These unsuccessful continuous dieters, feeling weak and tired, hungry and nervous, not willing to lose more



Figs. 9–12. A 45-year-old female with pendulous abdomen, resistant to 4 previous hypocaloric diets. She underwent therapy with gonadotrophin and a 500-calorie diet for 40 days and lost 15.9 kg (35 lb). A second medical course of this therapy is planned to improve the results further.

time or money on new dieting experiences are anxious to have the excessive fat removed by surgical operations. Two possibilities are offered:

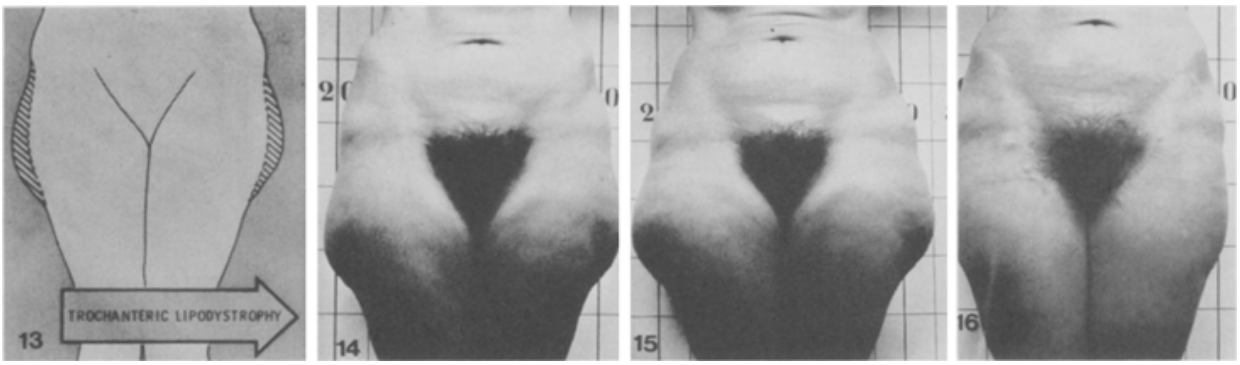
1. Plastic surgery: Candidates for all types of feasible contour surgery fall into this group.
2. Visceral surgery: An intestinal shunt, which leads through malabsorption to a massive weight loss, is reserved for the most desperate cases and will not be discussed here.

These "well nourished", seemingly healthy patients, scheduled for plastic surgery, in fact have many problems of overall disturbed body metabolism. In an evaluation of more than 6,000 patients, the risks of plastic surgical contour surgery became apparent in those patients who were not metabolically corrected prior to surgery by appropriate medical workups and supportive treatment. A particularly high incidence of pathologic blood parameters, generally unknown to the patients and their doctors, were detected in the medical workups. The necessity for more extensive preoperative chemical and blood studies for contour surgery patients must, therefore, be strongly emphasized.

In our clinic, several methods of obtaining a good weight loss prior to surgery were tried. The one which best satisfied the criteria of most interest to the plastic surgeon was found in the use of human chorionic gonadotrophin [125 IU Pregnyl (Organon) injected daily], combined with a special 500 calorie diet, advocated by A.T.W. Simeons of Rome [14, 15].

Method

Gonadotrophin was given for 3 days without any dietary restriction; then the patients were restricted to 2 meals a day, each consisting of 100 g of lean meat, a normal helping of leafy vegetables, an unsweetened rusk, and an apple or the equivalent in fruit, with salt and fluids and spices as desired. The average daily loss of weight was 250–600 g, without any inconvenience being caused, even to patients doing a hard day's work. In well over 6,000 patients treated during the past 12 years, this effect was regularly observed in all types of obesity, in both sexes of all ages. After about 40 days of this treatment and a loss of 9–13.6 kg (20–30 lb), normal appetite returned in spite of continued injections, evidently owing to the well-known "immunity" which the body develops to gonadotro-



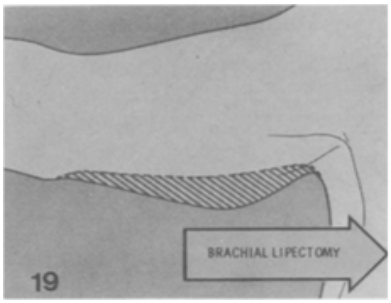
Figs. 13–18. A 30-year-old female with "Hottentot" deformity, resistant to 6 previous hypocaloric diets. After 44 days of gonadotrophin therapy with a 500-calorie diet, she had lost 11.4 kg (25 lb). She then underwent an extended thigh lift (20 cm skin resection) and a pretrochanteric lipectomy. The size reductions in the largest body circumferences were: chest, 4 cm; waist, 7 cm; hips, 16 cm; and thighs, 9 cm.

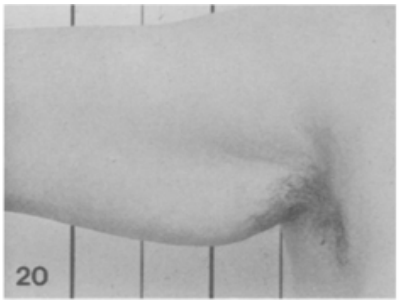
phin. This lasted for about 10 weeks to 3 months, after which time another course was given, if required, with the same effectiveness as the first. In extreme cases, a third and even a fourth course was given in this manner, so that up to 54.5 kg (120 lb) was reduced in 1 year without damage to the patient. In patients in whom only a slight reduction was required, the same feeling of inadequacy of the diet arose abruptly as soon as the visibly superfluous fat was removed. Similarly, patients who no longer received injections but continued the diet found that they could manage this for about 3 days, during which time they continued to lose weight, but that they then suddenly felt weak and hungry and were forced to increase their diet and ceased to lose weight. This indicates that the obtained results are not due to the 500-calorie diet alone.

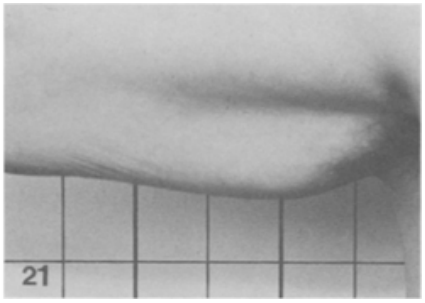
After successful treatment, each patient was carefully educated to new eating habits, according to the individual's degree of obesity, by trained dietary assistants.

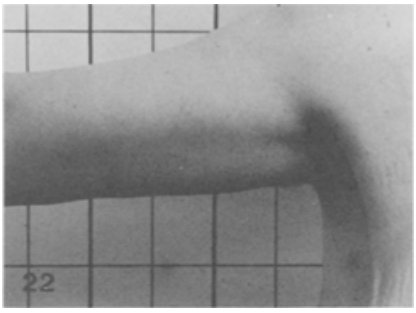
Results and Advantages

1. A weight loss on the biggest circumferences in a short period of time, avoiding flabbiness of the skin.
2. A sense of well-being throughout the weight loss treatment.
3. The treatment preoperatively on an outpatient basis with full ability of the patient to work at his or her usual job.
4. A reduced operative risk by regulation of the patient's pathologic blood parameters.
5. Surgical procedures often superfluous, thus avoiding scars, giving this treatment the nickname of "knifeless torsoplasty" (Figs. 9–12 and 19–22).
6. Better circumferential body proportions, with more accurate shaping of the hypertrophic deformations in any single body area (Figs. 1–8 and 13–18).

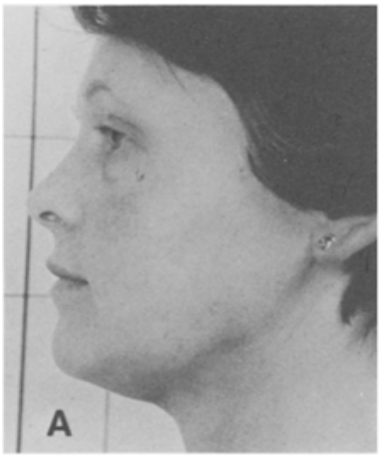








Figs. 19–22. A 28-year-old female, whose excessive weight had been resistant to 3 previous hypocaloric diets. She underwent 32 days of gonadotrophin therapy with a 500-calorie diet and lost 14.5 kg (32 lb). No surgical procedure was necessary; the "knifeless lipectomy" left no skin redundancy and avoided the long, visible scars of surgical lipectomy. The size reduction in the largest body circumference was 6.5 cm from the upper arms.



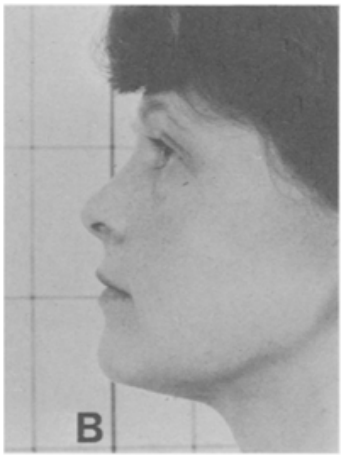


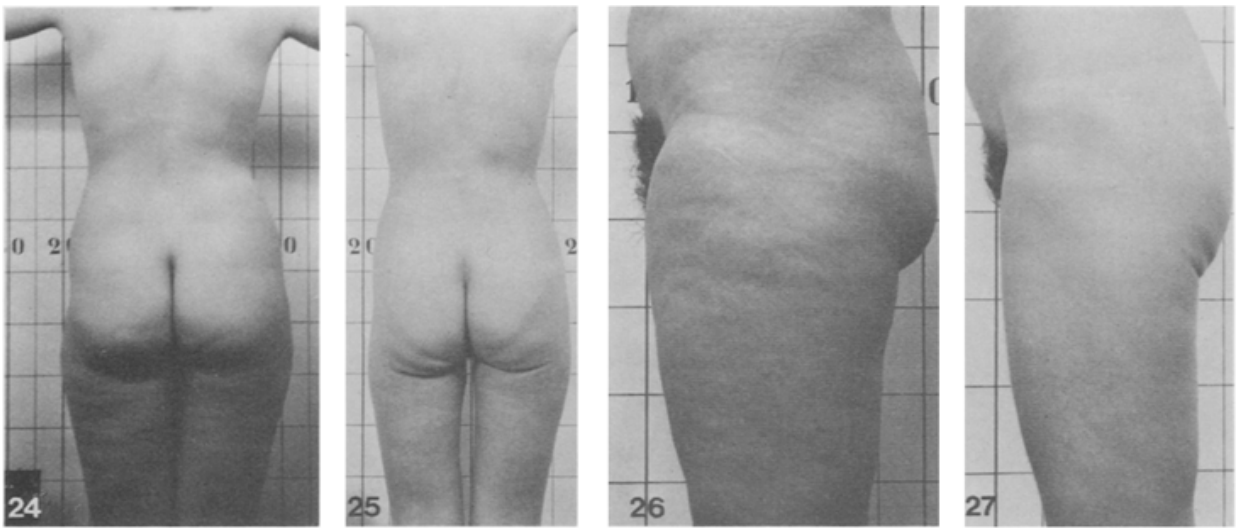
Fig. 23 A and B. Before and after therapy with gonadotrophin and a 500-calorie diet. The face retains its freshness and turgor.

7. A thin and elastic skin texture, a result of the treatment, that allowed refinement of our operative techniques and more extensive surgery when the latter was necessary (Figs. 1–8 and 13–18).

When obese patients were allowed to continue their usual feeding habits, within 10 days of treatment gonadotrophin distinctly decreased the measurements around the hips and the waist without a significant loss of weight. The patients invariably noticed a partial loss of appetite, and, in particular, that the sudden compulsive hunger, which many had experienced only a few hours after a substantial meal, had completely disappeared. The change in measurements was interpreted as a dispersal of fat away from the more favored sites, and it is thought that fat "in transit" might be more readily available for metabolic purposes than fat in "fixed deposits," in which case it would be possible to maintain such patients on 500 calories a day without their feeling weak or hungry.

The treatment does not deplete the cutaneous or other essential fat, the face retaining its freshness and turgor throughout (Fig. 23).

The disorder can be compared in its therapeutic management to diabetes;



Figs. 24–27. Same patient as in Figs. 19–22. After therapy, the massive cellulite has disappeared, and pretreated skin is thin and elastic.

either the need to balance the onset of obesity by nutritional correction is understood, and the patient is gratified by a permanent normal weight or, disregarding the personal rules, the disorder will recur.

Besides the effect this placental hormone has in obesity treatment [2–7, 13–15, 17], it has been used on large scale and has been safely tested at the university level for its extraordinary effects in treatment of arteriosclerotic vasculopathies [1, 9–11], cardiovascular disease [8], atherosclerosis [12], and degenerative arthropathies [16]. Moreover, a beneficial side effect is that it is an effective treatment for "cellulite" (Figs. 24–27). However, the method is not simple, unless one adheres strictly to the technique and interpretations outlined by Simeons [16].

The artistic part of our profession could be called "sculpture on the living." The use of this procedure in a previously well proportioned body not only restores a deformation, but it recreates lost contour beauty or creates it for the first time.

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17. Human chorionic gonadotropin treatment for obesity: a rebuttal (1974).

Human chorionic gonadotropin treatment for obesity: a rebuttal

Dear Sir:

We wish to thank Doctors Hirsch and Van Itallie for their letter (1) in the October 1973 issue of this journal, in which they re-analyzed portions of the data and also attempted to evaluate the experimental procedure and to interpret the results appearing in our original communication (2). It is reassuring that their re-analysis of our double-blind study, in which drug and placebo were assigned to patients on a random basis with injections planned daily 6 times/week for 6 weeks, duplicated the results of one portion of our analysis. Both their and our analyses indicated the mean percent of body weight lost by all patients in the human chorionic gonadotrophin (HCG) group was significantly greater ($P < 0.001$) than the mean percent body weight lost by all patients in the placebo group.

After this initial agreement, they consider several other points in their letter. We wish to comment on these as well as present some of our original data in a new manner. The thrust of their comments will be presented first with our response following.

1) There was a correlation between number of injections and weight lost.

Perhaps we should have pointed out in the original article that the number of injections was determined primarily by the length of time a patient stayed in treatment. We assumed readers would be aware that patients in studies, particularly obese patients, tend to drop out early when results do not come up to their expectations, when the treatment requires effort on their part, or when they believe they are experiencing undue side effects. The reasons for the patients not finishing treatment are: patient 5, moved; patient 6, work conflict; patients 10 and 24, discouraged and asked to quit; patient 20, didn't like diet; patient 21, went on vacation; patients 32 and 38, reached weight goal; patients 22, 23, and 35, finished series but missed an injection; patients 2, 19, 25, 26, 33, 36, and 37, unknown.

Hirsch and Van Itallie state that: "A t test of the differences in the number of injections received, 33.85 for the experimental group vs. 29.05 for the placebo, shows a barely significant t value of 1.95 at 38 degrees of freedom." They also state: "One must ask why the placebo group received fewer injections on the average than those in the treated group." The patients were randomly assigned so that variability of patient characteristics (including predisposition to stay with dietary programs) was randomly distributed between the groups, which guarantees the validity of tests of significance. Therefore, the logical answer to the question posed would be that the placebo group received fewer injections because they stayed in treatment for a shorter average time, as they were less successful in losing weight. Considering the randomization and the study design, the variable most apt to be causative in the increased weight loss appears to be the HCG.

Hirsch and Van Itallie further state that "A correlation coefficient relating number of injections received to percent weight loss shows a correlation of 0.683. Such a correlation, occurring with a t value of 3.97 and 18 degrees of freedom, is a highly significant observation. In fact, one can say that within the placebo group, nearly one-half of the variance observed is the result of the number of injections."

The key difference between our points of view and analyses seems to be in regard to random assignment of treatment to patients. Differences between treatment groups on post hoc measures of performance, correlates with the response variable (e.g., number of injections with weight loss), or other behavior of the patient are confounded with treatment effects. With the random assignment of treatments to patients, the only valid conclusion to be reached, and the usual justification for running a controlled experiment, is that it is the treat-

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ment that was or was not important. Usually a researcher does not say that post hoc correlates with the response variable (weight loss) may cause differences in the response variables (weight loss) among the treatment groups. Correlations usually have been used to indicate when two variables "co-vary," not as measures of cause and effect. Certainly a highly significant correlation is not a clear measure of strength of that correlation, as significance is so heavily dependent on sample size. Post hoc analyses, post hoc correlational statistics, systematic deletion of data, after the fact hypotheses, and preconceived notions just do not carry the same weight as a controlled randomized study for determining the existence of treatment effects.

2) When the patients receiving less than 36 injections are excluded from analysis, the significance of the increased mean percent weight loss of the HCG group compared with that of the placebo group "declined sharply."

They point out that their analysis indicates the significance level drops from less than 0.001 to a value close to 0.02. We agree.

In doing their re-analysis, 8 of 20 patients in the HCG group and 10 of 20 in the placebo group were deleted from consideration, leaving a total study sample of 22 rather than 40. Deleting observations can reduce the probability of significance irrespective of the relation between injections and treatment effects. The size of the standard error of the difference in means is basically a function of

$$1/\sqrt{\text{number of observations.}}$$

Decreasing the number of observations increases the standard error of the differences in means which reduces the t value. The number of degrees of freedom are reduced as well. Together these two can account quite easily for a drop in significance levels. Actually the 0.02 level found by Hirsch and Van Itallie is usually considered medically significant. Both Grinker, Hirsch and Smith (3) and Campbell, Hashim and Van Itallie (4) have considered $P < 0.05$ significant previously and in this letter, Hirsch and Van Itallie state, "shows a barely significant t value of 1.95 at 38 degrees of freedom." This yields a P value between 0.05 and 0.1. So by their own criteria, 0.02 is clearly significant.

When only the patients receiving 36 injections are considered, the mean loss in the HCG group is 21.75 lb versus 14.62 in the placebo group, a difference of 7.13 lb that is not too different from the 8.91 lb difference found when the weight loss of all starting patients is considered.

Too often, in studies of the treatment of obesity, dropouts are excluded from final analysis with the investigators frequently justifying this action by stating they are "uncooperative." Stunkard and McLaren-Hume (5) and Albrink (6) made appeals for an analysis of all starting patients. Of the most importance is the impact of a treatment modality on all starting patients rather than those finishing treatment. If a patient drops out because there are side effects from an active drug or lack of effect from a placebo, this is important. This was our reason for considering all starting patients in our analysis.

We have re-analyzed the total mean percent of body weight lost by each group on a weekly basis for those remaining in treatment and returning on a weekly basis, and we find the loss in the HCG group is greater than in the placebo group at each weekly interval with significances ranging from $P < 0.02$ to <0.001.

For interest, the mean weight loss per planned injection for both the HCG and the placebo group is shown in Fig. 1.

3) They question why the placebo group received fewer injections on the average than the treated group, whether this was a random occurrence and "Did the patients or someone know who was who?"

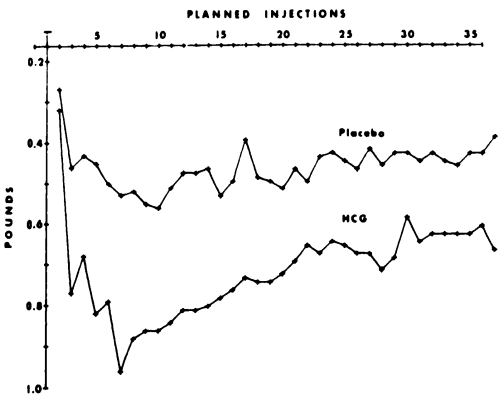

Fig. 1. Mean weight loss per planned injection.

In response, both the HCG and the placebo were prepared in identical appearing vials, randomized, labeled, and shipped from Colorado by Asher with instructions to Harper in California where the study was done. The code was not revealed to Harper until the study was over and the data had been received in Colorado. In addition, Harper saw the patients only at the initial and final visits. They were seen along with regular injectable patients in an office where the flow rate of patients was often 30/hr or more. Injections were given to all patients by a single girl. They were each seen daily for counseling, questioning, et cetera, by one of a number of other paramedical assistants. Few patients were seen continuously by one paramedical assistant for more than a few days at a time. Such a system would make biasing a study difficult, even if there were some way of knowing what was in each vial.

Another finding militating strongly against "cheating" was that HCG patients lost no more in the hip and thigh measurements per pound of weight lost than the placebo patients. There were some technical difficulties in making certain that measurements were done at the same levels before and after treatment; at the editor's suggestion, this material was deleted before the article was published.

Because the late Simeons and his followers have been about as vocal about selective loss of fat in the hips and thighs with HCG as they have about enhanced ability to follow a 500-kcal diet, if Harper or his assistants were aware of the coding and somehow cheated on reporting weight loss, hunger, and feeling of well-being, wouldn't it be likely they would have cheated on measurements also?

4) Because patients were told "the slighest deviation from any of the details will result in utter disaster," the placebo patients receiving fewer injections (and thus appearing to have more missed injections) might not unexpectedly show some difference from the treated group in their feeling and hunger response.

To check on this speculation, we calculated the percentage of missed visits in each group, and although the mean placebo treatment period is a little shorter than the HCG treatment period, there is no appreciable difference in the mean percentage of missed injections in either group while they remained in treatment. When the difference was tested for significance, a t value of 0.385 was found, which at 38 degrees of freedom does not approach significance. The mean percent of injections missed while in treatment for each of the patients in the HCG group was 7.53 and in the placebo group, 10.75.

The majority of these missed injections were for legal misses, i.e., holidays (the study was done between August and February and holiday injections were not required). In addition, as mentioned in the previous article, some patients did not receive shots during the time of heavy menstrual flow and a few of the misses occurred because of trips and for other "excused" reasons. So, it is highly unlikely this factor affects either group appreciably and certainly not one group significantly more than the other. Unfortunately, our original data were presented so that it may have appeared that a patient receiving only a few injections had many skips rather than having discontinued treatment early.

5) Analysis of hunger rated as "none," "little," "some," "much," and general feeling as "poor," "fair," "good," or "excellent" requires a special type of statistical analysis and that lumping two categories together was an "arbitrary and totally unwarranted procedure from a statistical viewpoint."

Although statisticians may differ in their personal preference for handling categorical data, all to whom we have talked agree there is no reason two categories cannot be lumped together.

The hunger and feelings questions that were used to classify the patients into four categories each do not define continuous variables, but categorical, having the scaling properties of order (perhaps Hirsch and Van Itallie might better have characterized these variables as "nonmetric" rather than "nonparametric"). The field of statistics provides several alternatives for the analysis of data. Some are based on parametric and others on nonparametric statistical procedures. We chose a parametric analysis which required the definition of a single random variable for each patient called "percent of none or little hunger responses." The none or little responses were totaled for each subject and this percentage was based on the total injections received. This variable can be

considered a continuous variable measured on two independent samples with 20 independent observations each. Thus, as with the weight loss data analysis, we followed the usual normality assumptions and performed a *t* test for significant differences which yielded the results originally reported. A comparable procedure was used to analyze the feeling of well-being data.

Perhaps a real criticism of these data presented in Table 3 of the original article should be leveled at similar tests performed on the complements "some" and "much" hunger and feeling "poor" and "fair." As these responses are dependent on the "none" and "little" hunger and "good" and "excellent" feeling responses, it is not surprising that the HCG group means were significantly different from the placebo group means.

In regard to degree of hunger, the categories of little or none could have been kept separate at the time of each patient visit as we did, or they could have been lumped together. The same is true of degrees of feeling. We have found it advantageous in gathering data to be as definitive as possible, because data can be "lumped" at the time of analysis if desired, but there is no way of subdividing these larger groups later. Generally, we attempted to assess whether or not the patients were hungry and whether or not they felt good.

6) Insufficient data are given in the article to permit re-analysis of hunger and feeling of well-being data as a function of receiving this mixture of hormones or the placebo.

We agree and have prepared a table showing for each patient the percentage of responses indicating little or no hunger or feeling good to excellent. The percentage of each patient's response indicating some to much hunger and feeling fair to poor can be obtained by subtracting these percentages from 100. To save space, we have not subdivided the little or none hunger categories or the feeling good to excellent categories. The means of the individual responses in each category vary slightly

TABLE 1
Percentage of patient responses (visit 2 to 37)

HCG			Placebo		
Patient No.	Little or no hunger	Feeling good to excellent	Patient No.	Little or no hunger	Feeling good to excellent
1	81.81	100.00	3	3.23	29.03
2	75.86	82.75	4	9.37	25.00
5	36.00	75.00	6	4.17	16.67
7	94.11	97.05	10	75.76	78.79
8	69.69	87.87	11	15.63	70.97
9	71.87	68.75	12	82.76	86.21
14	93.75	100.00	13		91.67
15	85.29	90.00	16		100.00
18	82.35	82.35	17	80.56	91.67
21	75.00	96.87	19	73.68	78.95
22	82.75	93.10	20	73.68	47.37
23	79.41	91.17	24	36.67	76.67
28	75.00	83.33	25	83.33	75.00
29	79.41	82.35	26	66.67	66.67
30	88.46	80.76	27	73.33	80.00
32	58.06	70.96	31	32.35	73.53
34	66.66	84.84	33	00.00	100.00
36	80.76	80.76	35	64.52	74.19
38	85.71	76.19	37	76.92	88.46
40	79.41	91.17	39	62.96	70.37
Mean percent of response	77.08* ±2.90[a]	85.81** ±2.05		50.87 ±8.81	71.06 ±5.32

Difference between HCG and placebo significant at: * $P < 0.002$; ** $P < 0.02$.
[a] SEM.

from the ones given in the original article, because in the re-analysis, the responses at the time of the initial visit (injection 1) were excluded and those on the day following injection 36 included (the patient thus reported on his response since the previous visit) (Table 1).

Our analysis of the difference between the mean percentage of responses of having little or no hunger for each patient in the HCG and the placebo group indicated a significantly greater value in the HCG category. The t value was 3.41, which with 36 degrees of freedom, gives a $P < 0.002$. The mean percentage of responses of feeling good to excellent for each patient was also significantly greater in the HCG group than in the placebo group. Here the t value was 2.59 which with 38 degrees of freedom yields a $P < 0.02$. It should be noted that the P value concerning the hunger rating given in the original article was less than 0.001 as compared with 0.002 in this re-analysis and that the P value of the feeling good to excellent rating changed from an original $P < 0.001$ to $P < 0.02$.

We erred in our original analysis in calculating degrees of freedom and are happy it is possible to correct this error. It should be noted, however, that the level of significance of the difference in means of the hunger ratings changed little, and although it changed more for the difference in the means of the feeling ratings, this difference still remains significant.

It is unfortunate that data on the hunger feelings of patients 13 and 16 are missing. If these patients had had high "little" or "none" hunger ratings, it might conceivably have changed the level of significance of the difference between the means found in the HCG and placebo groups. To test this, we took the highest percent of little or no hunger responses achieved by any patient in either group (94.11% by patient 7 in the HCG group) and arbitrarily assigned these values to patients 13 and 16. When this was done, a t value of 2.78 was found, which with 38 degrees of freedom, still gives a significant P value of less than 0.01.

We are happy to have this chance to respond to the letter by Hirsch and Van Itallie. It has allowed us to present further insights concerning the effectiveness of HCG and to correct two P values that were in error. Through the assistance of Hirsch and Van Itallie's re-analysis, we think it is fair to conclude as we did in the original article that there were several significant differences between the HCG and placebo groups.

First, the HCG group lost significantly more mean weight when all patients are considered ($P < 0.001$, our initial analysis), lost significantly more weight per injection when all patients are considered ($P < 0.025$, our initial analysis), lost a significantly greater mean percentage of their starting weight when all patients are considered ($P < 0.001$, Hirsch and Van Itallie's and our initial analysis), and when those receiving 36 injections are considered (P close to 2 in 100, Hirsch and Van Itallie), and lost a significantly greater mean percentage of their starting weight when those returning at the end of each of the 6 weeks are considered ($P < 0.02$ to $P < 0.001$, our re-analysis). The figure shows graphically that the difference in weight loss started early and that a difference of approximately 0.2 lb per injection persisted throughout the study.

Second, the mean of the percentage of daily patient responses indicating little or no hunger and feeling good to excellent was significantly greater in the HCG group than in the placebo group ($P < 0.002$ and $P < 0.02$, respectively, our re-analysis).

Third, as the number of injections is primarily a function of the time the patients remained in the study, Hirsch and Van Itallie's analysis suggesting that HCG patients received more injections than placebo patients ("barely significant t value of 1.95 at 38 degrees of freedom") is consistent with our contention that patients find the diet more bearable when they receive HCG. We thus conclude, as we did previously, that HCG did have a significant effect on the parameters studied.

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18. Effect of human chorionic gonadotrophin on weight loss, hunger, and feeling of well-being (1973).

Effect of human chorionic gonadotrophin on weight loss, hunger, and feeling of well-being[1,2]

W. L. Asher, M.D., and Harold W. Harper,[3] M.D.

Since Simeons (1, 2) introduced his method of treating obesity using human chorionic gonadotrophin (HCG), there has been continuing controversy concerning the effect of HCG on the program. Simeons and his followers have generally not claimed that patients eating 500 kcal daily will lose more weight when receiving HCG. They (2–4) have claimed that patients are less hungry and feel better because of the HCG and are thus more apt to remain in treatment. There have been a number of literature reports of double-blind studies (5–9) concerning the effect of HCG on weight loss. Only one (8) indicated HCG may be of more value than a placebo. However, as pointed out by Gusman (4), most investigators significantly altered Simeons' basic program. Both Simeons and his followers have vociferously maintained that strict adherence to the basics of Simeons' program is essential if HCG is to be useful.

Because of the increasing popularity of Simeons' program, it was felt further attempts should be made to assess, in a double-blind manner, not only weight loss but the degree of hunger and the feeling of well-being of patients receiving HCG or an identically appearing placebo.

Patients and methods

One of us (HH), who has an active practice using HCG in weight reduction, did the clinical work. The other (WA) prepared the protocol, labeled the vials of HCG and placebo, and analyzed the results. Forty female patients received, in a modified double-blind manner, either HCG injections or placebo injections. HCG and placebo were prepared by Glogau & Co., Chicago, Illinois, in identically appearing vials. The HCG preparation was prepared in the usual commercial manner. It contained, in addition to HCG, mannitol with monobasic and dibasic sodium phosphates as buffers. The placebo preparation consisted of mannitol with monobasic and dibasic sodium phosphates as buffers.

All patients were evaluated for weight loss and other parameters. The code was not broken until the clinical work was completed and the data had all been gathered.

Patient selection

All patients were females 18 years of age or older who had no known serious disease processes requiring significant medications. They were selected from apparently well-motivated patients desiring to enter the HCG program for weight reduction. None was selected who had previously been on Simeons' program. Also excluded from the study were patients who had received appetite suppressants or other weight medications in the 6 weeks prior to the start of the study. None had lost more than 5 lb in the 3 months prior to treatment. No patients were to receive diuretics during the study. Oral contraceptives, estrogen, or thyroid products needed to maintain a euthyroid state could be continued if the patients were receiving them prior to the start of the study. They were neither to be stopped nor started during the study period. Patients known to be pregnant were excluded from the study.

Parameters measured

Blood pressure was taken at the start and at the end of treatment with the patient in a sitting position. The patients were weighed with approximately the same amount of light clothing each day. They were questioned daily about hunger; the responses of those reporting hunger were recorded as "little," "some," or "much." Patients were also asked on each visit how they felt, and the responses were recorded as "excellent," "good," "fair," or "poor."

Injections

Three patients received injections from each vial. Numbers of the three patients to receive injections from each vial were assigned on a random basis before the vials were shipped to the clinical investigator (HH). A series of six vials, of either HCG or an identically appearing placebo, were

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labeled for each trio of patients. Two series of vials, however, had only two numbers on each vial. A new vial was used each 7 days. The study material was kept refrigerated after mixing with bacteriostatic water. Injections were given while cold; at no time did the medications remain at room temperature. Patients were to return to the office 6 days each week for 36 injections (unless the desired weight was achieved prior to this). They received 125 IU of the study material intramuscularly in the upper-outer quadrant of the buttocks on each visit. Injections were discontinued on the days of heavy menstrual flow of a few patients (usually 2 or 3 days). No appetite suppressants or other medications were given. Patients were advised to use no laxatives but were permitted to use a Fleet's or Baxter enema if needed.

Patients were advised to "avoid the use of any and all cosmetics containing fats or oils." They were also to avoid skin contact with other oils or fats. Chewing gum, throat pastilles, vitamin pills, cough syrups, and alcohol were not permitted. The patients were encouraged to drink 8 to 10 glasses of water daily.

Patients were repeatedly advised that absolute adherence to the program was essential. They were told the slightest infractions would slow or stop their weight loss. "The slightest deviation from any of the details will result in utter disaster."

Diet for days of the first three injections[4]

Patients were encouraged to eat all they wished of the foods allowed. No beverages containing caffeine were permitted during this period.

Breakfast and lunch, 1st day. Meat: (all lean) beef, veal, lamb, pork, chicken, turkey, beef or veal heart. Hard cooked eggs. Vegetables: brussels sprouts, cauliflower, green peppers, cucumbers, spinach (not canned), Swiss chard, cabbage, fresh asparagus, tomatoes, kohlrabi. Fruit: apples, oranges, and grapefruit at any time until lunch.

Afternoon of 1st day to noon 2nd day. Patients were to fast after lunch the 1st day until noon the 2nd day. There was no limit on noncaloric, noncaffeine fluids during this period.

Noon 2nd day until noon 3rd day. Patients could have only fruits and vegetables to be selected from the fruit and vegetable groups of the 1st day.

Lunch and evening meal 3rd day. Same as breakfast and lunch of the 1st day.

Diet for remainder of the study period

On the 4th day of injections, the patients were started on a low fat diet of 500 to 550 kcal (no mention was made of calories, however). They were warned "you must not make any changes or substitutions even though you may think they are an improvement or you will be utterly disappointed."

Patients were advised to keep a daily food diary and bring it with them each day. Two meals each day were to be eaten. Meals could be eaten at any time but foods from both meals could not be eaten at the same time. For each meal, one item was to be chosen from each of four food groups, protein, vegetable, bread, and fruit.

Protein group

All meat and fish were to be weighed on a postal scale. Three and one-half ounces (raw weight) were to be eaten at each meal.

1) Meat: Chicken breast (white meat, excluding skin), chicken livers purchased raw and cooked. Veal, in the following lean cuts only: *a)* sirloin, *b)* rump roast, *c)* loin chop. Lean beef hearts, dried chipped beef (3.5 oz). No other beef allowed. All meats and seafoods to be prepared by fat-free cooking.

2) Seafoods: White fish, fresh or frozen, unbreaded, as the following: flat fish (sole, flounder), haddock, pollock, perch, pike, white sea bass, halibut. *Shellfish:* Lobster, crab, shrimp, only. Irisbrand dietetic canned Cohoe salmon, 3.75 oz (oil must be washed from top). No dried, pickled, or smoked fish, or other seafood allowed.

3) Meat substitutions: Hoop (farmer or pot) cheese, 4 oz mixed with water and seasoning. Occasionally, the whites only of six hard-cooked eggs might be taken as a protein substitute. No cottage cheese was allowed.

Vegetable group

One-half to one cup of one type of the following vegetables at each meal: asparagus, beet greens (not beets), cabbage, celery, chard, chicory, Chinese cabbage, cucumbers, dill-sour pickles (these must be unsweetened), endive, escarole, fennel, kale, lettuce salad, Mung bean sprouts, mushrooms, onions, parsley, red radishes, spinach, string beans, summer squash, tomatoes, watercress. Low calorie dressings containing no more than 1 kcal/tablespoon might be used.

Bread group

Choice of one of the following: one average size bread stick (Grissino), melba toast, Finn crisp cracker (very thin), one square of Norwegian flatbread, or one-third of an English muffin containing 75 kcal or less per muffin (actual calories must be listed on the package).

Fruit group

Choice of one: apple, orange, handful of strawberries (approximately 8 oz), one-half cantaloupe, or one-half grapefruit, one-fourth casaba or honeydew melon, ½ cup sugar-free cooked rhubarb (artificial sweetener permitted), ½ cup of the following (fresh or waterpacked, and/or artificially

[4] The basic 500- to 550-kcal diet was suggested by Simeons. The specific details of this and the diet for the first 3 days in toto were designed by Peter G. Lindner, M.D., and are reprinted with his permission.

sweetened): sliced peaches, apricots, gooseberries, or papaya. One cup D-Zerta gelatine dessert (other sugar-free brands allowed).

The following were also allowed at any time: 1) juice of one lemon daily for all purposes; *2)* one tablespoon of milk/day; *3)* salt, Lawry's seasoning, pepper, vinegar, dry mustard powder, garlic, sweet basil, thyme or seasonings, but no oil, butter, or dressing; *4)* any amount of water, black coffee or tea, dietetic soft drinks marked 2 kcal/bottle or less, and artificial sweeteners.

The diet sheet ends with "Any slight change in the above diet rules will result in downright disappointment." The patient was also impressed that he was to lose weight each day or a reason must be found, i.e., fluid retention, dietary digressions, et cetera.

The initial workup included a medical and dietary history, physician examination, and a number of laboratory tests.

Results

Of the 40 patients starting this study, 17 of 20 in the HCG group and 13 of 20 in the placebo group completed 30 or more injections (Table 1). Data on all starting patients were included in the final analyses whenever possible. Final blood pressures and measurements were not obtained on patient 2 of the HCG group who left town due to a death in the family. These data were also unavailable on patients 19, 20, 25, 26, and 33 of the placebo group who dropped out of treatment early. Data concerning hunger in patients 13 and 16 were misplaced and thus not included in evaluating the degree of hunger for this group.

The mean age of the HCG group was 37.8 years (range 18 to 63) and that of the placebo group was 38.4 years (range 21 to 67). The mean height of the HCG group was 64.2 inches (range 60.2 to 70.0), whereas the placebo group had a mean height of 64.0 inches (range 58.5 to 67.5).

Weight loss data on all patients are included in Table 1. The mean starting weight was 6.3 lb greater in the placebo group than in the HCG group. This difference, however, was not significant. The mean weight loss in the HCG group was 19.96 ± 1.63 lb and 11.05 ± 1.29 lb in the placebo group ($P < 0.001$). The mean percentage of starting weight lost in the HCG group was 11.47 ± 0.58 and 6.77 ± 0.83 in the placebo group ($P < 0.001$). The mean weight loss per injection was 0.585 ± 0.044 lb in the HCG group and 0.403 ± 0.047 lb in the placebo group ($P < 0.025$). Fourteen patients lost 15 lb or more in the HCG group and in the placebo group five lost 15 lb or more.

The change in mean systolic and diastolic blood pressures during treatment was not significant in either group at the $P = 0.05$ level (Table 2). Patients 2, 19, 20, 25, 26, and 33 were excluded from analysis because of incomplete data.

In the HCG group, 76.6 ± 3.30% of the daily responses indicated little or no hunger. In the placebo group, 48.7 ± 4.44% of the daily responses indicated little or no hunger ($P < 0.001$) (Table 3).

Of the daily responses of patients in the HCG group, 86.5 ± 2.66% indicated they felt "good" to "excellent" as compared with 70.0 ± 3.82% of the responses in the placebo group ($P < 0.001$) (Table 3).

Discussion

The mean weight loss and the mean percentage of starting weight that was lost were significantly greater in the HCG group than in the placebo group. It seems unlikely that if both groups had followed their diets strictly there would have been a significant difference in weight loss between the groups. Advocates of this method, including Simeons (1–4) feel that with HCG the patients are less hungry and generally feel better. Responses to daily questioning regarding hunger and feeling of well-being in this study are consistent with these views. It thus seems probable that the increased weight loss of the patients on HCG was related to the fact that they followed more closely the dietary instructions than did the placebo group.

Of the four reports of double-blind studies in the literature, only the study of Lebon (8) showed a significantly greater weight loss in the HCG group than in the placebo group ($P < 0.05$). The results of our study were quite unexpected by the author responsible for study design because the results of our initial study were negative, as have been most double-blind studies reported in the literature.

There was strict attention given to limiting

dietary fat. Simeons (3) pointed out that American beef, which is feed lot fattened, contains much more fat than Italian beef. No beef other than beef hearts or dried chipped beef was allowed on this program. All fats were markedly restricted. Even cosmetics containing fats were curtailed, although it is difficult to see how this would affect the pro-

TABLE 1
Starting weight and weight loss

Patient no.	Age, years	Height, inches	No. of injections	Starting weight, lb	Loss, lb	Percent body weight loss	Loss, lb, per injection
HCG group							
1	26	64.5	36	177.5	31.75	17.9	0.882
2	23	63.5	32	149	13.25	8.9	0.414
5	18	64.5	28	141.5	11.5	8.1	0.411
7	27	62.25	36	135	11.25	8.3	0.313
8	51	70	36	222.5	20	9.0	0.556
9	36	64	36	156.5	14.5	9.3	0.403
14	43	68	36	280	41.5	14.8	1.153
15	57	64	36	141.5	17.5	12.4	0.486
18	22	65.5	36	166.5	20.25	12.2	0.563
21	59	66	33	165.75	21	12.7	0.636
22	51	62	35	259.25	18.25	7.0	0.521
23	34	63	35	164.75	22.25	13.5	0.636
28	37	66	36	144.25	17.75	12.3	0.493
29	47	62	36	151	17	11.3	0.472
30	34	62	36	180	22	12.2	0.611
32	21	65	32	123	13.25	10.8	0.414
34	38	64	36	221.75	28.75	13.0	0.799
36	33	62.5	28	171.25	21	12.3	0.750
38	36	64.5	22	137.5	14.5	10.5	0.659
40	63	60.25	36	145.75	18.75	12.9	0.521
Mean				171.7	19.96[a]	11.47[a]	0.585[b]
SEM					±1.63	±0.58	±0.044
Placebo group							
3	65	66	36	160.75	11.25	7.0	0.313
4	48	64.5	36	234.5	15	6.4	0.417
6	34	62.5	27	147	3.75	2.6	0.139
10	57	61	35	146.25	8.25	5.3	0.236
11	67	62	36	141.5	9.50	6.7	0.264
12	52	64	36	159.75	11.25	7.0	0.313
13	48	58.5	36	139	20.5	14.7	0.569
16	25	67	36	163.75	22	13.4	0.611
17	53	60	36	152.75	18.5	12.1	0.514
19	24	67	20	210	12.75	6.1	0.638
20	33	64	20	136.5	4.5	3.3	0.225
24	51	64	31	155	9.25	6.0	0.298
25	22	67.5	13	159.25	2.5	1.6	0.192
26	21	67	4	197	4.25	2.2	1.062
27	32	65	36	179.25	17.75	9.9	0.493
31	35	67.5	36	148	9.25	6.3	0.257
33	28	62	9	166.75	3	1.8	0.333
35	27	63	35	149	13.75	9.2	0.393
37	22	62.5	27	157.75	12.75	8.1	0.472
39	25	64.5	36	195.75	11.25	5.7	0.313
Mean				165.4	11.05[a]	6.77[a]	0.403[b]
SEM					±1.29	±0.83	±0.047

[a] Difference between the HCG and placebo groups, significant at $P < 0.001$. [b] Difference between the HCG and placebo groups, significant at $P < 0.025$.

TABLE 2
Blood pressure

	Mean starting blood pressure		Mean final blood pressure	
	Systolic	Diastolic	Systolic	Diastolic
HCG	120.7 ± 4.70[a]	77.4 ± 1.80	115.1 ± 3.89	72.5 ± 1.65
Placebo	122.1 ± 2.87	79.2 ± 2.16	120.0 ± 2.92	78.0 ± 2.50

Patients 2, 19, 25, 26, and 33 were excluded from analysis because final blood pressures were not obtained.
[a] SEM.

TABLE 3
Percentage of all daily patient responses of hunger and feeling of well-being

	Hunger				Feeling			
	None	Little	Some	Much	Poor	Fair	Good	Excellent
HCG	32.8	43.7	16.5	7.0	0.5	13.0	63.2	23.3
	76.6[a] ± 2.60[b]		23.4[a] ± 3.30		13.5[a] ± 2.66		86.5[a] ± 2.66	
Placebo	15.6	33.1	33.9	17.4	6.1	24.0	49.6	20.3
	48.7[a] ± 4.44		51.3[a] ± 4.44		30.0[a] ± 3.82		70.0[a] ± 3.82	

Patients 13 and 16 were excluded from hunger analysis because these data were unavailable.
[a] Difference between HCG and placebo group, significant at $P < 0.001$. [b] SEM.

gram as there is no evidence in the literature that fats are absorbed through the skin. It does, however, seem possible that such extreme measures may have impressed the patients with the necessity of curtailing their dietary fat intake.

A number of physicians using HCG in this manner feel that once the HCG is mixed with diluent it must not be allowed to stand at room temperature and, even when refrigerated, activity is uncertain after 1 week. In this study, each vial was refrigerated and used only 1 week after mixing. The material was injected cold.

HH saw the patients only at the time of the initial and final visits. His office assistants, who were quite enthusiastic about the program, saw the patients 6 days each week. Patient charts were reviewed periodically by HH and his assistants during the course of treatment. The patients had 125 IU HCG (or equivalent placebo) injected deep im in the buttocks on each visit, with the exception that no injections were given to a few patients on the days they experienced heavy menstrual flow. The patients were required, however, to report 6 days each week whether or not an injection was received.

Laxatives and other medications (with the exception of aspirin) were to be avoided if at all possible. Three patients received other medications. All were in the HCG group. One was on birth control pills (no. 2), one on estrogen (no. 15), and one on thyroid (no. 5). The patient on thyroid was retained in the study for the sake of completeness, although the dosage of desiccated thyroid which the patient was taking prior to the start of the study was reduced from 2 grains to 1 grain on the 12th day of the study. It is doubtful this change in dosage significantly affected the patient's weight loss.

Except for receiving the study injections, the subjects were treated in a manner similar to that used in treating HH's regular patients receiving HCG. At any given time, the study patients constituted only a small portion of the patients receiving injections at HH's office.

As we concur with Albrink (10) that all

starting patients should be included in the analyses rather than only those completing treatment, we have included all starting patients.

The placebo used in our study was as nearly like the HCG preparation as possible with only the HCG itself missing. Thus, the HCG and placebo preparations should have been essentially indistinguishable on the basis of appearance or the local sensation of the patient who received the injections.

In addition to the study reported here, we have also completed a double-blind study involving patients of four physicians using Simeons' programs modified to varying degrees. Three of these physicians had had little or no experience with the use of HCG in weight reduction. None of their programs approached the rigidness of the program considered in detail in this report. For instance, one physician allowed some patients to administer their own HCG injections at home. One physician at times gave injections three times/week and one gave injections five times/week.

Physicians were allowed to use diets of their own choosing, as these patients were seen in the course of their regular practice. None of these four physicians insisted on the patient's absolute attention to detail in contrast to the physician whose practice is reported here. This is particularly true in regard to the restriction of fat intake.

The dropout rate was high in all practices involved in the initial study. When weight loss was analyzed for each practice, there was no significant difference between the HCG and placebo groups in any practice. Combined data from all four practices revealed 28 patients were on HCG and 32 on the placebo. The mean number of visits in the HCG group was 18.0 and 18.5 in the placebo group (36 visits possible).

When all starting patients were analyzed, the mean weight loss in the HCG group was 6.8 lb and 6.5 lb in the placebo group. This difference in weight loss was not significant. Thus, it appears that insistence on strict adherence to details is correlated with success (even in the placebo group).

In these four studies and the study presented here only females were included. Because males tend to lose larger amounts of weight, we felt including a few males in each group was undesirable. A large enough series of males needs to be studied so the results in males can be analyzed in a statistically meaningful way.

Fleigelman and Fried (11) injected 50 IU HCG daily intraperitoneally for 7 days into rats. Controls received 0.2 ml saline. The rats were killed after 7 days. The levels of three enzymes involved in linking glycolysis to the esterification and synthesis of fatty acids were assessed. There was an 85%, 35%, and 48% reduction in the adipose tissue levels of alpha-glycero-phosphate dehydrogenase (AGPD), lactic dehydrogenase (LDH), and glucose-6-phosphate dehydrogenase (G6PD), respectively. Liver levels of G6PD and muscle levels of AGPD were also significantly reduced. These enzymes play significant roles in directing lipid synthesis. If these reductions in enzyme levels are in turn responsible for a decrease in the rate of fatty acid synthesis, a possible enzymatic basis for the finding in our present study is suggested.

The extraction method used in preparing HCG from pregnant human urine is similar to the extraction method used for the preparation of urogastrone, a hormone inhibiting gastric secretion (12, 13). These authors report HCG preparations cause inhibition of gastric secretions even when the gonadotrophal activity of HCG preparations is destroyed. Ghosh (14) reported different activity rates for gonadotrophic and antisecretory effects in rats when two purified gonadotrophin preparations were assayed. In addition, van Hell et al. (15) have presented evidence that HCG preparations may be fractionated into a number of HCG components differing from each other in biological potency, electrophoretic mobility, and sialic acid content.

It is conceivable that the activity of HCG preparations in regard to weight reduction could be related to a specific HCG fraction or fractions, or to urogastrone, or other unknown urine components extracted by this method. If this were the case, such "fat mobilizing" activity levels might vary considerably in different preparations and batches of HCG. This might in part explain the variability in results in various reports where HCG has been used.

Another possible explanation of negative results might be the loss of activity of HCG with time after mixing especially if not refrigerated. It is probable in most studies that an individual patient received injections from a single vial which, after mixing, would be a minimum of 6 weeks old by the time of the final injection.

The 500- to 550-kcal eating plan needs supplementation of certain items such as calcium to make it nutritionally complete. However, in the interest of simplicity, supplements were not included in the present study.

Whether the long-term results of weight loss using single or multiple courses of HCG injections are better than the usual dismal long-term results of weight reduction needs objective examination. It seems doubtful such would be the case unless the physician involved continued to work vigorously with the patient in the re-education of eating patterns.

The strict requirement that the patient must follow meticulously the various aspects of the program seems almost ritualistic. Whether certain aspects of this ritual are necessary for success when HCG is used remains to be seen. Proponents generally insist a minimal intake of dietary fats is necessary. The emphasis on strict attention to all details may at least motivate the patient to more careful restriction of his daily food intake.

It is interesting to note that HH's patients who were given a placebo lost more on the average than either the HCG or placebo patients of the other four practitioners (11.05 lb versus 6.8 and 6.5 lb, respectively). It therefore appears that HCG used in a casual program of weight reduction, as it often is in a general practice, is of no value. The fact that HH's placebo patients lost more weight in a 6-week period than most physicians' patients do on other diets and/or medications is in itself interesting. Certainly, the psychological impact of receiving a daily injection which the patient believes in is important.

It is hoped other investigators will repeat this study. The insistence on strict adherence to a low fat, low calorie eating plan seems critical. Ideally, each patient should have six or seven individual weekly vials that would make blinding more complete than in this study. Each vial should be kept refrigerated after reconstitution with bacteriostatic water, and should not be used longer than 1 week. Patients selected should be sufficiently overweight to assure they will not reach their desired weight before the termination of the study.

Summary

Twenty female patients on 500- to 550-kcal diets receiving daily injections of 125 IU of human chorionic gonadotrophin (HCG) were compared with 20 female patients on 500- to 550-kcal diets receiving placebo injections. Patients in both groups were instructed to return for daily injections 6 days each week for a total of 36 injections (unless desired weight was achieved prior to this). The HCG group lost significantly more mean weight, had a significantly greater mean weight loss per injection, and lost a significantly greater mean percentage of their starting weight. The percentage of affirmative daily patient responses indicating "little or no hunger" and "feeling good to excellent" was significantly greater in the HCG group than in the placebo group. Additional investigation of the influence of HCG on weight loss, hunger, and well-being seems indicated.

We wish to acknowledge the valuable assistance of Lynne Stone who was responsible for carrying out the details of the study on a daily basis.

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Special Article

Chorionic Gonadotropin in Obesity

Further Clinical Observations

HARRY A. GUSMAN, M.D.[1]

Sciences are judged by their fruits and in medical practice the outcome of a treatment is no less a test of the doctor's use of his conceptual scheme than is the outcome of a laboratory experiment a test of the theory of the experiment.

Lord Bacon (1)

It is universally acknowledged that to be overweight is a serious handicap. The literature abounds with insurance statistics which show that the death rate is higher among the obese of every age group. No informed person would deny that obesity is a cause for concern or that it is a legitimate—even essential—subject for much further scientific and clinical investigation.

The truth is that science has not yet produced an explanation for the disease, and obesity remains one of the most puzzling subjects in the practice of medicine. At a time when medicine can boast of successfully transplanting a human heart, it is only natural that our ego is pricked when we cannot answer the seemingly simple question of why some people get fat. The result is that a subject that is, in fact, still enshrouded in mystery calls forth many dogmatic and doctrinaire pronouncements from people otherwise famous for professional caution.

It is a little embarrassing to look back over my 40 years of medical practice and remember some of the far-fetched approaches I have been willing to try in the search for a breakthrough in the treatment of obesity (2), and I know that I am not alone. Suffice it to say that until the past decade, no technique—no matter how imaginative—has brought any significant success.

Although research in the past 20 years has developed much evidence to refute the traditional concepts of the cause of obesity, most physicians have clung to the view that obesity is caused by overeating, pure and simple, i.e., the intake of calories as food is greater than the expenditure of calories as energy.

Naturally, the treatment offered by these physicians consists of a reduced calorie diet, a lecture on self-discipline, and perhaps some medication. Otherwise, weight control has been relegated to a "do-it-yourself" project. Some have treated it as a moral problem rather than a medical problem, verbally punishing the patient for alleged deviation from the diet and thus adding more guilt to the already guilt-laden obese patient.

This treatment is doomed to failure in most cases, and the inevitable frustration it produces has caused many physicians to give up treating obesity altogether. Occasionally there is a tendency even to disparage—albeit subtly—other physicians who persist. The result has been a flourish-

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ing of fad diets and parascientific theories of metabolism.

I am one of the diehards who continue to treat the condition seriously. I believe that obesity is more than a simple disturbance of the caloric balance sheet and that there is a more intricate process at work. During the past 10 years I have been treating obesity with a method developed by Dr. A. T. W. Simeons (3) that uses human chorionic gonadotropin (HCG). I have treated well over 2,500 patients of both sexes, aged 15 to 75.[2] Since all were private patients no double-blind tests or other experimental studies were undertaken.

It is with consternation that I must admit I cannot yet fully explain why Dr. Simeons' method works. And, it should be noted that not everyone shares my finding that it does work.

My own early skepticism of the method quickly dissipated after I had an opportunity to observe Dr. Simeons' work at his clinic in Rome. Since that time, experience has shown his method to be not only the most scientific approach to the problem but also the safest and most productive.

According to the dictates of the scientific method, a new theoretical concept cannot be incorporated into the body of accepted knowledge except on the basis of empirical research. In order to test the new idea, replication research must, of course, adhere meticulously to the author's original techniques. However, while a new theory is being tested, the practicing clinician's main concern is whether the new technique works—as long as it is safe. In the meantime, as far as the clinician is concerned, the new theory should give an intellectually satisfying interpretation of the processes underlying observable phenomena, should not violate known clinical facts, and should afford a precise, replicable technique, the results of which are easily assessed. In my judgment, Dr. Simeons' method satisfies all of these requirements.

To understand Dr. Simeons' method one must appreciate the theoretical framework out of which he developed the technique.

Basic theoretical considerations:

1) Definition
2) Fat-regulating center
3) Existence of different types of fat cells
4) Obesity during pregnancy
5) Nature of HCG
6) Safety of HCG in the treatment of obesity

Dr. Simeons' new concept of obesity is that it is a definite metabolic disorder, much as is diabetes, caused by a breakdown of a regulating mechanism located in the diencephalon, or hypothalamus. He calls this the fat-regulating center (3).

Although Simeons was among the first to suggest the role of the hypothalamus in obesity, the literature abounds with evidence of some regulating mechanism in the hypothalamus that governs the intake of food and its utilization (4–8). Others in the field have expressed belief in the presence of a similar regulating mechanism. Sir Vincent B. Wigglesworth (9), the noted British biologist, in his work with insects emphasizes the importance of the nervous system as a source of secretions that regulate metabolism and insists that evidence points to similar action in mammals.

The genetic factor in obesity fits into this concept, since offspring can inherit various types of regulating mechanisms from their antecedents in the same way that they inherit various other attributes (10, 11).

Different Types of Fat Tissue

Dr. Lester B. Salans and his co-workers (12) at Rockefeller University found that

[2] For the original data of these patients, order Document 00337 from ASIS National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, N. Y. 10001, remitting $1.00 for microfiche or $3.00 for photocopies.

adipose cells in the obese differ from normal fat cells. These obese cells are not only more numerous, but the individual cell is larger and seems overstuffed. Furthermore, these overstuffed cells metabolize glucose less efficiently than the normal adipose cells. This cytological evidence would indicate that normal fat tissue differs from the abnormal fat deposits of the obese.

Normal fat tissue is essential to good health and serves two functions, as structural material and as reserve storage for fuel.

As structural material, it serves to protect such organs as the kidneys and the coronary arteries and it provides a pad in the sole of the foot, without which we could not walk. It also provides the padding underneath the skin which keeps it firm and smooth.

Since fat is the highest possible concentration of fuel for energy, a certain amount is distributed all over the body and serves as a reserve storage of fuel. This is converted into energy when starvation is forced on the individual or during a protracted illness. Even if the body stocks this normal fat to capacity this is not considered to be obesity.

Abnormal fat tissue is that accumulation, in certain parts of the body, from which the obese patient suffers. This type of fat is also a potential reserve for fuel, but is not immediately available in nutritional emergencies. Only after the normal fat reserves are exhausted will the body yield its abnormal fat to be utilized for the emergency.

When an obese patient severely reduces his diet he first utilizes his normal fat reserves to make up the nutritional deficit. By the time the normal reserves are exhausted and the abnormal fat tissues begin to make up the nutritional deficit, the patient is already complaining of weakness and hunger while the ugly fat deposits—of which he originally wished to rid himself—have hardly been reduced. At this point, the patient often becomes depressed and frustrated, and the diet is abandoned. The increased food intake that follows soon replenishes the normal fat stores, the patient feels much better, and the overweight is perpetuated or even increased. This is probably the best explanation for the many failures to reduce weight.

Pregnancy and Obesity

There does exist one special kind of nutritional emergency when all types of fat cells are immediately utilizable. During pregnancy every ounce of the normal reserve fat as well as the abnormal fixed deposits are placed at the disposal of the growing fetus. Simeons has suggested that it is the presence of large quantities of HCG during pregnancy that brings about this change through the hypothalamic center. If true, this would account for two interesting phenomena of pregnancy:

a) A woman may gain weight during pregnancy but she never becomes obese in the true sense of the word. The excess fat is more evenly distributed all over the body.

b) Secondly, if an obese woman does become pregnant, it is the best time, and the easiest, to reduce her excess weight without harm to herself or the fetus.

The presence of HCG in the body as such has no reducing action. A loss of weight can only be brought about by a concomitant nutritional deficit. During pregnancy the needs of the embryo act in this direction but in treating the obese with HCG this deficit must be obtained by a very low (500 kcal) diet.

The Nature of HCG

Found only during pregnancy, HCG has a protective influence on the health and nutrition of mother and baby. In fact, it has long been called "the protective hormone of pregnancy." It could well be one of the most important hormones in pregnancy and, therefore, in the propagation

of our race. Yet, it has not received much attention in research.

Human chorionic gonadotropin was first utilized by the two German scientists, Aschheim and Zondek, who discovered it in the urine of pregnant women. When several cubic centimeters were injected subcutaneously into immature mice, hemorrhagic follicles were produced in their ovaries and this became the basis for the first biological test for pregnancy, known as the Aschheim–Zondek test (13).

Because the immature ovaries were stimulated, the material in the urine was thought to be gonadotropic, and it was misnamed human chorionic gonadotropin (HCG). It has since been established that the observed changes can be brought about only in immature animals with intact anterior pituitary glands (14). The conclusion, therefore, is that HCG is not gonadotropic and not a sex hormone at all. Its action is probably produced by stimulation of the hypothalamus, which in turn influences the anterior pituitary gland. It should not be confused with the true gonadotropic hormones of the anterior pituitary, namely, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Only quite recently have some of the properties of HCG been actively researched. In 1967, an article in the *Journal of Endocrinology* referred to HCG as "a hormone complex" with probable metabolic capabilities (15).

Is HCG Safe?

Consider the following facts about HCG:

a) Its universal existence exclusively, and in large amounts, during a most important stage of human development.

b) Its presence in large quantities in the blood stream of both mother and fetus during the entire pregnancy, without any untoward effect on any organ system of either the mother or a fetus of either sex.

c) The excretion of surplus HCG through the kidneys for 9 months during pregnancy, reaching as much as a million units daily, as compared with a dosage of only 125 units daily for a course of treatment lasting 40 days.

Many physicians needlessly hesitate to use small doses of HCG for a limited time, although they prescribe daily doses of such powerful hormones as thyroid, insulin, cortisone, estrogen, and many others. In the many thousands of cases where HCG has been employed, not a single substantiated case of adverse reaction has been reported. Clearly, Dr. Simeons' HCG treatment can be acceptable to the clinician as a safe procedure.

What About Its Effectiveness?

Much has been written about Simeons' method, both in this country and abroad. Reports have been controversial, but most of the adverse criticism has come from men who have disregarded some of the basic rules of the procedure.

I have carefully examined all the adverse criticism in an attempt to reconcile it with my own clinical observations. In each case I have found basic methodological flaws or interpretive errors, and my confidence in the procedure remains unshaken.

Let us examine the opposition. In all, there have been six negative articles from which all adverse criticism has been quoted (Table 1).

Sohar. He treated 33 patients with HCG and 11 patients with saline. Both groups were prescribed a diet of about 500–600

TABLE 1

Author	Year	Number of cases	Double-blind tests
Sohar (16)	1959	33	11
Carne (17)	1961	196	12
Kalina (18)	1961	42	none
Craig et al. (19)	1963	20	11
Frank (20)	1964	48	24
McGanity (21)	1962	none	none

Numbers in parentheses are reference numbers.

kcal (in food amounts instead of calories), and a nurse visited their homes daily to administer the HCG. Patients were not observed by a physician except at the beginning and end of the experiment. Average loss of weight in all 44 patients was 20 lb. in 40 days. His series proved that patients can lead a normal life and perform their usual daily tasks on the prescribed diet. Conclusion: Simeons' method is effective, but HCG is only a placebo.

Carne. He used Simeons' method in about 200 patients (only 12 were placebo tests) and his patients lost an average of over 20 lb. in a 6-week period. He approved of the 500 kcal and the time limit of 6 weeks. He admitted "the treatment has some value," but found that those patients receiving saline injections in place of HCG lost in weight almost as much as those that received HCG. In other words, he approved of the method, but questioned the effectiveness of HCG.

Kalina. He used Simeons' method in 42 patients over a period of 2 years. His report was in the form of a letter to the editor of *The Lancet,* in which he claimed that he did not get the good results reported by the others, but concluded, "In spite of the shortcomings and the unknown mechanisms involved, I continue to find this procedure a useful tool in some obese patients." He further agrees with Sohar about the doubtful value of HCG.

Craig et al. This report covers 20 women patients, 11 of whom received HCG by double-blind technique. The diet consisted of 550 kcal, including many foods not found in the recommended 500 kcal of Simeons' diet. They were all treated by a clinic nurse and weighed once weekly. The average weight loss in a 6-week period was about 6.5 lb., considerably less than the expected 20 lb. or more as reported by Sohar and Carne. Thus, the technique received another negative vote, despite the small number of cases in the study and the admittedly poor cooperation of the subjects in the matter of proper diet.

One significant feature of this report bears emphasis. A considerable number of laboratory tests was performed on all patients treated, including BMR, fasting blood sugars, PBI, serum cholesterol, and serum lipid concentrations. All of these were done at the beginning and end of treatments with no appreciable change in values. This indicates that HCG does not produce any untoward effect on any of the organ systems.

Frank. This author treated 24 obese subjects with HCG, but because "it was thought to be impractical from both the standpoint of office traffic and convenience of the patient" he altered the diet and the technique to such a degree that it was unrecognizable from the original. To list a few of the author's important discrepancies: *a*) He prescribed a daily diet of 1,030 kcal (instead of 500); *b*) Each patient received three weekly injections of 200 units of HCG (instead of daily injections of 125 units); *c*) Each injection was given by an Army corpsman subcutaneously (instead of deep intramuscularly). The author states that he examined and interviewed each participant at the beginning of the study, but he does not mention whether he ever saw them again after that. Naturally, this study failed to prove or disprove anything.

McGanity. His criticisms were published in the *Journal of the American Medical Association* in answer to a query on HCG. Since he does not claim to have tried HCG in treating obesity, it is reasonable to assume that he was asked by the editors of the journal to answer the query because he is a member of the Obstetrics–Gynecology Department of the University of Texas Medical Branch and is undoubtedly familiar with the physiology of the human hormone of pregnancy known as HCG.

He takes Dr. Simeons to task for choosing a commercial lay magazine to disseminate his information instead of a medical journal. This is entirely untrue as the first publications appeared in *The Lancet* and *The Journal of the American Geriatric*

Society years before anything appeared in the lay press. His remarks are rather caustic and decidedly unjust, considering that he does not claim to have tried the method.

Furthermore, he neglected to investigate the background of the individual whom he was attacking.[3] He carelessly links him with the author of *Calories Don't Count*—a book which the Pure Food and Drug Department finally made possible to be transferred to the Fiction List of "best-sellers." This link is about as pertinent as linking the author of *Calories Don't Count* with Dr. McGanity because both are obstetricians and gynecologists.

McGanity prefers his method of choice for weight reduction, namely, the old unreliable reduction of calorie intake while maintaining the usual level of activity or the increase of energy demands by increasing activity while maintaining the same level of calorie intake. This recommendation is about as realistic as recommending the reduction of sugar intake for the sole treatment of diabetes mellitus. While it is true that all weight-reducing regimens must include a calorie deficit during the treatment, and it is also true that normal exercise will help all programs, we can no longer claim that overweight is simply a disturbance of the caloric balance sheet. If it were, the problem would have been solved long ago.

It is interesting to note that of all the above authors, only McGanity has not tried the method clinically in obese patients—yet only McGanity contends that adherence to the daily 500 kcal for 40 days is "potentially more hazardous to the patient's health than continued obesity." All the others found no untoward effects and some actually praised the diet of 500 kcal.

In an overview of these critical articles, several points emerge:

a) The number of cases studied by each author is too small to draw any conclusions. I well recall that after using the technique in about the first 200 patients, I too was skeptical about the results that Dr. Simeons claimed. Only after my visit to his clinic in Rome and after adjusting exactly to his technique[4] did my results improve.

b) Although Sohar was the only author to admit that he assumed from the start that the procedure would not work, it appears that the others also had misgivings at the outset of their studies. This is unfortunate, for it is hardly conducive to unbiased research.

c) Where individual adherence to a strict diet is the key factor of a clinical experiment, the double-blind method is of very little value unless the daily intake of food is carefully prepared for all participants in the same diet kitchen and the exact number of calories for each of them carefully calculated. Unless this is observed, the individual variance of diet by each participant invalidates the double-blind aspect of the experiment. This is important since the obese patient is notorious for his inability to evaluate the caloric values of his food or to keep to a rigid diet.

[3] Long before he became interested in this field, Dr. Simeons had distinguished himself as a research scientist in the field of tropical medicine. With his contributions to the diagnosis and treatment of malaria, bubonic plague and leprosy, can be included the discovery of the use of injectable atebrin for malaria (for which he was awarded a Red Cross Order of Merit) and a new method of staining malaria parasites now known as "Simeons stain." He also built the first model leper colony in India and has a long list of scientific papers to his credit. Under the British Government of India he was Director of Medical and Health Services (*Who's Who in Europe*).

[4] *1*) The exact diet of 500 kcal (of the prescribed foods) in the exact division of two meals, including daily minimum intake of 2 quarts of liquids.

2) The daily dose of 125 units of HCG given deep intragluteally, 6 days weekly for 40 treatments.

3) Daily interviews with patient to scrutinize and discuss daily progress.

4) Encouragement to stay with the program until approximate normal weight is reached and attempt to direct reeducation toward good eating habits and normal amount of exercise at the conclusion of the program.

d) Of the above six studies, five substantially altered the original technique of Dr. Simeons, so that they cannot claim they tested his method.

e) Most of the above authors stressed the same criticism "no significant difference in weight loss between patients given HCG or a placebo." It is my impression that Dr. Simeons concurs with this conclusion. Neither Simeons nor anyone else ever claimed that the injection of HCG alone could accomplish the loss of weight.

Even without any medication at all, there has always existed the strong-willed overweight patient who successfully reduced his weight in spite of all the difficulties. Unfortunately, the vast majority of obese patients do not fall into this category. To most of them, dieting is a most unhappy time of their lives. They are constantly hungry, weak, complaining, and generally out of sorts. This is not so with patients under the HCG and 500 kcal technique. The most hardened "professional dieters" will often volunteer their reactions that somehow this time they feel different. Most of them are neither hungry nor tired, and they experience a sense of well-being, something they never had on previous diets.

The above six reports constitute the entire literature from which criticism is quoted against Simeons' method. They are put forth as scientific evidence from controlled experiments that the use of HCG is not effective. After careful scrutiny, I do not feel the criticism holds up.

On the other hand, the evidence of several hundred clinicians all over the world treating many thousands of cases successfully is completely discounted. These include published papers by Simeons (22–24); Lebon (25–27); Harris and Warsaw (28); Hutton (29–31); Politzer, Bersohn and Flaks (32); and others.

Neither Dr. Simeons nor any of the alleged several hundred adherents to his technique have ever claimed that this is the last word on the subject. However, those of us older physicians who have been treating obesity for a long time and who have had an opportunity to employ other methods and compare them with each other find this method more fruitful than any other so far recommended.

Clinical Findings

I have chosen to study the records of my last 500 patients only in order to present a current picture of about the last 3 years. The patients were divided into two groups, those of 3 weeks treatment and those of 6 weeks. If they did not conclude at least 20 days they were not included. For those patients who did not conclude 6 weeks, the weight recorded at the end of 3 weeks was used and their category changed to 3 weeks.

Of the last 500 patients who consulted me, 450 completed 3- or 6-week courses. This in itself indicates an advantage over previous methods in that 90% of those attempting treatment for their obesity were able to stay with the program long enough to receive some benefit of treatment.

Table II is a record of 450 patients who

TABLE II

Patients receiving treatment

	Number	%	Age, years	Average age	Number at 3 weeks	Average loss, lb., at 3 weeks	Number at 6 weeks	Average loss, lb., at 6 weeks
Males	81	18	15–75	41	67	15	90	28
Females	369	82	15–72	39	327	12	320	23
Total	450	100		40	394	13.5	410	25.5

received a total of 804 courses of treatment of either 3 or 6 weeks duration. (Some patients received more than one course of treatment; the outcome of each course is charted separately.)[5]

A follow-up of all these 450 patients in order to establish the present status of their overweight proved impossible; however, several pertinent conclusions can be drawn from the study as a whole:

1) Ninety percent of the patients attempting to reduce their obesity were able to receive some degree of benefit of treatment.

2) About 60–70% were able to reach its desired normal weight or approximately so.

3) A majority of the patients, when asked to compare this regimen with previous forms of treatment, proclaimed this to be the easiest and most successful.

4) Many of the patients who had regained some or all of their weight claimed that they were able to keep their weight down for longer periods than previously and did not mind returning for further treatment. Some even went as far as confessing that they did not try very hard to keep their weight down because they knew that they could return and repeat their loss of weight.

5) An almost universal finding in nearly all of the patients is the "euphoria" that patients experience. This occurs in spite of the marked low intake of food. I have worked with many obese patients on diets twice the 500 kcal used here and do not recall many who were happy about their situation of dieting. We do not yet have an exact explanation for the "euphoria" and the high rate of "patient acceptance" so often encountered with our method, but I cannot believe that it is due to a placebo effect or a psychological reaction between patient and physician. It is far too regular.

6) As in all the other methods of treatment of obesity the markedly obese show the most striking and the most satisfying results. With regulated rest periods between 6-week courses of treatment, many of these obese successfully reduced 100 lb. or more. Of special gratification are the results we obtain with those markedly obese who have accompanying diabetes mellitus of the maturity onset or stable type. Most of these patients show a marked improvement in their diabetic state as well as in their obesity. While this is true with all forms of successful weight reduction, the improvement is more marked with HCG.

[5] In 1964 Simeons published a series of 500 cases with results which closely match my own (33). His 122 males and 378 females with average age of 41 lost an average of nearly 17 lb. in 20 days.

SUMMARY

After 40 years of trying every new approach to the treatment of obesity with little or no success, I believe a new method that works has been made available to us. It works with about 60–70% of obese patients of both sexes aged 15 and up, provided the method is followed meticulously as the author has developed it.

No one can yet say for certain how or why it works, and a great deal of research will be needed. I hope that this report of my own clinical findings together with some possible tentative explanations will act as a stimulus for this research.

While it is true that obesity is due to excessive calorie intake, this tells us nothing of the basic causes. What needs further explanation and discovery are the mechanisms that regulate calorie intake and output as well as the reason for the failure of these regulating mechanisms in some individuals that results in obesity.

Recently, Dr. Margaret Albrink (34) has made a very interesting observation that while man has elaborate and efficient mechanisms for surviving starvation, his techniques for handling a surplus of food—a frequent necessity in modern societies of abundance—are limited and easily saturated. As a result, she suggests, the metabolic abnormalities leading to

atherosclerosis may be a result of overburdening the mechanisms for storage of fuel, i.e., overstuffing the adipose cell. It is intriguing to speculate on a parallel explanation for the metabolic abnormality that leads to obesity.

Further weight to this possible explanation is brought to bear by the fact that the adipose cell in the obese has been found to be larger than the normal fat cell. It follows, therefore, that at least two types of fat cells exist, the normal cell storing the reserve fuel that is necessary for good health and the abnormally large cell that becomes overstuffed and forms the excess fat tissue of the obese.

This approach to obesity also lends further credence to the belief that the manner in which food is utilized and stored in the body is a more complicated mechanism than previously believed and that there is a controlling center in the brain.

Medicine must not neglect nor abandon the problem of obesity for many reasons, not the least of which is its relationship to cancer and the process of aging.

A. Tanenbaum and H. Silverstone (35) suggest that nutrition plays a role in the formation of cancer in man. "When living cells are subjected to carcinogenic influences they may undergo changes that finally result in growing neoplasm. The energy and substance for the development of the first cancer cells are derived principally from the animal; the new cell type increases in number by assimilating nutrients from the host. It may be expected then that the diet and the nutritional state of the host influence the formation and the growth of tumors."

The process of aging as defined by Howard J. Curtis of the Brookhaven National Laboratory "may be considered as an increasing probability of developing a degenerative disease." Furthermore, M. H. Ross (36) in his experimental studies with rodents has shown that a calorie-restricted diet delays the onset of development of all the degenerative diseases in rodents (and presumably in man) and obesity speeds their development.

Medicine must neither accept nor abandon Dr. Simeons' method until it has been properly tested through research or until a completely different and a better method is discovered. Dr. Simeons himself has begun such testing and research in his clinic. He has often told me in person and has more than once said publicly that critics and researchers in this field are welcome at his Clinic to study his results and observations. Let us hope some of them will accept his offer soon.

> A clinician must contribute to science from the great wealth of material as chance presents it. He must weigh, observe and analyze at every opportunity. Often, he can neither plan nor control his experiments, yet critical evaluation of his successes as well as his failures can add immeasurably to the sum total of our knowledge and clinical judgment (T. Messerman, personal communication).

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It is also known that polyunsaturated fatty acids, tocopherol and selenium have definite interrelationships in cellular metabolism. Polyunsaturated fatty acids, in general, increase the pathologic response to tocopherol deficiency. This is presumably owing to the oxidatively labile and antioxidant properties of the polyunsaturated fatty acids and tocopherol, respectively. Recently, Witting and Horwitt[11] have indicated that fatty acids containing more than four unsaturations, such as pentaenes and hexaenes, also will accentuate tocopherol deficiency states in the rat. Interestingly, the docosahexaenoic acid contained in cod liver oil may or may not be identical to the docosahexaenoic acid found in mammalian tissue.[11,12]

If muscular dystrophy is concerned with the inability to form the more unsaturated fatty acid(s) from arachidonic acid through the mediation of tocopherol, then unessential polyunsaturated fatty acids might be expected to augment tocopherol deficiency by a competitive mechanism even in the presence of adequate biological antioxidant activity other than vitamin E cofactor activity. Excessive intake of the essential fatty acids, linoleic and arachidonic acid, would cause utilization of tocopherol as an antioxidant in the absence of adequate biological antioxidant activity, thereby accentuating the tocopherol deficiency. Fatty acids of the hexaene and pentaene series, structurally different from those synthesized in mammalian tissues, could interfere with the further desaturation and chain lengthening of arachidonic acid to docosahexaenoic acid. Thus, the metabolic defect occurring in muscular dystrophy might be the inability of the tissue to convert arachidonic acid into the more highly polyunsaturated fatty acids such as Δ 4, 7, 10, 13, 16, 19-docosahexaenoic acid. In dystrophy cases of genetic origin, the enzyme may be incapable of performing its function adequately, whereas, in nutritional deficiency states, tocopherol or a derivative thereof becomes limiting for this specific system.

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Chorionic Gonadotrophin in the Treatment of Obesity

Dear Sir:

May I refer to the article entitled "The Use of Chorionic Gonadotrophin in the Treatment of Obesity" by Capt. Barry W. Frank, MC, in your March 1964 issue.

This study shows that some obese patients (eight out of the author's series of forty-eight) can lose 20 to 30 pounds in fifty to sixty days on a 1,000 calorie diet with or without human chorionic gonadotrophin. This entirely negative result as regards the value of human chorionic gonadotrophin could have been predicted. The author's patients were kept on a 1,000 cal. diet (instead of 500 cal.) and 600 International Units of human chorionic gonadotrophin (instead of 875 I.U.) was given subcutaneously (instead of deep intragluteally) in doses of 200 I.U. three times a week (instead of daily doses of 125 I.U.). On such a regimen no action of human chorionic gonadotrophin on the reducing procedure can possibly be expected to appear.

For this there are two main reasons: (1) It is well known that about 80 per cent of injected human chorionic gonadotrophin is inactivated in the body within 24 hours; hence

the need for daily injections. This cannot be compensated by giving larger doses at longer intervals. Administering human chorionic gonadotrophin in such a staccato manner (Hormone Stoss) is extremely effective when used in gonadal disorders, particularly in hypogenitalism, but this is quite unsuitable as a method of reproducing the uninterrupted physiological action of human chorionic gonadotrophin in pregnancy and it is just this action, as yet only vaguely understood, which I have found of greatest help in treating obesity.

(2) Most obese patients can get along comfortably on a 1,000 cal. diet without further assistance, but this is certainly not the case when the average obese patient going about his usual occupation is kept for periods of up to seven weeks on a diet of strictly 500 cal. only. Occasionally one does encounter a very determined patient who is able to do this, but only with considerable discomfort. Yet when human chorionic gonadotrophin in the correct dosage is added to this diet, there is not only no discomfort, but at least 80 per cent of patients who have been hardened crash dieters for many previous years spontaneously express enthusiasm over the unexpected ease and well being with which they can follow this regimen.

Glancing over the author's charts one notices that of his forty-eight patients twenty-seven (56 per cent) lost less than his mean of 12 pounds, and that among these patients ten (20.8 per cent) lost less than 5 pounds. This suggests that his relatively high mean loss is due to the eight cases (16 per cent) in which the loss was exceptionally high (20 to 30 pounds). I think that most workers in the field of obesity would agree with me that obese patients strictly observing a 1,000 cal. diet for fifty to sixty days can be expected to lose more than a mean of 12 pounds.

The conclusion must then be that in the majority of cases in the series the diet was not strictly maintained. (See also my Letter to the Editor criticizing the article by Craig et al., *Am. J. Clin. Nutrition*, 12: 230, 1963, in the September 1963 issue of the *Journal*, p. 197.) If the twenty-seven cases in which loss was minimal, presumably due to faulty dieting, are excluded from the author's charts, the mean loss for the remaining ten cases in which placebos were given works out to 19.4 pounds, and for the eleven remaining cases in which human chorionic gonadotrophin was given to the almost identical figure of 19.3 pounds. This can be considered a reasonable mean loss in patients dieting rather carefully on 1,000 cal. for fifty to sixty days.

For the purposes of comparing these figures with our own results, we picked from a card index in which all patients treated for obesity are arranged alphabetically by surnames, the first 500 consecutive cases in which there was at least twenty days of treatment. On analyzing the case sheets we found that the group was composed of 122 males and 378 females who ranged in age from eleven to seventy-eight years. The mean age was forty-one years. The degree of overweight above statistical norms ranged from 4.5 to 234 pounds. The mean overweight was 42 pounds. On the twentieth day of treatment the loss of weight ranged from 2.3 to 35 pounds and the mean loss was 16.94 pounds. Only seven patients lost less than 10 pounds (1.4 per cent) and only fifteen (3 per cent) lost more than 25 pounds, showing that the remaining 478 patients (95.6 per cent) clustered very closely around the mean loss of 16.94 pounds in twenty days.

Obviously we have extensively checked our results against patients receiving a placebo but only few were able to adhere to the diet for twenty days and in these cases we always found wide variations in the observance of the diet, producing results quite comparable to those of Capt. Frank. Never were we able to produce uniformity of weight loss.

We share the author's regret that we have so far been reluctant to report blood chemical studies. This is because—as more and more workers are pointing out—our present knowledge of metabolic processes in obese subjects and their reaction to underfeeding is still scanty. We have found it impossible to draw any useful conclusions for or against human chorionic gonadotrophin from such studies. For the moment, therefore, we must content ourselves with hard clinical evidence and pliable hypotheses. What has, however, been

accomplished (Politzer et al. Biochemical changes resulting from drastic weight loss. *South African M. J.*, 37: 151, 1963) is to show that a 500 cal. diet with or without human chorionic gonadotrophin does not bring about any significant biochemical changes.

To what extent the psychologic effect of seeing the treating physician, being weighed and having an injection daily plays a role in our procedure is difficult to assess, because the suggestability of patients varies so widely. On the other hand, since our results are so uniform, we have not, in many years and in close cooperation with a clinical psychiatrist, been able to convince ourselves that the daily visit is an important therapeutic factor in patients receiving human chorionic gonadotrophin, although it may have some deterrent effect on a few patients who cannot resist the temptation occasionally to transgress. However, we do find that such patients cheerfully confess a *lapsus linguae* when confronted with a gain of a few ounces. If further studies should prove us to be wrong in this view, the extra work involved would then be most rewarding.

Our results are decidedly better than any we have hitherto found published elsewhere. Since obesity is a major health problem, we look for the day that a qualified and unbiased observer, who is experienced in the management of obesity, will come to Rome (perhaps under the auspices of your Society?) to check our figures, to study our cases and to familiarize himself with our technic and all its details. This knowledge could then be applied to his own cases, without introducing arbitrary deviations of his own invention. Only when this is accomplished in a large series of cases can the value of our method be definitely established.

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21. Treatment of overweight patients with chorionic gonadotropin: follow-up study (1966).

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TREATMENT OF OVERWEIGHT PATIENTS WITH CHORIONIC GONADOTROPIN: FOLLOW-UP STUDY

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Since Simeons' (1) original article describing the use of human chorionic gonadotropin (H.C.G.) in the treatment of obesity, there have been many criticisms as to its efficiency and as to the mode of action of H.C.G.

This paper is presented to draw attention to some of these factors. Particular reference is made to the use of human chorionic gonadotropin in the obese patient with complicating orthopaedic problems; also included are the results of a double-blind trial.

All would agree that the excess weight imposed upon the skeletal system by obesity is a burden on health. When complicating an existing pathological condition, the obesity tends to aggravate symptoms and retard effective progress towards recovery. Indeed, all too often, little or no progress can be expected in the treatment or amelioration of symptoms in the patient who is obese. A vicious cycle is established whereby the skeletal pathologic lesion causing pain and restricting movement so immobilizes the patient as to become an additional factor in further increasing the gain in weight.

The patient becomes aware of this situation and is increasingly depressed by his own ineffective methods of trying to reduce, hampered by his semiambulant condition. He often finds his weight steadily increasing despite all efforts. This in turn adds to the burden that has to be supported by his joints. The result is more pain and immobility, a consequent further increase in weight, and a steady continuance of the vicious cycle—to the alarm and frustration of both the patient and the attending physician.

In a previous series (2) we had found that by the use of Simeons' technique (1) the patients lost weight safely, rapidly and effectively, with little discomfort. In the present series we tested the effect of H.C.G. (Simeons' technique) in patients who were drawn at random from the normal running of an orthopaedic department.

MATERIALS AND METHODS

Most of the patients were from out-patients clinics and fracture clinics, but a few were in-patients; there were also some obese patients referred from other departments because of failure to reduce by other methods.

After the initial group of patients were established in their treatment, the study was continued by the double-blind control method.

Each patient was given 125 international units of human chorionic gonadotropin daily by gluteal intramuscular injection. The diet was restricted to 500 calories daily—200 gm of protein, virtually no fat, and the balance in carbohydrate.

The human chorionic gonadotropin and placebo were supplied by Messrs. Paines and

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Byrne, Ltd. (Greenford, Middlesex) in serially numbered identical vials, to which they held the "key." Neither myself, the dispensary staff nor the patients were aware of which patients were receiving H.C.G. and which were receiving placebo. After the series had been completed and the results recorded, the "key" was provided by Messrs. Paines and Byrne, Ltd.

Weights were recorded daily. The patients were seen once a week in the out-patient department, where their treatment was supervised and their progress noted.

In order to simplify interpretation, the records for this study were limited to the amounts of weight lost and the number of days of treatment. No attempt was made to correlate the initial weight of the patient with the amount of weight lost or the age and sex.

All patients expressed an initial willingness to adopt this method of treatment and were encouraged by being assured that the method was effective and safe, that they could remain ambulant and engaged in their usual activities, and that they would achieve results rapidly, and with a minimum of discomfort.

The objective criteria for assessing the results were:

a) the amount of weight lost,
b) the reduction in the dose of analgesic required, and
c) the reduction in the amount of ancillary physiotherapy required.

The results, in terms of weight lost, were rated as follows:

Poor—less than 10 pounds lost
Fair—10 to 14 pounds lost
Good—14 to 18 pounds lost
Very good—18 pounds (or more) lost.

RESULTS

Table 1 shows the effect of treating 40 patients (Group I) with human chorionic gonadotropin (1–2 courses). The weight losses were greater than those obtained in previous unsuccessful attempts or in hospital-supervised programs to reduce weight. There was also an overall reduction in the amounts of analgesics that had to be prescribed to reduce pain, and less pressure on the physiotherapy department for ancillary methods of treatment. Because of the improvement, it was possible to discharge several chronic cases from orthopaedic care.

Table 2 shows the results obtained in the double-blind trial of treating 24 patients with H.C.G. (Group II) and a placebo (Group III). Again, some patients needed repeated courses.

Overall, as shown in Table 3, 94 courses of treatment were administered to the 64 patients. The average 21-day weight losses were:

Group I (H.C.G. and diet)—11.1 pounds.
Group II (H.C.G. and diet, d-bl.study)—13.0 pounds.
Group III (placebo and diet, d-bl.study)—9.6 pounds.

The observations on patients from all 3 groups who were treated for the first time are recorded in Table 4. The data on second or third courses of medication are excluded. The improved results (12.6, 15.8 and 11.3 pounds respectively) are no doubt due to the elimination of several partial failures represented by patients who returned for repetition of treatment.

TABLE 1

Group I—Treated with H.C.G.

Patient				Days Treated	No. of Courses of Treatment	Pounds Lost
Name	Hosp. No.	Age & Sex				
Ward	4519	69	F	37	1	19
Walters	50051	55	M	39	1	33
Willcox	27430	78	M	39	1	26
Toombs	12822	58	F	40	1	21
				18	2	5
Sumner	4739	49	F	36	1	18
				28	2	6
Reeves	47300	64	F	29	1	15
				39	2	14
Renshaw	49496	—	F	40	1	18
Rollin	12009	—	F	15	2	—
Pitcheta	27865	44	F	39	1	32
				39	2	17
Payton Smith	1842	78	F	32	1	12
Pesakoff	1125	74	F	39	1	11
Paston	37256	54	F	36	1	17
Porter	9433	51	F	39	1	27
Pask	21082	68	F	39	1	18
O'Mahoney	51419	12	M	27	1	15
Neil	27018	36	F	36	1	17
Kenny	14932	52	M	39	1	14
Jardine	51522	33	M	39	1	23
Horton	10420	61	F	37	1	24
Gordon	34361	51	F	35	1	25
Gates	50119	40	F	36	1	30
				39	2	23
Foster	50229	52	F	37	1	28
Francescott	52121	60	F	40	1	26
Fredman	39565	43	F	39	1	23
				40	2	14
Gilley	35603	61	F	40	1	26
Darrington	6007	12	M	14	1	7
				22	2	7
Dorin	46958	67	F	40	1	30
Cox	49474	52	F	19	1	14
Damionou	—	—	—	27	1	5
Cops	15283	48	F	21	1	19
Cooper	12917	56	F	37	1	19
Allison	80919	53	F	39	1	21
Chattell	39259	70	F	23	1	21
Clark	21165	67	F	32	1	17
Beecroft	48808	69	F	34	1	21
Bates	5160	51	F	38	1	23
Beamish	9862	63	F	31	1	16
				36	2	9
Boot	7251	43	F	36	1	25
Brown, E.	49867	45	F	39	1	30
Brown, H.	21759	70	F	39	1	22

Figure 1 shows the distribution of the weight losses for all 64 patients, and the curves denoting the averages for the 3 groups. Figure 2 is a comparison of the weight losses in the 2 groups (H.C.G. and placebo) of the double-blind study. It may be seen that apart from the central group who achieved weight

TABLE 2

Double-Blind Trial, H.C.G. Versus Placebo (Groups II and III)

Patient				Days Treated	No. of Courses of Treatment	Pounds Lost
Name and Medication No.	Hosp. No.	Age	& Sex			
Group II. Human Chorionic Gonadotropin						
Norton (#1)	16764	60	F	18	1	12
Rumsey (#2)	50523	49	F	6	—	6
Lambert (#3)	51630	58	F	4	1	8
Foster (#11)	50229	52	F	34	2	18
Earl (#12)	34745	56	F	25	1	15
Fredman (#16)		—	F	24	3	13
Pitcheta (#17)		—	F	12	3	14
Everett (#18)	51137	57	M	23	1	22
Barraud (#19)		52	F	26	1	16
Saville (#20)	48805	33	F	23	1	12
Hornby (#21)	38730	68	F	21	1	12
Brooks (#25)	6034	53	F	21	1	18
Sumner (#26)		—	F	20	3	9
Saville (#27)	48805	33	F	22	2	15
Domb (#34)		—	F	34	2	11
Sunshine (#35)	54481	56	F	36	1	24
Cook (#37)		—	F	24	2	10
Brooks (#38)	6034	—	F	10	2	6
Foster (#39)	50229	52	F	36	3	13
Barraud (#43)		52	F	34	2	12
Collier (#49)	44320	—	F	32	1	16
Bryden (#50)		—	F	17	2	21
Cook, D. (#51)		—	M	23	1	29
Group III. Placebo						
Hudson (#4)	51128	48	F	23	1	13
Parker (#5)	7614	62	F	25	1	17
Hobbs (#6)	1299	80	F	32	1	17
Reeve (#8)	47300	—	F	29	3	13
Domb (#9)		59	F	26	1	14
Beecroft (#13)		—	F	29	2	9
Taylor (#14)	14236	42	F	23	1	17
Jones (#15)	9181	55	F	25	1	14
Hale (#23)		—	F	13	2	4
Jones (#28)	9181	—	F	11	2	—
Francescotti (#29)	52121	61	F	28	2	15
Cook (#30)	5100	57	F	26	1	13
Mortlock (#31)		16	F	31	1	19
Fredman (#32)	39565	43	F	37	3	19
Bryden (#33)	19031	48	F	27	1	10
Francescotti (#40)	52121	61	F	26	3	7
Mortlock (#41)		—	F	28	2	13
Brown (#42)	3440	16	F	22	1	12
Hale (#46)		—	F	30	1	10
Brown, L. (#47)		—	F	40	2	12
Cook (#48)	5100	57	F	28	3	13
Earl (#52)	34745	—	F	24	2	2
Mortlock (#53)	54303	—	F	25	3	10
Barnett (#54)	49445	—	F	27	1	12

TABLE 3

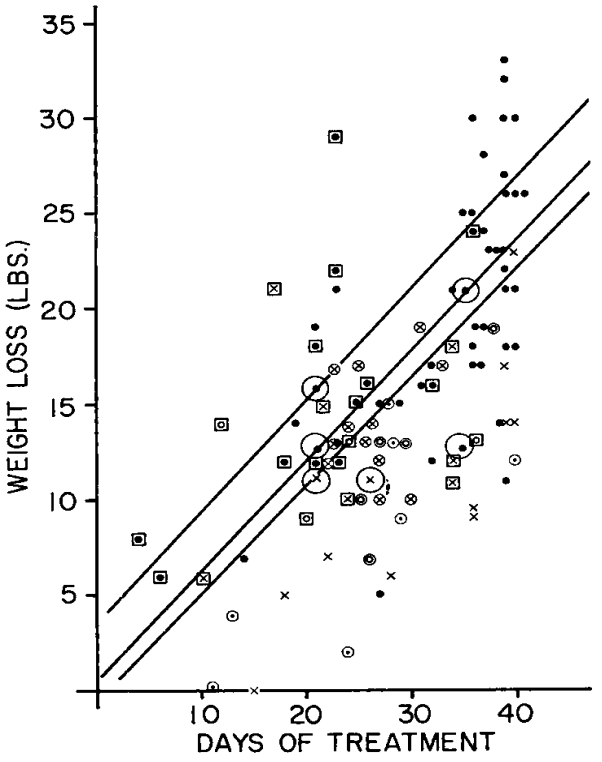
Summary—Results of All Courses of Medication Given 94 Times to 64 Patients

Group	No. of Courses	Av. Length of Treatment (days)	Av. Weight Loss (lbs.)	Av. Weight Loss in 21 Days
Group I, H.C.G.	48	34	18.7	11.1
Group II, (Double-Blind) H.C.G.	23	23	14.1	13.0
Group III, (Double-Blind) Placebo	24	27	12.3	9.6

TABLE 4

Results of Treatment in Patients Presenting for the First Time (Total 64)

Group	No. of Patients	Av. Length of Treatment (days)	Av. Weight Loss (lbs.)	Av. Weight Loss in 21 Days
Group I, H.C.G.	40	35	20.7	12.6
Group II, (Double-Blind) H.C.G.	12	21	15.8	15.8
Group III, (Double-Blind) Placebo	12	26	14	11.3



Top line is the average for the H.C.G. double-blind study (half of Group II, Table 2). Key = ▣ ⊠ ⊡

Middle line is the average for the initial study with H.C.G. alone (Group I, Table I). Key = • ×

Lower line is the average for the placebo double-blind study (half of Group II, Table 2). Key = ⊙ ⊗ ◎

FIG. 1. Weight loss in all 64 cases treated.

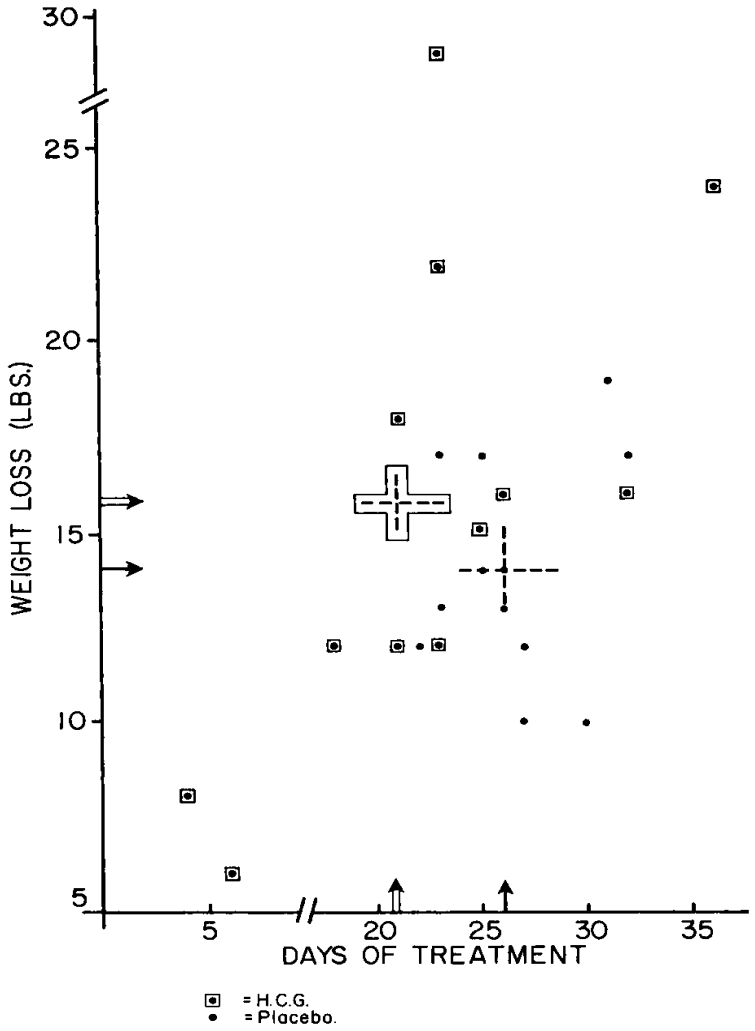


FIG. 2. Weight loss in patients of the double-blind trial (H.C.G. versus placebo).

TABLE 5

Results—Weight Loss	H.C.G.-Treated	Controls	Totals
Very Good (18 lbs. or more)	5		5
Good (14–18 lbs.)	2	2	4
Fair (10–14 lbs.)	5	7	12
Poor (less than 10 lbs.)		3	3
Total	12	12	24

reduction whether the medication was H.C.G. or placebo, there was a small group who did extremely well while receiving H.C.G., and another small group who did poorly while receiving placebo.

In Table 5 is a summary of the weight losses in the double-blind study, based on a minimal 21-day period of medication. In 5 of the 12 H.C.G. patients the

results were "very good" (loss of 18 or more pounds), and in the remaining 7 patients they were "good" or "fair" (10–14 pounds). On the other hand, in the 12 placebo patients the results were "good" or "fair" in 9, and "poor" in the remaining 3; no patient obtained "very good" results.

Statistical analysis. The data were submitted to Medical Data Systems Division, Elliott Medical Automation, Ltd., for statistical comment and analysis. They reported: "Restricting the analysis to the 22 patients who continued on treatment for a reasonably long time.... Considering only the 6 patients who did well or badly, we see a clear cut break between the controls and the treated cases (see Fig. 2).

"With such a small number of cases it is possible that this division could be a chance effect and would not be upheld in a larger series of cases.

"If, say in over 60,000 cases, there were no difference between the treated and controls and we took 10,000 samples of 6 from them, then we would expect only 1 in 20 of such experiments to split in this fashion. This is a fairly small proportion and it therefore seems reasonable to *reject* the hypothesis just postulated that there was no difference between the treatment and control, and accept instead the hypothesis that the treatment represents an improvement over the control. This is standard statistical technique of testing 'significance.'

"The improvement may, in fact, be restricted to the bad or very good cases. Certainly when we take the middle portion of the series into account the chance of observing such a discrepancy as this with the hypothesis of no difference rises to 1 in 8.

"If on the other hand the treatment does cause a general shift of a few pounds per three weeks and the variation in response is as great as seen here, then more than 22 cases would be required to dismiss with reasonable certainty the hypothesis of no difference.

"In summary the trial figures suggest an improvement due to treatment. When considering only the Bad and Very Good cases this is established at the usually quoted '5%' level of significance. More cases would be required to establish or refute the hypothesis of overall improvement.

"Commenting upon the two failures to continue treatment, both these came from the treated group and this might be thought of as being in some way due to the treatment.

"If this was just an unlucky split of the patients we could expect such a split to occur in about 1 in 5 similar random examples from a large group which falls inside the levels usually considered acceptable."

Comment. Unlike the findings of Carne (3), who conducted a double-blind study, it would appear that these differences are significant at the 5% level.

DISCUSSION

The weight reduction was more readily maintained in the patients who had the greatest incentive, i.e., those who were previously suffering the most pain and the severest restriction of mobility. These patients either maintained their new weight or lost some more weight without additional supervision,

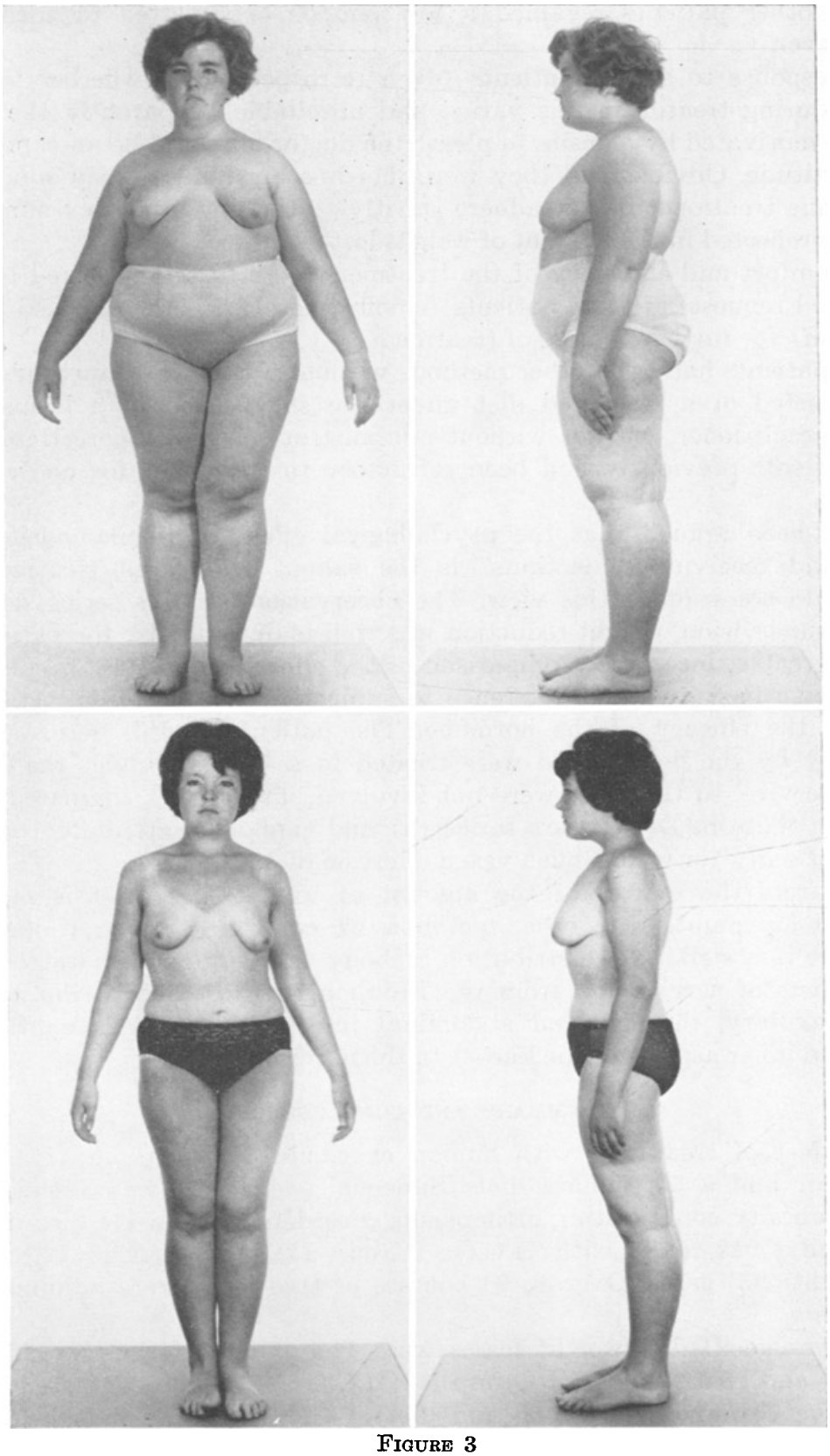


FIGURE 3

whereas other patients regained a few pounds or reverted to their former weight level.

The response to asking patients (even retrospectively) whether they were hungry during treatment was varied and unreliable. Apparently the answers could be motivated by a desire to please the doctor, or could be an expression of their fortitude. Obviously if they were inordinately hungry they would either discontinue treatment or not adhere strictly to the diet, and this immediately would be reflected in the amount of weight lost each week.

The comfort and efficiency of the treatment were further attested to by the unsolicited requests of some patients (chiefly those who had obtained the most pain relief) for further courses of treatment.

Most patients had tried other methods without avail. These methods usually had consisted of a restricted diet under the supervision of a hospital or a general practitioner, with or without administration of an anorectic drug. All these patients previously had been refractory to treatment for one reason or another.

It has been argued that the psychological effect of regular visits to the doctor and receiving "injections" is the salient feature in treatment. Our findings do not support this view. The observations in this series show that, without supervision, weight reduction was well maintained by the patients who had the greatest incentive. Comparison of the effects of H.C.G. and placebo on an objective basis, without reference to subjective considerations, at once establishes the efficacy of the hormone. The patients in this series were not seen daily by the doctor, and were treated in a hospital under the National Health Service, so that fees were not involved. The results compared favourably with those in Dr. Carne's series (3) and cannot be attributed to "seeing the doctor daily" or to the much vexed question of fees (4).

Aside from the matter of the amount of weight loss by this method of treatment as compared to other methods, we confirmed Simeons' observation that there is a striking redistribution of body fat (Fig. 3). Characteristically this consists of a reversion from the Fröhlich type of fat distribution (neck lipoma, axillary, thoracic and abdominal folds, and fat pads on the upper thighs and inner aspects of the knees) to the normal habitus.

SUMMARY AND CONCLUSIONS

The effect of treatment with human chorionic gonadotropin (H.C.G., 125 I.U. daily) and a 500-calorie diet (Simeons' technique) was assessed in 40 cases of obesity complicating orthopaedic disorders (Group I); also a double-blind study was made with H.C.G. (Group II) and placebo (Group III) in 24 additional cases. Overall, 94 courses of treatment were administered to 64 patients.

The average 21-day weight losses were 11.1 pounds for Group I (H.C.G. and diet) and 13.0 pounds for Group II (H.C.G. and diet), compared with 9.6 pounds for Group III (placebo and diet). When only the initial courses of therapy were included (thus eliminating the factor of refractoriness to re-

peated H.C.G. courses), the corresponding average weight losses were 12.4 and 15.8 pounds versus 11.3 pounds. Statistical analysis indicated that these differences between H.C.G.-treated and placebo-treated cases were in the area of 5% significance.

Criticisms of the method are discussed, and the need for further study in a more extensive series is stressed.

Simeons' technique for reducing weight in cases of obesity is a safe and effective procedure, without undue discomfort for the patient.

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22. Chorionic gonadotrophin in the treatment of obese women: a rebuttal (1963).

Letters to the Editor

Fatty Acid Content of Margarines and Other Table Fats

Dear Sir:

In regard to the recent Letters to the Editors about the fatty acid content of margarines (in your March 1963 issue), I wish to mention that the Bernfeld, Homburger and Kelley paper entitled "Fatty Acid Content of Margarines and Other Table Fats" in the December 1962 issue of the Journal omitted what I consider to be a pertinent reference to previous work.*

I would also like to point out that the data as given by Bernfeld et al. are not easily usable by dietitians and practical nutritionists, since no values for fat or water content are listed. Therefore, the amounts of a given fatty acid per unit weight of margarine cannot be calculated from their data (also see*).

This is not to detract from the additional valuable data offered by Bernfeld et al. It is hoped that an increasing number of such investigations will provide the consumer with valid and meaningful information about the composition of the foods he buys.

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* OSTWALD, R. Fatty acids in eleven brands of margarine. *J. Am. Dietet A.*, 39: 313, 1961.

Chorionic Gonadotrophin in the Treatment of Obese Women

Dear Sir:

May I refer to the article "Chorionic Gonadotrophin in the Treatment of Obese Women," by Leela S. Graig et al. published in your March 1963 issue?

That twenty obese women maintained on a diet of 550 calories over a period of forty days, with or without chorionic gonadotrophin, have shown an average loss of only 9 pounds is entirely contrary to all experiences so far recorded. Evidently, as the authors themselves admit, the diet was not scrupulously controlled and observed. The diet described by the authors is hardly as they claim "a modification" of the one used by Simeons, Sohar, Lebon and others. In caloric value and composition it differs considerably from the diet I have recommended for use in association with human chorionic gonadotrophin.

It does, moreover, seem a little wayward to conduct an elaborate double blind experiment when the most important factor, the diet, is poorly controlled. If the authors had excluded from their series all the cases in which they had doubts about the strict observance of the diet throughout most of the treatment, the value of their study would have been enhanced. As it stands, their work on the use of human chorionic gonadotrophin is rather like testing the value of insulin in diabetic patients whose carbohydrate intake is unestablished.

Before a new method is tested one does rather expect the student to have first fully acquainted himself with the technic under investigation. Had these authors done this, they would have excluded from their series all the patients who required vitamins, thyroid and diuretics "for other conditions" which are

not explained, knowing as they then would that such additions drastically alter the mechanism of weight reduction with human chorionic gonadotrophin.

What so many investigators seem to overlook is that human chorionic gonadotrophin as such has no weight-reducing action whatsoever, nor has this ever been claimed to be the case. In fact, those quite exceptional patients who have the willpower to stay on a 500 calorie diet for forty days without human chorionic gonadotrophin often lose more weight than those who are receiving it; but they look drawn and haggard and regain their weight rapidly as soon as they stop dieting, because they have depleted normal fat reserves. The function of human chorionic gonadotrophin is exclusively to make drastic reduction over a short period of time safe, comfortable and entirely confined to abnormal fat deposits. It is the latter peculiarity which accounts for the relative ease with which patients can hold their weight after this treatment, a fact which Dr. Craig's paper confirms.

Unless the student is fully familiar with this interesting action of human chorionic gonadotrophin in obesity, he completely fails to recognize its absence when patients reduce their weight by diet only. The experienced worker, on the other hand, sees the marked difference within the first week of treatment and cannot, therefore, carry out a double-blind experiment. He can always pick out the control subjects who are receiving the placebo long before the end of treatment, since they have trouble with the diet, look weary and completely lack the bright exhilaration which obese patients receiving human chorionic gonadotrophin almost invariably experience. Moreover, the excessive measurements do not regularly decrease at the rate of at least 1 cm. per kg. of weight lost as is usual in patients on a reducing diet and human chorionic gonadotrophin.

We treat patients from most parts of the world, among them many Americans. We hardly ever see a loss of less than 20 pounds, while many patients on a forty day diet lose over 30 pounds. We have little trouble with the diet even in ambulatory patients who eat at home. Perhaps this is because we consider it worthwhile to investigate even the slightest gain which, with the exception of premenstrual water retention, is always due to a dietary error. Once the reason for the gain has been elicited, the error is rarely repeated.

May I use the hospitality of your *Journal* to say how much we would welcome a visit to our clinic from our critics so that they may be in a position to compare their results with those of our standard technic before condemning a method which gives us, and others who follow it strictly, such consistently satisfactory results?

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23. Action of chorionic gonadotrophin in the obese (1961).

to indicate,[1] [2] that the problem of the extrapyramidal disorders is the same no matter what the pathogenesis.

Dr. Purdon Martin declares that the basal ganglia control the centre of gravity. To the psychiatrist these ganglia are the centre of gravity.

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S. M. CONWAY.

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DANGER OF AIR EMBOLISM IN HIGH-PRESSURE BLOOD-TRANSFUSIONS

SIR,—Dr. Bewes [3] has eliminated a cause of air embolism but in doing so has defeated the purpose of the drip-counting chamber. The counting chamber often fills during the ordinary course of intravenous therapy, and as with pressure transfusion the air displaced goes into the patient. Having read the article by Dr. Bewes, I carried out experiments extending his technique.

As a result of these experiments, first using water and then blood, may I suggest the inclusion of a second counting chamber 6-8 in. below the first. When expelling air from the giving-set, the second or lower chamber is filled but the first counting chamber is left almost empty.

During transfusion the second chamber acts as an air trap for the air which is displaced from the upper counting chamber.

This method prevents air from entering the patient and yet retains the function of the upper counting chamber in that the flow of fluid can be observed under conditions of high pressure mechanically exerted, free gravity flow, or controlled " drip " method.

For encouragement and the supply of blood, my thanks are due to the Regional Blood Transfusion Centre, Newcastle upon Tyne.

Nurse Teaching Department,
Newcastle upon Tyne General Hospital,
Newcastle upon Tyne, 4. ROBERT WOODWARK.

WHAT MAKES THE PATIENT BETTER?

SIR,—Dr. Meares' article (June 10) and the subsequent correspondence point to the frequency with which rapid and often lasting improvement takes place without anyone understanding how the change comes about. The word " suggestion " is often used to describe the process but this takes us no further in explaining it.

We hear often enough how suggestion works, meaning the way in which it is applied by the therapist, but we hear little of what goes on in the patient. We need an explanatory model for the consideration of these processes, and in my view this is provided by the object relation theory of personality. Elsewhere [4] I have put forward the idea that during treatment the patient introjects something of the therapist's personality. This is the same process by which we grow when, as infants, we absorb and incorporate representations of parts of the personalities of our parents. These representations are based partly on the reality of their personalities and partly on the fantasies which we project on to their persons before absorbing them back into ourselves.

In treatment a patient may take from the therapist something the therapist actually has, or he may project what he needs on to the therapist and then absorb it back as material out of which he makes his own cure.

An analogy of the difference between these two processes is the difference between love and infatuation. Love is the development of two personalities in contact with each other. Infatuation is the process whereby an individual becomes attached to a fantasy that he imposes upon another individual. Cures based on fantasy perception about the therapist may disappear as suddenly as an infatuation.

Quick cures can also occur when rational medical procedures are being used. They happen when what is supplied to the patient, either in the therapist's personality or in the process used, exactly suits the patient's need. Thus, in medical practice, quick cures can accompany rational or irrational procedure, and so can they in paramedical treatments and spiritual healing.

The underlying process is the same in all these cases—namely, the incorporation of " good objects " which exist in, or are projected on to, the person held responsible for the cure.

The question remains whether we should deliberately seek these quick cures. I hold that we should be cautious in this matter because what applies to the therapeutic process could apply equally to a pathogenic process, or " sudden worsenings ".[5] When we try to force a cure on to patients by methods which invoke deceptions of the patients, or of ourselves, we are using unconscious processes with unforeseeable results.

As doctors, we should aim at using rational processes; but the irrational processes are proper subjects for our study.

London, N.W.3. J. H. KAHN.

ACTION OF CHORIONIC GONADOTROPHIN IN THE OBESE

SIR,—Simeons [6] suggested a suitable method of pre-operative and postoperative treatment for the obese patient, and I adopted his methods in a series of 100 patients.

68 patients completed forty consecutive days of treatment and the other 32 patients twenty-one days. The average weight-loss was 28 lb. after forty days' treatment and 17 lb. after twenty-one days. Of these 100 patients, 20 were surgical cases: 18 required surgery either during or after their course of treatment, and 2 required a course of treatment postoperatively.

All the patients were ambulant and continued to work full-time over the treatment period. They were given 125 units of chorionic gonadotrophin daily by deep intragluteal injection, and maintained on a 500-calorie, fat-free diet containing 200 g. of protein. None of the patients felt hungry or weak or had difficulty in coping with his normal daily activities. The best results were achieved when the patient cooperated fully, but even those who dieted irregularly lost weight more readily than with any other treatment tried. For the first time many previously refractory to other regimens lost weight. The symptoms commonly associated with obesity—lassitude, breathlessness on exertion, " rheumatic " aches and pains, and headaches—all subsided a few days after starting treatment.

From the surgical point of view it was noteworthy that in no case did the skin sag or become flaccid despite the rapid loss of 25–40 lb. The loss of subcutaneous fat so usual in other forms of weight-reduction did not occur. After operation the skin always healed by first intention, and this was particularly important and gratifying after reduction mammaplasty and abdominal lipectomy. In 2 patients acute appendicitis developed during the treatment, which was nevertheless continued throughout their stay in hospital. There was no difficulty in inducing or maintaining anæsthesia; and after an uneventful postoperative recovery both were discharged from hospital within ten days. 5 other patients had operations during their therapy. None had any ill-effects and they recommenced therapy immediately after the operation.

3 patients with radiologically demonstrable diaphragmatic herniæ, causing severe symptoms, were all trouble-free within a few days of starting treatment and remained so throughout the course. They required no further treatment.

A diabetic had previously been treated with insulin for five months and then maintained on daily chlorpropamide (' Diabinese ') 500 mg. and a 1200-calorie diet. She lost 45 lb.

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in two courses of treatment, and her urine is now sugar-free without any other form of medication. Her " before and after " glucose tolerance curves were as follows:

	Blood-sugar (mg. per 100 ml.)		*Urine-sugar*		*Acetone*
	Before	*After*	*Before*	*After*	
Fasting specimen	205	104	++++	Absent	Nil
½ hour		176		,,	,,
1 hour	488	214	++++	+	,,
1½ hours ..		238		++	,,
2 hours	500	171	++++	++++	,,

This patient has not increased in weight during the past four months since her treatment finished, and only requires to restrict her eating habits to a dietary level which does not permit weight to increase. She is allowed a free choice of food.

I think this series substantiates Dr. Simeons' original work and illustrates particularly the advantages in planned abdominal and plastic surgery; the method is rapid, effective, and safe, and causes no hardship to the patient. A number of patients who would otherwise be unfit for operation, or, at best, a bad risk, may be safely operated upon. Patients treated preoperatively will avoid the cardiovascular and respiratory embarrassments of the obese.

London, W.1. PHILLIP LEBON.

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After a single intramuscular injection of 4 or 5 ml., serum-iron levels attained a variable peak in one or two days and returned to about normal after six or seven days in both anæmic patients and healthy people.

There was no evidence of increased urinary excretion of iron after injection of the preparation.

The injected iron disappears from the serum more slowly than does saccharated iron oxide.

In spite of serum-iron levels as high as 13·8 mg. per 100 ml. no toxic reactions were observed after intramuscular injections.

38 out of 40 cases of iron-deficiency anæmia responded adequately to intramuscular treatment with the iron preparation. It was found that 43 mg. of iron intramuscularly would raise the Hb level by 1%, and the period taken to achieve the maximum rise in Hb was 4–9 weeks.

A difference in Hb response was observed between the present preparation and saccharated iron oxide.

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THE ACTION OF CHORIONIC GONADOTROPHIN IN THE OBESE

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IN most cases of obesity the distribution of excess fat somewhat resembles that obtaining in Fröhlich's syndrome. It therefore seemed worth while to experiment with the anterior-pituitary-like chorionic gonadotrophin derived from human pregnancy urine * which has long been advocated for the treatment of Fröhlich's syndrome.

Method and Results

Daily injections of a small dose—125 I.U.—were preferred to a wider spacing of larger doses. The results observed were not enhanced by increasing the daily dose.

Simple Obesity

When obese patients were allowed to continue their usual feeding-habits, gonadotrophin distinctly decreased in ten days the measurements round the hips and the waist without a significant loss of weight. The patients invariably noticed a partial loss of appetite, and particularly that the sudden compulsive hunger, from which many suffered even a few hours after a substantial meal, had completely disappeared.

* 'Antuitrin S' (Parke Davis) and 'A.P.L.' (Ayerst Laboratories Inc.) were used.

The change in measurements was interpreted as a dispersal of fat away from the more favoured sites, and it was thought that fat "in transit" might be more readily available for metabolic purposes than fat in "fixed deposit," in which case it should be possible to keep such patients on 500 calories a day without their feeling weak or hungry.

Gonadotrophin was given three or four days without dietary restriction; then the patients were restricted to two meals a day, each consisting of 100 g. of lean meat, a normal helping of leafy vegetables, an unsweetened rusk, and an apple or the equivalent in fruit, with salt and fluids ad lib. The average daily loss of weight was 250–600 g., without any inconvenience being caused, even to patients doing a hard day's work. In well over 500 cases, treated during the past twenty years, this effect was regularly observed in all types of obesity, in both sexes, at all ages, including women who had had both ovaries removed.

After about forty days of this treatment and a loss of 20–30 lb. a normal appetite returned in spite of continued injections, evidently owing to the well-known "immunity" which the body develops to gonadotrophin. This lasted for about six weeks, after which another course could, if required, be given with the same effectiveness as the first. In extreme cases a third and even a fourth course could be given in this manner. In cases in which only a slight reduction was required the same feeling of inadequacy of the diet arose abruptly as soon as the visibly superfluous fat was removed. Similarly, patients who stopped the injections but continued the diet found that they could manage this for about three days, during which time they continued to lose weight, but that they then suddenly felt weak and hungry and were forced to increase their diet and ceased to lose weight. Three days after the last injection patients were allowed to resume an unrestricted diet and only held to weigh themselves regularly and to compensate a gain after an excessive meal by skipping the next one. About 70% of the patients had no difficulty whatever in maintaining the weight reached, provided neither pregnancy nor the menopause intervened, in which case another course could be given.

When patients were given quantitatively and qualitatively exactly the same food every day, the weight would occasionally remain stationary for three or four days and then suddenly drop to the usual average. During such phases there was either more thirst or less urinary output, or both.

Though signs of protein or vitamin deficiencies were never observed, some patients occasionally complained of the typical symptoms of hypoglycæmia. A teaspoonful of sugar controlled these at once and did not, when taken in these circumstances, interfere with the loss of weight.

The treatment did not deplete the cutaneous or other essential fat, the face retaining its freshness and turgor throughout.

When, unknown to the patient, physiological saline solution was substituted for the gonadotrophin, the regular loss continued for about three days, after which the patients complained of feeling weak or dizzy, became irresistibly hungry, lost no further weight, and either ate secretly or declared themselves unable to continue the treatment. As soon as treatment with gonadotrophin was resumed, they again felt fit and perfectly satisfied with their 500 calories.

Diabetes

When overweight diabetics were reduced in this way they did not develop acetonæmia, and in mild cases with blood-sugar levels ranging up to 200 mg. per 100 ml., the blood-sugar level remained normal after the treatment so long as the weight was not regained. When, as occasionally happened, some weight was later regained, with a concomitant rise in the blood-sugar level, a second course

had the same effect as the first. At least twenty injections were necessary to produce this effect. Apart from the fact that it is almost impossible to keep a diabetic on 500 calories a day for several weeks, a more gradual reduction with diet only did not have this effect on the blood-sugar level. Gonadotrophin alone given in any dose to underweight diabetics had no effect whatsoever on the blood-sugar level.

Gout

Analogous conditions obtained in gout. After a gonadotrophin diet treatment the blood-uric acid level was much reduced or even normal, and though most patients experienced an acute attack during the treatment they remained well after the treatment, regardless of what they ate so long as they did not regain weight.

Blood-cholesterol

An abnormally high blood-cholesterol level behaved in the same way, with the further interesting feature that during treatment the free cholesterol increased while the esterified fraction decreased until values otherwise only seen in pregnancy were sometimes reached.

Effect on Gonads

Apart from its action on abnormal fat, which appeared to be independent of the gonads, treatment stimulated the generative system. There was a great increase in libido in its broadest sense, and the frequency with which pregnancy took place during or soon after treatment was such, even in women who had hitherto considered themselves sterile, that it became an ethical obligation to warn women of childbearing age about this before treatment was started. Oligomenorrhœa and hyperœstrogenic dysmenorrhœa were promptly relieved. Fluor albus simplex usually ceased within ten days. An abnormal loss of head hair stopped. Brittle finger-nails became normal. Professional singers noticed an improvement in the quality of their voices.

The characteristic "pituitary" headaches and the lethargy of the obese were relieved within a week. As in pregnancy, arthritic and vaguer "rheumatic" pains disappeared to a great extent, long before the loss of weight could furnish a mechanical explanation of the phenomenon.

Peptic Ulcers

It was repeatedly observed that, though peptic ulcers did not necessarily heal, symptoms therefrom were completely relieved.

Skin Disease

During treatment a large variety of dermatoses cleared up in a matter of days, particularly those of allergic origin; even psoriasis showed an unmistakable, though temporary, improvement. Again the analogy to pregnancy was striking.

Conclusion

These results seem to suggest that chorionic gonadotrophin plays a rather more important rôle in the body's endocrine regulations than has hitherto been assumed; that there are vitally important reasons for its overproduction in pregnancy; and that it is in some way specifically concerned with the control of obesity in both sexes and at all ages. Although gonadotrophin alone does not reduce weight, it does make a very drastic caloric curtailment possible, and is then therapeutically active in comparatively small doses in all those clinical conditions which are known to improve during pregnancy.

Summary

The results of administering small daily doses of chorionic gonadotrophin from pregnancy urine, combined with a severely restricted diet, to obese patients are reported.

In such patients gonadotrophin appears to render abnormal fat deposits readily available, enabling the obese to live comfortably on 500 calories a day for several weeks.

Other conditions often associated with obesity rapidly improved.

It is suggested that chorionic gonadotrophin is specifically concerned with the control of obesity.

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C. HCG Diet Clinics Around The World

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   Phone: (205) 731-9090

   Pell City Office:
   Address: 311 26th ST. N, Pell City, Al., 35215, USA
   Phone: (205) 338-1169

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   http://heritagemedicine.net/index.php

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www.xtrimmedspa.com

52.Rejuvena Health & Aesthetics

Address: 9977 N 95th Street, Suite 101, Scottsdale, AZ 85258, USA
Phone: (480) 551-9000
www.werejuvenate.com

53.Body By Skinovative

Address: 1900 W. Frye Road, Suite 1, Chandler, AZ 8522, USA
Phone: (480) 855-7546
www.hcgdoc.com

54. Castro William PC MD

Address: 18555 N 79th Avenue, Glendale, AZ 85308, USA
Phone: (623) 412-3100

55. Mesa OB-GYN

www.mesaobandgyn.com

East Office:
Address: 7233 E Baseline Rd, Suite 101, Mesa, AZ 85209, USA
Phone: (480) 985–8151

Country Club Office:
Address: 1039 N Country Club Drive, Mesa, AZ 85201, USA
Phone: (480) 834–3784

56. Aging and Hormonal Health, Inc.

Dr. John D. Carr, MD
35400 Bob Hope Drive, Suite 108, Rancho Mirage, CA 92270, USA
(760) 548-0413

57. Women's Health & Wellness

Dr. Christine Paoletti, MD, FACOG
1304 15th Street, Suite 405, Santa Monica, CA 90404
Phone: (310) 319-1819
http://www.drpaoletti.com/

58. Laser, Beauty & Wellness Center

Dr. Angelina Devera MD
11100 Warner Ave, Suite 120, Fountain Valley, CA 92708
Tel: (714) 850-0780
http://www.laserandvitalityinstitute.com/

59. Fleur Woman's Health

Dr. Enrique Jacome, MD
72780 Country Club Drive, Suite A103, Rancho Mirage, CA 92270
(760) 779-5511 / (760) 773-3320
http://www.fleurhealth.com/

60. Estea Laser & Cosmetic Center, Inc.

Dr. Jiri A. Konecny
(562) 595-6961
790 E Willow Street, Suite 200
Long Beach, CA 90806-2718
http://www.esteacosmetic.com/

61. Dr. Kenneth R. Kafka, MD

Address: 955 Carrillo Drive, Suite 210, Los Angeles, CA 90048, USA
Phone: (310) 888- 7778
http://www.kennethkafka.com/

62. Dr. Kristy Vermeulen, N.D.

Address: 364 Hayes Street. 2nd Floor, San Francisco California 94102, USA
Phone: 800-775-5201 Ext. 222
www.sanfranciscohcgdoctor.com

63. Dr. Kenneth Kafka, MD

Address: 955 Carrillo Drive, Suite 210, Los Angeles California 90048, USA
Phone: 800-775-5201 Ext. 213
www.santamonicahcgdoctor.com

64. Life Balance Centre

Address: 115 E. Micheltorena Street, Santa Barbara, CA 93101, USA
Phone: (805) 564-2900
www.thelifebalancecentre.com

65. Soboba Medical Group / Medical Weight Loss Clinic

http://www.sobobamedspa.com/

Los Angeles County:
Long Beach Branch
Address: 6621 E. Pacific Coast Highway, Ste 120, Long Beach, CA 90803, USA
Phone: 562-431-2858

Orange County:
Costa Mesa Medical Weight Loss Clinic
Address: 1901 Newport Boulevard – Suite 156, Costa Mesa, CA 92627, USA
Phone: 949-646-0251

Laguna Hills Clinic
Address: 27001 Moulton Pkwy A-103, Laguna Hills, CA 92653, USA
Phone: 949-362-4560

Rancho Santa Margarita Clinic
Address: Aventura Business Park Ste 118, 22521 Avenida Empresa, Rancho Santa Margarita, CA 92688, USA
Phone: 949-459-3952

Riverside County:
Corona Medical Weight Loss Clinic
Address: 720 Magnolia Ste. A-2, Corona, CA 92879, USA
Phone: 951-371-5600

San Diego County:
San Diego Medical Weight Loss Clinic
Address: 8312 Lake Murray Blvd., Suite L, San Diego, CA 92119, USA
Phone: 619-461-1791

66. Alternative Health and Weight Loss Center

Dr. Tracy Darling, MD
Address: 31639 South Coast Hwy, Laguna Beach, CA 92651, USA
Phone: (949) 610-9950
http://www.darlingmd.com/

67. Maximum Weight Loss Medical Center

Address: 5597 E Santa Ana Canyon Road, 2nd Floor, Anaheim Hills, CA 92807, USA
Phone: (714) 974-6900
http://www.mdweightlossca.com/

68. Pounds Off Medical Center

Address: 4183 Chino Hills Pkwy, Ste B, Chino Hills, CA 91709, USA
Phone: (909) 529-6565
www.medicalweightlosschinohills.com

69. Advanced Wellness Center

Address: 6423 E Pacific Coast Hwy, Long Beach, CA 90803, USA
Phone: (562) 356-8521
www.advancedwellness.org

70. AG Clinic

Address: 425 S Fairfax Ave, Los Angeles, CA 90036, USA
Phone: (323) 954-0231
http://www.agcliniclosangeles.com/index.html

71. Vortex Wellness & Aesthetics

Address: 2126 S La Brea Ave, Los Angeles, CA 90016, USA
Phone: (866) 420-9453
http://shop.vortexwellness.com/

72. Be Hive of Healing

Address: 11695 National Blvd, Los Angeles, CA 90064, USA
Phone: (310) 914-4567
http://behiveofhealing.com/

73. Pacific Wellness Group

Address: 9400 Brighton Way, Suite 410, Beverly Hills, CA 90210, USA
Phone: (310) 913-9539 / (310) 606-3826
http://www.fastweightlosscenter.com/

74. Horizons Medical Weight Loss

Address: 17777 Ventura Blvd, Suite 120, Encino, Los Angeles, CA 91316, USA
Phone: (818) 654-5720
http://www.horizonsmedicalweightloss.com/

75. A New Me

Address: 800 Torrance Blvd #200, Redondo Beach, CA 90277, USA
Phone: (310) 792-2345
http://www.iamanewme.com/

76. California Medical Weight Loss

Address: 413 S. Central Ave, Glendale, CA 91204, USA
Phone: (818) 241-2321
http://www.camedicalweightloss.com/

77. American Weight Loss Center

Address: 4321 Woodman Ave, Sherman Oaks, CA 91423, USA
Phone: (818) 582-3754
http://www.americanweightlosscenter.com/

78. Biologix + Med

Address: 7901 Santa Monica Blvd, West Hollywood, CA 90046, USA
Phone: (213) 309-8612
http://www.biologixmed.com/

79. Robertson Blvd Med Spa

Address: 317 S Robertson Blvd, Beverly Grove, Los Angeles, CA 90048, USA
Phone: (310) 276-1080
http://www.robertsonblvdmedspa.com/

80. Medilean Medical Weight Loss

Address: 827 Deep Valley Dr, Rolling Hills Estates, CA 90274, USA
Phone: (310) 541-3900
http://medileanhcg.com/

81. Skin Perfect Medical

Address: 6501 Greenleaf Ave, Whittier, CA 90601, USA
Phone: (562) 222-4151
http://skinperfectmedical.com/

82. California Medical Weight Loss

Address: 11823 E Del Amo Blvd, Cerritos, CA 90703, USA
Phone: (562) 924-3141
http://camedicalweightloss.com/

83. Bella Medical Aesthetics & Weight Loss

Address: 13470 Telegraph Rd, Whittier, CA 90605, USA
Phone: (888) 789-4851
http://dralija.com/

84. Accesa Health

Address: 21730 S Vermont Ave, Torrance, CA 90502, USA
Phone: (310) 606-3877
http://www.accesahealth.com/

85. Vida Health Clinic

Address: 202 W La Habra Blvd, La Habra, CA 90631, USA
Phone: (888) 987-1219
http://vidahealthclinic.com/

86. LA Vitamin Injections

Address: 3001 Main St , 2nd Fl, Santa Monica, CA 90405, USA
Phone: (424) 278-4325
http://www.lavitamininjections.com/home.html

87. Ceres Wellness & Anti-Aging

Address: 2693 E Washington Blvd, Pasadena, CA 91107, USA
Phone: (626) 798-2000
http://www.cereswellness.com/

88.Ruben M Ruiz III, MD

Address: 3012 San Gabriel Blvd, Rosemead, CA 91770, USA
Phone: (626) 572-8692
http://www.calldrruiz.com/

89.Long Beach Medical Weight Control

Address: 1934 N Lakewood Blvd, Long Beach, CA 90815, USA
Phone: (562) 270-9800
http://lbweightcontrol.com/

90.ibody

Address: 956 Huntington Dr, San Marino, CA 91108, USA
Phone: (626) 593-5993
http://theibody.com/

91.Cosmetique Medspa

Address: 10744 W Washington Blvd, Culver City, CA 90232, USA
Phone: (310) 837-5555
http://www.cosmetiquemedspa.com/

92.Holtorf Medical Group

Address: 23456 Hawthorne Blvd, Torrance, CA 90505, USA
Phone: (310) 421-4261
http://www.holtorfmed.com/

93.Optimal Health and Wellness

Address: 670 Monterey Pass Rd Monterey Park, CA 91754, USA
Phone: (626) 551-5155
http://www.opthealthwellness.com/

94.Natura Medical Center

Address: 638 E Colorado Blvd, Pasadena, CA 91101, USA
Phone: (626) 788-0023
http://www.naturamc.com/

95.Los Reyes Clinica Medica

Address: 7936 Seville Blvd, Huntington Park, CA 90255, USA
Phone: (323) 583-0450
http://www.losreyesclinicamedica.com/

96.Weightwise Medical Clinics

Dr. Rita Thakur, MD
800 Charcot Ave, #113, San Jose, California 95131, USA
(408)-931-2062 | (408)-307-2123
www.weightwise101.com

97. Vibrance Medical Group in Westlake Village

Dr. Darren Clair, MD
2772 Townsgate Road, Suite D, Westlake Village, CA 91361, USA
866-677-6919
http://www.bevibrance.com/

98. Portal to Healing / Naturopathic Clinic

Dr. Andrea Purcell, N.MD
http://www.portaltohealing.com/

Arizona Office:
Address: 15849 N 71st St. Suite 235, Scottsdale, AZ 85254, USA
Phone: (888) 691-6881

California Office:
Address: 2000 Harbor Blvd Suite C100, Costa Mesa, CA 92627, USA
Phone: (800) 318-8582

99. Studio27 Inc.

Address: 2631 W. Colorado Avenue, Colorado Springs, CO 80904, USA
Phone: (719) 329-0304
http://www.studio27co.com/index.html

100. Restore Health Center

Dr. James Howton, DO
Address: 3553 Clydesdale Pkwy. Suite 210, Loveland, CO 80538, USA
Phone: (970) 800-2098
http://restorehealthcenter.net/

101. Body Solutions RX

Dr. Brett B. Abernathy, MD
Address: 2500 North Circle Drive #202, Colorado Springs, CO 80909, USA
Phone: (719) 228-9035
http://www.bodysolutionsrx.com/

102. Biotwin Medical Weight Loss & Bioidentical Hormone Therapy

Lori Moore, FNP
Address: 7180 East Orchard Road, Suite 307 Centennial, CO 80111, USA
Phone: 80111 800-775-5201 Ext. 274
http://www.hcgdenvercolorado.com/

103. BioHarmony Medical

Dr. Shauna Wright, DO
Address: 300 S. Jakson st., Suite 250, Denver, CO 80209, USA
Phone: 80209 800-775-5201 Ext. 206
http://www.denverhcgdoctor.com/

104. Kenton Bruice, MD

Address: 55 Madison St., Suite 575 Denver, Colorado 80206, USA
Phone: 80206 800-775-5201 Ext. 238
http://www.hcgdenver.com/

105. Living Great

Dr. Calvin T. Wilson II, MD, Gynaecology and Bariatric Medicine Specialist
Address: 1027 S. Bradford St, Dover, DE 19901, USA
Phone: (302) 734-9200
http://www.timeisonyourside.net

106. Serrão Rejuvenation Center

Dr. E. John Serrao, MD, FACOG, FAACS, FAAAAM
Address: 2905 Mcrae Avenue, Orlando, FL 32803, United States
Phone: (407) 896-3772
http://www.cosmeticsurgeryandwellness.com

107. Health Point Medical Group

Dr. John Paul Sosa, MD, Family Medicine
Address: 4902 Eisenhower Blvd., Suite 300, Tampa, FL 33634, USA
Phone: (813) 636-2000
http://healthpointmedicalgroup.com/

108. Healing Alternatives, Inc

Dr. Kathleen A. MacIsaac, MD
Address: 25 West Pineview Street, Suite 1009, Altamonte Springs, FL 32714, USA
Phone: (407) 682-7111
http://www.healingalternativesinc.com/index.aspx?A=0

109. New Beginnings Medical - Florida Locations

http://newbeginningsmedical.com/

Vero Beach Office:
Address: 3740 20th St, Suite A, Vero Beach, Florida 32960, USA
Phone: (772) 778-6727

Palm Beach Gardens Office:
Address: 12300 Alternate A1A, Suite 112, Palm Beach Gardens, FL 33410, USA
Phone: (561) 776-7177

West Palm Beach Office:
Address: 2001 Palm Beach Lakes Boulevard, Suite 102, West Palm Beach, FL 33409, USA
Phone: (561) 795-4000

Boca Raton Office:
Address: 2300 Glades Road, Suite 450W, Boca Raton, FL 33431, USA
Phone: (561) 910-7878

110. Smart for Life Weight Management Centers

Dr. Scott R. Greenberg, MD, Allan Magaziner D.O.

International Headquarters:
Address: 190 Glades Rd, Boca Raton, FL 33432, USA
Phone: (561) 338-3999
http://www.smartforlife.com

Boca Raton Office:
Address: 190 Glades Rd. Suite E, Boca Raton, Florida 33432, USA
Phone: (561) 338-3999

Wellington Office:
Address: 11903 Southern Blvd., Royal Palm Beach, Florida 33411, USA
Phone: (561) 792-2000

Beverly Hills Office:
Address: 352 S. La Cienega Blvd., Los Angeles, California 90048, USA
Phone: (310) 623-1999

Palm Beach Gardens Office:
Address: 4210 Northlake Blvd, Palm Beach Gardens, Florida, 33410, USA
Phone: (561) 745-4888

Montreal Office:
Address: 6525 Boul. Decarie GR3, Montreal, Quebec, H3W 3E3 Canada, USA
Phone: (514) 489-8840

Orlando Office:
Address: 451 N Maitland Avenue, Maitland, Florida 32751, USA
Phone: (407) 740-0036

Cherry Hill Office:
Address: 1907 Greentree Road, 1st Floor, Cherry Hill NJ 08003, USA
Phone: (856) 424-4747

111. National Medical Clinic

Address: 7491 N Federal Hwy., Building C-5 Suite 296, Boca Raton, FL 33487, USA
Phone: (561) 241-3412
http://www.nationalmedicalclinic.com

112. GHI Medical

Address: 2020 Seven Springs Blvd New Port Richey, FL 34655, USA
Phone: (877) 721-1200
http://www.ghimedical.com/index.html

113. Nu Image Medical

Address: SunTrust Tower, 401 East Jackson Street, Suite 2340, Tampa, FL 33602, USA
Phone: (888)520-3438
http://nuimagemedical.com/

114. Sarasota Weight Loss Clinic

Dr. Steven Gupta, MD
Address: 4541 Bee Ridge Road, Sarasota, FL 34233, USA
Phone: (941) 371-9355
http://www.sarasotaweightloss.com
http://www.stevenvgupta.com/

115. GLORY MEDICAL CENTER & WEIGHT LOSS CLINIC

Dr. David Ikudayisi, MD
www.glory-center.com

Tampa Office:
Address: 8019 N.Himes Avenue, Suite #200, Tampa, FL 33614, USA
Phone: (813) 932-9798

New Port Richey Office:
Address: 6641 Madison Street. Suite 3, New Port Richey, FL 34652, USA
Phone: (727) 232-0826

Lakeland Office:
Address: 5131 S.Florida Avenue, Suite 1, Lakeland, FL 33813, USA
Phone: (863) 248-6881

116. Ravi's Weight Loss

Dr. Himagiri Ravi, MD
Address: 6155 S Florida Ave Suite 1, Lakeland, FL 33813, USA
Phone: (863) 607-6400
http://lakelandweightloss.com/

117. Thin Again

Dr. Louis Huesmann, MD
Address: 2131 Murfreesboro Pike #101, Nashville, TN 37217, USA
Phone: (615) 942-7413
http://www.thinagainrx.com

118. Natural Med Therapies

Dr. Machelle Perkins
Address: 7600 Bryan Dairy Road, Suite C, Largo, FL 3377, USA
Phone: (727) 541-2211
www.naturalmedtherapies.com

119. Fountain of Youth Medical Spa

Dr. Victor E. Mendoza, MD
5130 Cyrus Cir, Birmingham, AL 35242, USA
(205) 981-0414
http://www.foyms.com/

120. Lake Oconee Urgent and Specialty Care

Dr. Jameelah Gater, MD
Address: 105 Harmony Crossing, Suite #3, Eatonton, GA 31024, USA
Phone: (706) 484-0884
http://www.lakeoconeeurgentcare.com/

121. Transformations Medical Weight Loss Company

http://www.transformationsmedicalweightloss.com/
http://www.yweight.cc/

A- Lake Mary:
Address: 917 Rinehart Rd, Suite #2001, Lake Mary, FL 32746
Phone: (407) 268-6411

B- Orlando:
Address: 920 Lee Rd, Orlando, FL 32810
Phone: (407) 278-1115

C- Oviedo:
Address: 7560 Red Bug Lk Rd, Suite #2084, Oviedo, FL 32765
Phone: (407) 278-4045

D- Kissimmee:
Address: 222 Broadway Ave., Suite #212 Kissimmee, FL 34741
Phone: (407) 705-2710

E- Metro West:
Address: 6150 Metrowest Blvd Suite #201, Orlando, FL 32835
Phone: (407) 378-4859

F- Melbourne:
Address: 1513 S Harbor City Blvd., Melbourne, FL 32901
Phone: (321) 622-2340

G- Tampa:
Address: 2727 W M.L.K. Jr. Blvd, Suite #570 Tampa, FL 33607
Phone: (813) 217-5894

H- Clermont:
Address: 17335 Pagonia Rd, Bldg B, Suite #101, Clermont, FL 34711
Phone: (352) 432-1633

I- South Orlando:
Address: 3872 Oakwater Circle, Orlando, FL 32806
Phone: (321) 800-4920

J- Tulsa Southeast:
Address: 7731 E 91st St Suite #D, Tulsa, OK 74133
Phone: (918) 770-4572

122. Atlanta Wellness and Aesthetics

Dr. Neil S. Gladstone, MD
Address: 3115 Piedmont Rd NE Suite A101, Atlanta, GA 30305, USA
Phone: (404) 816-0222
http://www.atlantawellnessandaesthetics.com/

123. Taylor Medical and Aesthetic Group

Eldred B. Taylor, M.D. / Ava Bell Taylor, M.D.
Address: 5901-C Peachtree-Dunwoody Rd NE, Suite 25, Atlanta, GA 30328, USA
Phone: (678) 443-4000
http://taylormedicalgroup.net/index.php

124. WELLNESS DOCTORSTUDIO

Dr. Mark Wright, MD
http://www.doctorswellness.com/index.html

NORCROSS Branch:
Address: 5775 Jimmy Carter Blvd, Suite 200, Norcross, GA 30071
Phone: (678) 646-3627

MARIETTA Branch:
Address: 2475 Windy Hill Road, Suite B, Marietta, GA 30067
Phone: (770) 937-0937

125. Cumming MedSpa

Dr. Germaine Cummings, M.D.
Address: 2950 Buford Hwy, Suite 140, Cumming, GA 30041, USA
Phone: (678) 455-8800
http://www.cummingmedspa.com/

126. Slender SpaMed

Dr. Donald Alfred Ruf, MD
http://www.slenderspamed.com/

ROSWELL Branch:
Address: 1475 Holcomb Bridge Rd. Suite 165, Roswell, GA 30076
Phone: (678) 701-4020

DULUTH Branch:
Address: 1611 Satellite Blvd. Ste.3, Duluth, GA 30096
Phone: (678) 256-2804

127. Slim Again Clinical weight Loss

http://www.slimagain.com
Phone: (770) 933-7546

MARIETTA:
Address: 2359 WINDY HILL RD SE STE 300, MARIETTA GA 30067, USA

CAMP CREEK:
Address: 3830 PRINCETON LAKES CT SW STE 600, ATLANTA GA 30331, USA

128. Northside Family Medicine, LLC.

Dr. Haroon Rashid, MD, Family Physician
Address: 580 Atlanta Road, Suite 230 A, Cumming, GA 30040, USA
Phone: (770) 781-9824
www.northsidefamilymedicine.org

129. Prestige Medical Group

Phone: (706) 692-9768
http://www.prestigemedicalgroup.org/index.php

Jasper:
Address: 51 Gordon Road, Jasper, GA 30143

Holly Springs:
Address: 684 Sixes Road, Holly Springs, GA

130. AMI Wellness Center

Address: 3365 Piedmont Rd NE Suite 1250, Atlanta, GA 30305, USA
Phone: (404) 410-0276
http://www.amiwellnesscenters.com/

131. Crabapple Internal and Integrative Medicine

Dr. Forrest Smith, MD
Address: 45 West Crossville Road, Suite 501, Roswell, GA 30075, USA
Phone: 800-775-5201 Ext. 233
http://www.hcgroswellga.com/

132. hCG Weight Loss Atlanta

http://hcgweightlossatlanta.com/

Sandy Springs Plaza:
Address: 6309 Roswell Rd., Suite 9-2BM
Atlanta, GE 30328, USA
Phone: (404) 968-9642

The Station at Vinings
Address: 2810 Paces Ferry Rd, Atlanta, GE
30339, USA
Phone: (678) 305-7066

133. Absolute Health Care of GA, Inc

http://www.absolutehealthcareofga.com/

Griffin:
Address: 1857 West McIntosh Road,
Griffin, GA 30223, USA
Phone: (770) 710-6734

Newnan:
Address: Stone Wall Square, Suite 10, 20
Baker Rd, Newnan, GA 30265, USA
Phone: (770) 710-3225

134. Holistic Hands Chiropractic

Address: 20605 North Main Street, Cornelius, NC 28031, USA
Phone: (980) 833-3616
http://drjessie.com/

135. Natural Wellness Center

Dr. Ryan Ferchoff / Dr. Phuong Nguyen / Dr Stephen Benchouk
www.drferchoff.com
Phone: (808) 988-0800

Manoa Marketplace Office:
Address: 2752 Woodlawn
Dr. #5-215, Honolulu, HI
96822, USA

Aiea - Waimalu Plaza Office:
Address: 98-1277
Kaahumanu St #142A, Aiea,
HI 96701, USA

Kailua Medical Row Office:
Address: 305 Uluniu St.
#104, Kailua, HI 96734, USA

136. Complete Clinics

http://www.completeclinics.com/

Downtown Chicago Office:
Address: 2266 North Lincoln Avenue 2nd Floor, Chicago, IL 60614, USA
(877) 269-5160

North Chicago Suburbs Office:
Address: 1800 Nations Drive, Suite 112, Gurnee, IL 60031, USA
Phone: (877) 269-5160

Oak Brook Office:
Address: 1919 Midwest Road, Suite 100A, Oak Brook, IL 60523, USA
Phone: (877) 269-5160

Oak Lawn Office:
Address: 6311 W. 95th Street, Oak Lawn, IL 60453, USA
Phone: (877) 547-6567

137. Essence Skin Clinic

Dr. Leighanne Holmes, MD
Address: 25 2nd Street SW, Rochester, MN 55902, USA
Phone: (507) 285-5505
http://essenceskinclinic.com/

138. Lift Body Center

Dr. Mir Joffrey MD
Address: 1321 Tower Road, Unit A, Schaumburg, IL 60173, USA
Phone: (847) 995-9000
http://www.liftbodycenter.com/

139. Hensler Medical Weight Loss

Address: 1010 W. Eighth St., Suite 2, Anderson, IN 46016, USA
Phone: (765) 644-3626
http://www.weightlossindiana.com/

140. Lawrence Family Practice Center

Carla Phipps, MD
Address: 4951 W 18th Street, Lawrence KS 66047, USA
Phone: (785) 841-6540
http://lawrencefamilypractice.com/

141. Rock Creek Wellness

Dr. Mark Strehlow, MD, Family Medicine specialist
Address: 5401 College Blvd, Suite 203, Leawood, KS 66211, USA
Phone: (913) 727-7700
http://www.rockcreekwellness.com/

142. Midwest Medical Aesthetics Center

Address: 11213 Nall Avenue, Suite 140, Leawood, KS 66211, USA
Phone: (888) 311-1931
http://www.lookmybest.net/

143. Gateways to Integral Health

Dr. Regina Forster, MD
Address: 2716 Old Rosebud Road, Suite 230, Lexington, KY 40509, USA
Phone: (859) 351-1310
http://www.gatewaystointegralhealth.com/

144. Simply Slim Medical, L.L.C.

Dr. Matthew Wolins, MD
Address: 10401 Old Georgetown Road, suite 307, Bethesda, MD 20814, USA
Phone: (301) 658-2019
http://www.simply-slim.com/

145. Simply Slim Medical LLC

Address: 10401 Old Georgetown Rd, Bethesda, MD 20814
Phone: (301) 658-2019
http://www.simply-slim.com/

146. Just Lose Weight, MD

Address: 501 N Frederick Ave, Gaithersburg, MD 20877
Phone: (240) 780-7442
http://justloseweightmd.com/

147. Holistic Physician in Maryland

Dr. Fred Bloem, MD, Bariatric & Family Medicine
Address: 4108 Alfalfa Terrace, Olney, MD 20832
Phone: (301) 260-2601
www.drbloem.com

148. Advanced Body Sculpting of New England

Dr Mark X. Lowney, MD, Obstetrician & Gynaecologist, Cosmetic Surgeon
Address: 484 Highland Ave, Fall River, MA 02720, USA
Phone: (508) 672-3700
http://www.massachusettscosmetic.com/

149. Massachusetts Medical Weight Loss Centers

Dr. Joseph Palma, MD
http://massmedicalweightloss.com/

Northborough Office:
Address: 1 East Main Street, Suite 101, Northborough, MA 01532, USA
Phone: (508) 244-1327

Weymouth Office:
Address: 210 Winter Street #103, Weymouth, MA 02118, USA
Phone: (508) 244-1327

150. Medical Aesthetics of New England

Dr. Gert Walter, , MD, FACEP
http://www.medicalaestheticsne.com/

Acton Office:
Address: 274-2A Great Road, Acton, MA 01720, USA
Phone: (978) 263-1406

Fitchburg Office:
Address: 1123 South Street, Leominster/Fitchburg, MA 01420, USA
Phone: (978) 627-0233

151. Body By Design Weight Loss Center

Dr. Joseph Russo, MD
Address: 1418 Boston-Providence Highway, Norwood MA 02062, USA
Phone: (781) 269-2824
http://www.bodybydesignweightloss.com/

152. SoundShapes Skin & Body Rejuvenation Center

Dr. Gert Walter, , MD, FACEP
Address: 230 Commercial Street, Boston, MA 02109, USA
Phone: (617) 367-1900
http://www.sound-shapes.com/

153. The Village Chiropractor

Dr. Kelly Delorey
Address: 591 North Ave, Ste 4-2, Wakefield, MA 01880, USA
Phone: (781) 246-2888
http://www.villagechiropractor.com/

154. Pain Relief Centers of Massachusetts

Dr. Robert Sprague, MD
Address: 24 Route 134 South Dennis, MA 02660, USA
Phone: (800) 617-3610
http://www.capecodpainrelief.com/

155. Optimal Wellness MD

Dr. Joseph Kaye, MD, LLC
Address: 300 Trade Center, Suite 4400, Woburn, MA 01801, USA
Phone: (781) 933-4200
http://www.optimalwellnessmd.com

156. Minnesota Gynecology & Aesthetics

Dr Lisa Ohman Erhard, MD, FACOG
Address: 1421 Wayzata Blvd East Suite 200, Wayzata, MN 55391, USA
Phone: (952) 473-6642
http://www.mngaclinic.com/

157. Vivify Emotional Eating Solutions

Dr. David Christianson, MD
Address: 6600 France Avenue South, Suite 164, Edina, MN 55435, USA
Phone: (952) 920-8644
www.vivifyhcgdiet.com

158. Rapid Body Reducers

Address: 4121 South Fremont Ave, Suite 104, Springfield, MO 65804, USA
Phone: (479) 464-8446
www.rapidbodyreducers.com

159. HCG DIET SPRINGFIELD

Address: 1675 E Seminole, Suite O, Springfield, MO 65804, USA
Phone: (417) 882-7447
http://hcgdietplansmo.com

160. Meta-Health Weight Loss Management Inc.

www.meta-health.com

Columbia Center:
Address: 108 East Green Meadows, Suite 2, Columbia, MO 65203, USA
Phone: (573) 441-9400

Kansas City Center:
Address: 7301 Mission Road, Suite 143, Prairie Village, Kansas 66208, USA
Phone: (913) 722-3800

161. Alternatives

Dr. Patricia Ryan, MD
Address: 11036 Oak St. Omaha, NE 68144, USA
Phone: 800-775-5201 Ext. 271
http://www.nebraskahcgdoctor.com/

162. Miracle Image Medaesthetic Institute

Dr. Jeffrey Liu, MD
3040 W. Charleston Blvd, Las Vegas, NV 89102, USA
Tel: (702) 878-8089
http://miracle-image.com/

163. HCG Diet & Weight Loss Clinic

Address: 5875 S Rainbow Blvd, Ste 206, Las Vegas, NV 89118
Phone: (702) 275-9969

164. Wise Chiropractic, Inc.

Dr. Jonathan Wise
Address: 5875 S. Rainbow Blvd. #100, Las Vegas, NV 89118, USA
Phone: (702) 248-6292
www.revive-weightloss.com

165. Dr. Emma's Weight Loss

DR. SHERI L. EMMA, MD
Address: 340 Route 34, Suite 202, Orchards Colts Neck, Colts Neck, NJ 07722, USA
Phone: (732) 903-6090
http://www.dremma.com/

166. Re-Vita'-Life

Dr. Joann Richichi, MD, Obstetrics and Gynecology
Address: 239 Hurffville-Crosskeys Road, Suite 250, Sewell, NJ 08080, USA
Phone: (856) 262-4750
http://www.revitalifesouthjersey.com/

167. JC Medical Care

Dr. Amy Patel, MD
Address: 844 Newark Ave, Jersey City, NJ 07306, USA\
www.jcmedicalcare.com

168. Physicians Weight Loss Centers

Dr. Alkesh Patel, MD, LLC
Address: 710 Main Street, Building 1, Plantsville, CT 06479, USA
http://www.ctwellnesscenter.com/home.html

169. Tuscan Sun Spa & Salon

Jann Foley, ARNP
http://tuscanspaandsalon.com/

Clarksburg Office:
Address: 482 Emily Drive, Clarksburg, WV 26301, USA

Fairmont Office:
Address: 1013 Fairmont Avenue, Fairmont, WV 26554, USA

Morgantown Office:
Address: 376 Patteson Drive, Morgantown, WV 26505, USA

170. Magaziner Center for Wellness

Dr. Allan Magaziner, D.O. / Dr. Scott Greenberg, MD / Dr. Robert Steinfeld, MD / Dr.Henry Sadek, D.O.
Address: 1907 Greentree Road, Cherry Hill, NJ 08003, USA
Phone: (856) 424-8222
http://www.drmagaziner.com/

171. Improve Health Solutions

Address: 200 Atlantic Ave Ste G, Manasquan, NJ 08736, USA
Phone: (732) 930-2753
http://improvehealthsolutions.com/

172. Jenyons' Medical Weight Loss and Rejuvenation Center

Address: 449 Avenue C, Bayonne, NJ 07002, USA
Phone: (201) 844-6309
http://drjenyons.com/

173. Advanced HCG Rapid Weight Loss System

Dr. Radu Kramer, MD
Address: 1 Sears Dr. Fl#3, Suite 306, Paramus, NJ 07652, USA
Phone: (862) 225-9693
http://www.hcgdietplansnj.com

174. HCG Diet Center

http://www.hcgdietnj.com/

Paramus Branch:
Address: 494 N State Rt 17, 2nd Fl, Paramus, NJ 07652, USA
Phone: (800) 917-5864

Millburn Branch:
Address: 90 Millburn Ave., Suite 201, Millburn, NJ 07041, USA
Phone: (855) 732-3381

175. Just Melt

Address: 30 E 40th St, Ste 806, Manhattan, NY 10016, USA
Phone: (212) 447-1155
http://justmelt.com/

176. The ChinQuee Center for Wellness & Aesthetics

Dr. Karlene ChinQuee, MD, FACOG
Address: 880 Fifth Avenue, NY 10021, USA
Phone: (212) 861-3130
http://chinqueecenter.com/

177. Nu Image Medical

Address: 140 East Ridgewood Avenue, Paramus, NJ 07652, USA
Phone: (888) 520-3438
www.nuimagemedical.com

178. Davidson Medical Wellness

Dr. Arthur Davidson
Address: 699 Teaneck Road, Suite 106, Teaneck, NJ 07666, USA
Phone: (201) 530-7070
http://davidsonmed.com/

179. Serenity Medical Spa

Dr. Sharon Gertzman
Address: 2425 Pennington Road, Pennington, NJ 08534, USA
Phone: (609) 737-7737
http://serenitynj.com/

180. Dr. DePrince Cosmedical Clinic

Daniel DePrince, D.O.
Address: 300 Route 38, Moorestown, NJ 08057, USA
Phone: 800-775-5201 Ext. 263
http://www.southnewjerseyhcg.com/

181. Healthy Aging Medical Centers

Dr. Johanan D Rand, MD
Phone: (800) 775-5201 Ext. 268

West Orange Headquarters:
Address: 667 Eagle Rock Ave, Suite 2A, West Orange, NJ 07052, USA

Basking Ridge Branch:
Address: 233 Mt. Airy Road, 1st Floor, Basking Ridge, New Jersey, 07920, USA

Red Bank Branch:
Address: 125 Half Mile Road, Suite 200, Red Bank, New Jersey, 07701, USA

Woodcliff Lake Branch:
Address: 50 Tice Blvd, Suite 340, Woodcliff Lake, New Jersey, 07677, USA

Cherry Hill Branch:
Address: 923 Haddonfield Rd, Suite 300, Cherry Hill, New Jersey, 08002, USA

Fort Lee Branch:
Address: 1 Bridge Plaza, 2nd Floor, Fort Lee, New Jersey, 07024, USA

Woodbridge Branch:
Address: 581 Main Street, 6th Floor,
Woodbridge, New Jersey, 07095, USA
http://www.northnewjerseyhcg.com/

182. Integra Health

Dr.Natasha Fuksina MD
556 Bloomfield ave, North Newark, NJ 07107, USA
800-775-5201 Ext. 234
http://www.newarknewjerseyhcg.com/

183. Health and Wellness Center

Dr.Natasha Fuksina, MD
2 West Northfield Road, Suite 211, Livingston, NJ 07039, USA
800.775.5201 Ext. 235
http://www.essexcountynewjerseyhcg.com/

184. Corrigan Center for Integrative Medicine

Dr.Lynn Corrigan, D.O.
184 Pompton Avenue, Verona, NJ 07044, USA
800.775.5201 Ext. 239
http://www.newjerseyhcgdiet.com/

185. Nu Image Medical

Address: 41 Vreeland Ave, Totowa, NJ 07512, USA
Phone: (973) 256-3074

186. Ocean Health & Weight Loss

448 Lakehurst Rd, Toms River, NJ 08755, USA
(732) 608-9681
http://www.oceanhealth4you.com/

187. Mesotherapie & Estetik

Dr. Lionel Bissoon, MD
http://www.mesotherapy.com/

New York Office:
Address: 10 West 74th Street, Suite 1E, New York, NY 10023, USA
Phone: (212) 579-9136

Los Angeles Office:
Address: 9735 Wilshire Blvd. #309, Beverly Hills, CA 90212, USA
Phone: (310) 859-8051

San Francisco Office:
Address: 15 Princess Street, Sausalito, CA 94965, USA
Phone: (310) 467-2301

Del Ray Office:
Address: 5210 Linton Blvd, Del Ray, FL 33484, USA
Phone: (561) 838-4991

Palm Beach Office:
Address: 1411 North Flagler Drive, Suite 4100, West Palm Beach, FL 33401, USA
Phone: (561) 838-4991

188. Westchester Wellness Medicine

Dr. Angelo Baccellieri, MD
http://www.westchesterwellnessmedicine.com/

Mount Vernon Office:
Address: 704 Locust Street, Mount Vernon, NY 10552, USA
Phone: (914) 610-3505

Harrison Office:
Address: 500 Mamaroneck Avenue, Suite 211, Harrison, NY 10528, USA
Phone: (914) 610-3505

189. Patients Medical

Address: 800 2nd Ave, Ste 900, Manhattan, NY 10017
Phone: (212) 661-4441
http://www.patientsmedical.com/

190. Cosmetic And Maxillofacial Elective Outpatient Surgery

Dr. Scott M Blyer
http://www.osurgery.com/

Long Island Office:
Address: 3750 Expressway Dr South, Islandia, NY 11749, USA
Phone: (631) 232-2636

Manhattan Office:
Address: 965 Fifth Avenue (1B), New York, NY 10021, USA
Phone: (646) 201-5273

191. Nu Image Medical Associates LLP

Address: 230 Hilton Ave, Hempstead, NY 11550, USA
Phone: (516) 292-8900

192. Weight To Go

www.weightogocarolina.com

Salisbury Office:
Address: 221 Jake Alexander Blvd., South Salisbury, NC 28147, USA
Phone: (704) 216-0229

Concord Office:
Address: 320 Copperfield Blvd., Suite A, Concord, NC 28025, USA
Phone: (704) 787-9772

Albemarle Office:
Address: 636 NC 24-27 Bypass, Unit#9, Albemarle, NC 28001, USA
Phone: (704) 986-2266

Thomasville Office:
Address: 1040 Randolph St., Suite 41, Thomasville, NC 27360, USA
Phone: (704) 216-0229

193. Sentara Albemarle Medical Center

Dr. Steven P. Manuli, MD
Address: 104 Mill End Court, Elizabeth City , NC 27909, USA
Phone: (252) 338-5183
http://www.albemarlehealth.org/

194. New Day Wellness Center, LLC

Dr. Kristin S. Black, MD, Family Physician
Address: 12105 Copper Way - Ste 204, Charlotte, NC 28277, USA
Phone: (704) 697-1116
http://www.newdaywell.com/

195. Let's Get Thin MD

Dr. Michael P. Girouard, MD
Address: P.O. Box 1209, Cornelius, NC 28031, USA
Phone: (704) 766-1000
http://www.letsgetthin.com/

196. Your Personal Wellness Center

Dr. Christopher K. Nagy, MD
Address: 605 Grove Street, Salisbury, NC 28144, USA
Phone: (704) 738-2015
http://yourpersonalwellnesscenter.com/

197. Alpha Med Aesthetics

Dr. Babatunde Ojo, MD
Address: 1815 Fort Bragg Rd, Fayetteville, NC 28303, USA
Phone: (910) 221-3301
http://alphamedaesthetics.com/

198. North Carolina hCG Weight Loss Clinic

Dr. Steven Weston, MD
Address: 2131 Ayrsley Town Blvd, Suite 200, Charlotte, NC 28273, USA
Phone: (980) 297-7400
http://www.westonmedsurg.com

199. The Metabolic Weightloss Clinic

Dr. John Ross M.D
7531 Patriot Drive, Findlay, OH 45840, USA
Phone: (419) 423-6879 / (888) 351-8794
http://www.hcgmetabolicweightlossclinic.com/

200. Warm Springs Wellness Center

Address: 567 Cason Lane, Suite C-1, Murfreesboro, TN 37128, USA
Phone: (615) 426.0472
http://warmspringswellness.com/

201. Weight Loss & Wellness Clinic

http://www.letsgetthin.com

Raleigh Office:
Address: 3100 Duraleigh Road, Suite 200, Raleigh, NC 27612
Phone: (919) 977-4842

Huntersville Office:
Address: 15806 Brookway Dr., Suite 400, Huntersville, NC 28078
Phone: (704) 766-1000

Clemmons Office:
Address: 2554 Lewisville-Clemmons Rd., Suite 109 Clemmons, NC 27012
Phone: (704) 766-1000

Statesville Office:
Address: 1893 East Broad Street Suite B-4, Statesville, NC 28625
Phone: (704) 766-1000

Charlotte Office:
Address: 10512 Park Road Suite 210
Charlotte, NC 28210
Phone: (704) 766-1000

202. Mid-Carolina Surgery, Vein And Aesthetics

Dr. Wendell A. Goins, MD, FACS, RVT
http://www.midcarolinasurgery.com/

Blakeney Office:
Address: 9336 Blakeney Centre Drive, Suite 100B, Charlotte, NC 28277, USA
Phone: (704) 759-1770

Lancaster Office:
Address: 106-C N. Woodland Dr., Lancaster, SC 29720, USA
Phone: (803) 286-8211

203. Bio-Matrix Weight Loss

Dr. Samson K. Orusa, MD
Address: 2237 Lowes Dr. Ste. F,, Clarksville, TN 37040, USA
Phone: (931) 906-2424
http://biomatrixweightloss.com/

204. Indian Lake Medical Weight Loss & Wellness

Address: 133 Indian Lake Road #204, Hendersonville, TN 37075, USA
Phone: (615) 822-9002
http://www.sumnerdietrx.com/

205. Live Fit Medicine

Address: 1901 Brookside Dr, Ste 105, Kingsport, TN 37660, USA
Phone: (423) 765-9500
http://livefitmed.com/

206. Premier Age Management and Medical Weight Loss Center

http://www.premiernashville.com/

Nashville Office:
Address: 229 Ward Circle, Suite A-23, Brentwood, TN 37027, USA
Phone: (615) 649-9600

Hendersonville Office:
Address: 115 Hazel Path #1, Hendersonville, TN 37075, USA
Phone: (615) 649-9603

207. GO!!!FIGURE Weight Loss Clinic

Address: 5661 Hwy 11-E, Suite 2, Piney Flats, TN 37686, USA
Phone: (423) 391-0135
http://gofigureweightloss.com/

208. Genesis Weight and Age Management

Address: 2207 Crestmoor Rd. Suite 204, Nashville,TN 37215, USA
Phone: (615) 442-8586
http://www.genesisweightandagemanagement.com/

209. Performance Medicine

Dr. Tom Rogers , M.D.
http://performancemedicine.net/

Kingsport Office:
Address: 109 Jack White Dr. Kingsport, TN 37664, USA
Phone: (423) 245-2078

Knoxville Office:
Address: 9700 Kingston Pike Suite 17 Knoxville, TN 37922, USA
Phone: (865) 249-7672

Johnson City Office:
Address: 3135 Peoples Street Suite 400 Johnson City, TN 37604, USA
Phone: (423) 854-9200

210. Healthy Lifestyle Wellness Center

Address: 248 North Peters Rd., Suite 3, Knoxville, TN 37923, USA
Phone: (865) 671-3630
http://lifestylewellnessctr.com/

211. Advanced Medical Weight Loss Center

Address: 2308D Memorial Blvd, Springfield, TN 37172, USA
Phone: (615) 382-8143

212. Comprehensive Wellness Center

Dr. Walter Rucker, MD
Address: 2535 Georgetown Road NW, Cleveland, TN 37311
Phone: (423) 244-0311
http://www.ruckercwc.com/

213. Magnolia Medical Center

Dr. David P. Morris / Dr. Danielle Cranfield
Address: 210 Robert Rose Drive, Suite D, Murfreesboro, TN 37129, USA
Phone: (615) 953-9007
http://www.magnoliamedicalcenters.com/

214. Sieveking Plastic Surgery

Dr Nicholas Sieveking, MD, Plastic Surgeon
Address: 204 23rd Avenue North Nashville, TN 37203, USA
Phone: (615) 321-1010
http://sievekingplasticsurgery.com/

215. The Osteopathic Center

Dr. Kristopher Goddard, D.O.
http://www.theosteocenter.com/

Miami Office:
Address: 3915 Biscayne Boulevard Ste 406 Miami, FL 33137, USA
Phone: (305) 367-1176

Knoxville Office:
Address: 224 S Peters Rd SUITE 212, Knoxville, TN 37923, USA
Phone: (865) 693-8772

216. Brookhaven Chiropractic Center

Dr. Richard Hathcock
Address: 721 W. Brookhaven Circle , Memphis, TN 38117, USA
Phone: (901) 767-8077

217. The Medical Weight Loss of Cool Springs

Dr. Cynthia E. Collins, MD
Address: Physicians Plaza, 100 Covey Drive, Suite 107, Franklin, TN 37067
Phone: (615) 771-8753
http://www.medicalweightlossofcoolsprings.com/

218. Balanced Life Family Medicine

Dr. Paul Miranda, MD
Address: 1667 Ooltewah-Ringgold Road, Suites 1 & 2, Ooltewah, TN 37363, USA
Phone: 423-825-4881
http://www.blfamilymedicine.com/

219. The Bradshaw Clinic

Dr. James C. Bradshaw Jr. MD
Address: 1409 Baddour Parkway St. D, Lebanon, TN. 37087, USA
Phone: (615) 444-4126
http://www.bradshawclinic.com/

220. Platinum Weight Loss Center

http://www.platinumweightlosscenter.com/

Nashville Office:
Address: 424 Church St., #2000, Nashville, TN 37219, USA
Phone: (800) 498-0473

Franklin Office:
Address: 725 Cool Springs, #600, Franklin, TN 37067, USA
Phone: (800) 498-0473

Kansas City Office:
Address: 4811 Lamar Avenue, Suite # 8, Mission, Kansas 66202, USA
Phone: (800) 498-0473

Omaha Office:
Address: 1299 Farnam St., #300, Omaha, NE 68102, USA
Phone: (800) 498-0473

221. Gallatin Women's Center

Dr. William R. Caldwell, MD, Obstetrics & Gynaecology Specialist
Address: 437 East Main Street, Gallatin, TN 37066
Phone: (615) 452-8705
http://www.gallatinwomenscenter.com/

222. Embrace Advanced Gynaecology and Wellness

Dr. David W. Marden, DO
Address: 1 Medical Park Boulevard, Suite 305 East, Bristol, TN 37620
Phone: (423) 844-5640
http://askembrace.com/

223. M.T. RX Weight Loss & Laser Center

Dr. Michael D. Tino II, MD
Address: 105 Meadow View Road, Bristol, TN 37620, USA
Phone: (423) 878-5100
http://www.mtrxweightloss.com/

224. Wellness Associates of Katy

Dr.Arlene M. Loeschen MSN, FNP-BC, BC-ADM
Dr.Bethany Powell, MD
Address: Kingsland Medical Plaza, 777 S Fry Rd., Suite 105, Katy, TX 77450, USA
Phone: (281) 647-9950
http://www.wellnessassociatesofkaty.com/

225. Fit Weight Loss System

Dr. Naila Malik MD
http://www.nailamalikmdskin.com

Southlake Texas Office:
Address: 175 Miron Dr, Southlake, TX 76092, USA
Tel: (888) 210-9693

Dallas Texas Office:
Address: 3001 Knox St, #407, Dallas, TX 75205, USA
Tel: (888) 210-9693

226. Equilibrium Weight Loss and Longevity Centers

Dr. Alise Jones-Bailey
Address: 4914 Bissonnet St., Suite 100, Bellaire, TX 77401, USA
Phone: (713) 668-0094
http://www.hcg-diet-houston.com/

227. Family Practice Center

Dr. Manuel J. Sánchez, MD, P.A., Family Practice
Address: 501 N. Ware Rd., McAllen, TX 78501, USA
Phone: (956) 668-0044
http://www.familypracticecenter.com/

228. The Wellness & Aesthetics Medical Center

Dr. Vernon F. Williams MD
Address: 19016 Stone Oak Parkway, Suite 240, San Antonio, TX 78258, USA
Phone: (210) 338-8228
http://www.twaamc.com/

229. The Woodlands Institute for Health and Wellness

Dr. Mila McManus, MD
Address: 26110 Oak Ridge Dr. Woodlands, TX 77380, USA
Phone: (281) 298 6742
http://www.woodlandswellnessmd.com/

230. The Image Enhancement Center

Dr. James H. Kern, MD
Address: 21830 Kingsland Boulevard, Katy, TX 77450, USA
Phone: (281) 599-8900
http://www.imageenhancementcenter.net/

231. Natural Bio Health

Dr. Joseph R. Feste, MD FACOG
http://naturalbiohealth.com/

Austin Office:
Address: 211 Ranch Road 620 South, Suite #220, Austin, TX 78734, USA
Phone: (512) 266-6713

San Antonio Office:
Address: 18626 Hardy Oak Blvd., Suite #220, San Antonio, TX 78258, USA
Phone: (210) 497-5371

College Station Office:
Address: 422 Tarrow Street, College Station, Texas 77840
Phone: (979) 691-8100

232. True MD

Dr. Robert L True MD, FACOG, FAACS
Address: 5203 Heritage Ave. Colleyville, TX 76034, USA
Phone: (817) 399-8783
http://www.truemd.com/

233. Institute For Health

Kimberley A. Schroeder, D.O.
Address: 115 Baker Drive, Tomball, TX 77375, USA
Phone: (281) 290-0531
http://schroederwellnessinstitute.com/

234. Plano Aesthetics

Dr. Jeffrey C. Caruth, MD
Address: 3108 Midway Road, Plano, TX 75093, USA
Phone: (972) 985-8080
www.planoaesthetics.com/

235. Austin Weight Loss & Wellness Clinic

Address: 2541 South I H-35, Suite 500, Round Rock, TX 78664, USA
Phone: (512) 271-2560
http://www.austinweightlosstoday.com/

236. Dr. Liesa MD

Dr. Liesa Harte, MD, Family Medicine
Address: 1524 South IH35, Suite 140M Austin, TX 78704, USA
Phone: (512) 537-8859
http://drliesa.com/

237. BodysculptMD Wellness Institute

Dr. Janice Vaughn, MD
Address: 9900 SW Greenburg Rd #235, Tigard, OR 97223, USA
Phone: (503) 747-3760
http://bodysculptmd.com/

238. Memorial Weight Loss Clinic

Address: 1458 Campbell Road, Suite 200, Houston, Texas 77055, USA
Phone: (713) 468-3322
http://www.memorialweightlossclinic.com/

239. Radiance Advanced Skin and Body Care

Address: 6777 Woodlands Parkway #300, The Woodlands, TX 77382, USA
Phone: (281) 367-4700
http://www.woodlandsradiancespa.com/

240. Cornerstone Chiropractic

Dr. Drake Tollenaar D.C., CCSP
Address: 11565 SW Durham Rd #110, Tigard, OR 97224, USA
Phone: (503) 639-0778
http://cornerstonechiropractic.com/

241. The Doctor's Office PC

Address: 5720 Williamson Rd, Ste 109, Roanoke, VA 24012, USA
Phone: (540) 283-9861
www.thedoctorsofficeroanoke.com

242. Creative Healing Solutions

Dr Roxie Strand NMD
Address: 14300 N. Northsight Blvd, Suite 217, Scottsdale, AZ 85260
Phone: (480) 689-4200
http://www.docrox.com/

243. MD Diet Weight Loss & Nutrition

http://www.mddietclinic.com/

Salt Lake City Office:
Address: 3655 S. State Street, Salt Lake City, UT 84115, USA
Phone: (801) 293-3100

Orem Office:
Address: 337 E. University Parkway, Orem, UT 84058, USA
Phone: (801) 226-1800

244. Le Nouveau Belle

Dr. Shahriar S. Shahzeidi, MD
Address: 8180 Greensboro Dr, McLean, VA 22102, USA
Phone: (703) 992-0226
http://www.lenouveaubelle.com/

245. Dr. Jonathan Colllin, MD

http://drjonathancollin.com/

Port Townsend Office:
Address: 911 Tyler Street, Port Townsend, WA 98368, USA
Phone: (360) 385-4555

Kirkland Office:
Address: 12911 120th Avenue NE, Suite A-50, P.O. Box 8099, Kirkland, WA 98034, USA
Phone: (425) 820-0547

246. McQuinn Naturopathic

Dr. Beth McQuinn
Address: 2808 Hoyt Ave, Ste 201, Everett, WA 98201
Phone: (425) 905-2497
http://www.mcquinnnaturopathic.com/

247. Radiant Med Spa

Dr. Dawn Hunter, DC
Address: 18415 33rd Avenue West, Suite Q, Lynnwood, WA 98037, USA
Phone: (425) 640-5900
http://www.radiantmedspa.net/

248. Butte Healing Arts Center

Dr. Shahab Samieian, N.D.
Address: 1820 Harrison Ave., Butte, MT 59701, USA
Phone: (406) 723-6609
http://www.buttehealingarts.com/

249. Glenmore Healthcare

Address: A305, 1600 – 90th Avenue, SW Calgary, Alberta T2V 5A8, Canada
Phone: (403) 452-5699
http://www.glenmorehealthcare.com/

250. Diet Doc Hcg Diet Center

Address: 12925 El Camino Real, San Diego,CA 92130
Phone: (858) 356-5982
http://www.hcgtreatments.com

251. Improve Health Solutions

Dr. Robert Frankel, MD, DC, FACEP
Address: 200 Atlantic Avenue, Suite G, Manasquan
Phone: (866) 807-8686
www.ImproveHealthSolutions.com

252. Wiseman Family Practice

Dr. Richard J. Wiseman, MD, Dr. Jeremy D. Wiseman, MD
Address: 2500 S Lakeline Blvd #100, Cedar Park, TX 78613, USA
Phone: (512) 345-8970
http://www.wisemanfamilypractice.com/

253. The Youth Fountain, LLC / Center for Weight Control

Dr. Emil Shakov, MD, F.A.C.S.
Address: 501 Stillwells Corner A Freehold NJ 07728, USA
Phone: (866) 514-0025
http://www.njskinny.com/

254. Spectrum HRT

Dr. Vinson Di Santo, D.O.
Address: 51 SW 42nd Ave #104 Miami, FL 33134, USA
Phone: (866) 306-8139
http://www.spectrumhrt.com/

255. True Balance

Dr. Ron Brown, MD,
Sutter Davis Hospital
Address: 2000 Sutter Place, Davis, CA 95616, USA
Phone: (530) 756-6440
http://www.mytruebalance.ca/contact/

256. Integrative Family Wellness Center

Dr. Michele Nickels, N.D.
Address: 16535 W. Bluemound Rd, Suite 222, Brookfield, WI 53005, USA
Phone: (262) 754-4910
http://www.ifwcenter.com/

257. Women for Women / Holistic Gynaecology

Dr. Felecia L. Dawson, MD, FACOG , Obstetrics and Gynaecology
Address: One Baltimore Place NW, Suite 350, Atlanta, GA 30308, USA
Phone: (404) 733-6334
http://www.wmn4wmn.com/

258. Cedarburg Family Wellness Center

Dr. Janice Hoehner Alexander, RN, MD, FACOG, FAAFP, NCMP
Dr. Michele A. Nickels, NMD, LAc
Address: W62 N225 Washington Ave., Cedarburg, WI 53012, USA
Phone: (262) 376-1150
http://www.ndaccess.com/CBFWCenter/

259. RejuveCare Clinic

Shelley Otoupalik, APRN
Phone: (406) 240-7396
www.rejuvecareclinic.com

Kalispell Office:
Address: 77 3rd Ave. West North, Kalispell, MT 59901, USA

Arlee Office:
Address: 92524 Hwy. 93 North, Arlee, MT 59821, USA

260. New Leaf Centers, PLLC

Beverly Rutledge, WHCNP
Address: 5000 West 36th Street, Suite 205, St. Louis Park, MN 55416, USA
Phone: (952) 807-0415
http://www.newleafcenters.com/

261. LaVita Laser Medi Spa

Dr. Kimberly Ridl, MD
Address: 13545 Watertown Plank Road, Suite 3, Elm Grove, WI 53122, USA
Phone: (262) 784-8888
www.lavitalaser.com

262. WMC Health Group LLC

Dr. Aleida Hernandez, MD
Address: 1380 NE Miami Gardens Dr #210, Miami, FL 33179, USA
www.worldmedicalcare.com

263. MD Transformations

Dr. Rombola, MD
Address: 50 Cypress Point Parkway, Palm Coast, FL 32164, USA

264. Candace Koney, MD

Address: 8401 Balm Street, Weeki Wachee, FL 34655, USA
www.loseitrightwithDrCandace.com

265. Bodyology Center an HCG Assisted Diet Clinic

Dr. Don Willems
Address: 801 S. Federal Highway, Hollywood, FL 33020, USA

266. Weightloss MD Inc.

Dr. John Ouderkirk, MD
Address: 9925 Haynes Bridge Road, Suite 320, Alpharetta, GA 30022, USA
www.weightloss-md.com

267. Healthcare

Dr. Rebecca Appleton, MD
Address: 542 Williamson Road, Suite 5, Mooresville, NC 28117, USA
www.md-healthcare.com

268. Blue Ridge Acupuncture & Integrative Health

Claudia Burkhalter, NP
Address: 610 State Farm Road, Suite B, Boone, NC 28607, USA
www.booneholistichealth.com

269. Dr. Scott's Weight Loss and Wellness

Dr. Scott B. Shapiro, MD
Address: 6640-G Old Monroe Rd., Indian Trail, NC 28079, USA
www.doctorscotts.com

270. Indian Lake Medical Weight Loss & Wellness

T. Taylor Minchey, NP-C
Address: 133 Indian Lake Road, Suite 204, Hendersonville, TN 37075, USA

271. The Shot Clinic, LLC

Dr. Fred E. Wilson
Address: 10720 N. Rodney Parham Rd. Ste B5, Trellis Square Shopping Center, Little Rock, AR 72212, USA
www.theshotclinic.net

272. Total Care Physicians (Thinner You Weight Loss Clinic)

Dr. Kristy King
1 St. Vincent Circle, Suite 330, Little Rock, AR 72205, USA

273. The Centre For Vibrant Health And Wellness

Dr. Christine Salter
Address: 777 S. New Ballas Road, Suite 230 W, St. Louis, MO 63141, USA

274. New Leaf Wellness

Dr. David Ryker
Address: 3705 West Memorial Road (Chase Plaza), Suite 601, Oklahoma City, OK 73134, USA
newleafcenters.com

275. Selah Medi-Spa

Dr. Amir Rasheed, MD
Address: 21715 Kingsland Blvd, Suite 100, Katy, TX 77450, USA
www.selahmedispa.com

276. WinWinWellness, LLC

Dr. Winnie King
Address: 23114 Seven Meadows Parkway, Suite 400, Katy, TX 77494, USA
www.winwinwellnessmd.com

277. A New You-Health and Wellness

Dr. Amelita Basa
Address: 1535 West Loop South, Suite 340, Houston, TX 77027

278. Valley Wellness Center

Lisa Hunt
Address: 1300 Mable Ave., Suite C, Modesto, CA 95355, USA
www.drlisahunt.com

279. John F. Hsu

Address: 416 North Bedford Drive, Suite 100, Beverly Hills, CA 90210, USA
www.drjohnhsu.com

280. DeBruin Medical Center

Dr. Mark De Bruin
Address: 9352 Madison Avenue, Suite 1, Orangevale, CA 95662, USA
www.debruinmedicalcenter.com

281. Bella Medical Aesthetics

Dr. Alijah Ali
Address: 13470 Telegraph, Suite B, Whittier, CA 90605, USA

282. Bella Med Spa & HCG Weight Loss

Dr. Alijah Ali
Address: 20072 SW Birch, Suite 170, Newport Beach, CA 92660, USA

283. MD WeightLoss & Wellness

Dr. Rouzbeh Tehrani
Address: 16880 Bernardo Center Drive, Suite C, San Diego, CA 92128, USA

284. Silhouette Medspa and Weight Management

Dr. Soraya Esteva, MD FACOG
Address: 101 E. Vineyard Avenue, Suite 107, Livermore, CA 94550, USA
www.silmedspa.com

285. Weight Loss MD

Dr. Ellyn Levine, MD
Address: 5358 Jackson Drive #1, La Mesa, CA 91942, USA
www.myoptimalweightloss.com

286. Sierra Metabolic and Cellular Medicine

Laurence McClish
Address: 1885 South Arlington, #108, Reno, NV 89509, USA

287. Cameron Wellness Center

Todd Cameron
Address: 1945 South 1100 East, #202, Salt Lake City, UT 84106, USA
www.drtoddcameron.com

288. Studio 27 Inc.

Dr. Joseph William Wright
Address: 2631 W. Colorado Avenue, Colorado Springs, CO 80904, USA
www.studio27co.com

289. Jeffrey Passer

Address: 4239 Farnam Street, Suite 800, Omaha, NE 68131, USA
www.jeffreypassermd.com

290. New Leaf Wellness

Dr. Robert Sieman, D.O.
Address: 12129 University Ave., #1500, Clive, IA 50325, USA
www.newleafcenters.com

291. Medical Aestethetics & Wellness Center

Dr. Paul Bolger
Address: 5510 Utica Ridge Road, Suite 300, Davenport, IA 52807, USA
medawc.com

292. New Leaf Wellness

Dr. Robert Sieman, DO
Address: 1150 5th Street, #160, Coralville, IA 52241, USA
newleafcenters.com

293. Gail M. Gagnon, DO

1165 North Clark Street, Suite 608, Chicago, IL 60610, USA

294. Kentuckiana Medical Weight Loss

Dr. Rafael Cruz, MD
Address: 443 Spring Street, Suite 302, Jefferson, IN 47130, USA
www.awesomewtloss.com

295. Ohio Weight Loss

Dr. Donald Epstein
Address: 3619 Park East Drive, 214 South, Beachwood, OH 44122, USA

296. Medical Group Robinson, LLC

Irina Vinarski
Address: 5855 Steubenville Pike, McKees Rocks, PA 15136, USA

297. I Am Center Of Regenerative Medicine

Dr. Valerie Donaldson
Address: 17 Brilliant Avenue, Suite 202A, Aspinwall, PA 15215, USA

298. Vivify Medical

James B. Watson, DO
Address: 31 East Fornance Street, Norristown, PA 19401, USA
vivifymedical.com

299. Dr. Hernan Brizuela, MD

Address: 8019 N Frankford Ave, Philadelphia, PA 19136, USA

300. Body By Design Weight Loss Center

Audrey Rose, AG-ACNP
Address: 1418 Boston Providence Hwy, Norwood, MA 02062, USA
www.burnfatmass.com

301. Weightloss MD Inc.

Dr. John Ouderkirk, MD
Address: 9925 Haynes Bridge Road, Suite 320, Alpharetta, GA 30022, USA
www.weightloss-md.com

302. Lake Oconee Urgent and Specialty Care

Dr. Jameelah Gater
Family Medicine/ Integrative Medicine/Emergency Medicine
Address: 105 Harmony Crossing, Suite #3, Eatonton, GA 31024, USA
Phone: 706-484-0884
http://www.lakeoconeeurgentcare.com

Canada

303. Balance Medical Center

Dr. Rishi Verma,MD
Address: 1590 West 7th Ave., Vancouver, BC V6J 1S2, Canada
Phone: (604) 569-0488
http://www.balancemedical.ca/

UK

304. THE MAAS CLINIC

Dr. Laurens Maas B.Sc Ost. DI.
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Address: 1 Lockyear Ct, Inmans Lane, Sheet, Hampshire, GU32 2NA, UK
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Address: 95 Hibiscus Avenue, Sunset Crest, St. James, Barbados, West Indies
Phone: (246) 432-6227

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305. The Bodyclinic AG

Dr. Ulrich Ledermann, MD
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Phone: +41 (0) 44 387 99 20
http://thebodyclinic.ch/index.php?lang=en

306. LIPOCLINIC

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307. Dr. Cynthia Ann Wolfensberger

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Phone: +41 44 260 6862
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308. Holistic Nutrition Consulting & Coaching Weight

Melanie Strauss
Address: Lorsbacher road 62, 65719 Hofheim, Germany
Phone: 06192-9622460
http://www.ernaehrungsberatung-mtk.de/

309. Momentum Spa

Sandra Broekhuizen
Address: Daendelsstraat 64, 3531 GE Utrecht,
Phone: +31 (0)33 489 0510
http://www.bio-hcg-kuur.nl/

310. DR. MED. SUSANNA MEIER

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http://praxisdrmeier.de/HCG.php

Netherlands

311. Heijne Health Centre

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Phone: 020-345 18 38
http://www.hcg-praktijk.nl/index.html

Australia

312. Dr Cabot Clinics

Dr Sandra Cabot (McRae) MBBS, DRCOG
Phone: 02-4655-4666 / 02-4655-8855
http://www.drsandracabotclinics.com.au/

Camden Clinic, NSW:
1/33 Elizabeth St, Camden
2570, Canberra Clinic, ACT

Ainslie Chemmart Compounding Pharmacy:
17 Edgar St, Ainslie ACT 2602
Phone: 02 4655 4666

Adelaide Clinic, SA:
Better Health Pharmacy
Target Shopping Centre,
Tapleys Hill Road, Fulham Gardens
Phone 02 4655 4666

Pambula Clinic, South Coast of NSW:
2/23 Quondola St, Pambula
NSW 2549
Phone: 02 6494 3051

Camden, NSW:
Natasha Flynn, Herbalist
phone: 0412 117 552

Engadine and Enmore, NSW:
134-146 Enmore Rd, Enmore,
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New Zealand

313. Face Doctors Botany

Dr. Mark Morunga, MD & Adri Ferreira ND
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www.facedoctorsbotany.co.nz

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314. GNQ Medicina Antienvejecimiento

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