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Obesity

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Abstract

The hormonal understanding of obesity has dramatically changed our understanding of this disease. Although the behavioural aspects play a part in some patients, obesity is now thought of as a disease which is amenable to hormonal therapy. Bariatric surgery (metabolic surgery) is a very effective way to alter the hormonal aspects of obesity. Low calorie diets, when followed be a GLP-1 agonist, seem equally effective without the complications of surgery. The prospect for better hormonal surgery to combat obesity would make bariatric surgery obsolete.

Keywords: Obesity; Bariatric surgery; Metabolic surgery; Cushing's disease; Pituitary gland

Mini Review

Dickens in Pickwick Papers describes an obese boy who suffered from somnolency. 'Joe manages the open barouche, the picnic and much else. He keeps on falling asleep but can be woken by pinching'. Dickens is describing a classical syndrome of obesity. His description is a beautiful representation of Cushing's disease and the Pickwickian syndrome as it was later termed. "On the box sat a fat and red faced boy, in a state of somnolency Joe! -damn that boy .he's gone to sleep again… be good enough to pinch him .Sir -in the leg, if you so please; nothing else wakes him-thank you…the fat boy, who had effectively roused by the compression of a portion of his leg, between the finger and thumb of Mr Winkle". The description is so vivid and well-drawn that the syndrome, "The Pickwickian syndrome" is now a well-known medical syndrome and became so when it was discovered that sever sleepiness can be caused by poor muscular effort that inhibits proper breathing and the carbon dioxide in the blood rises causing the syndrome. This should not be confused with sleep apnoea which also causes sleepiness but due to periods of cessation of breathing during the night. The unfortunate Joe had a plethoric face and probably Cushing's disease. Cushing was a famous neurosurgeon in Boston (1869-1939) and he described a tumour of the pituitary gland in the brain causing the hormonal condition by stimulating the adrenal gland to produce excess cortisone. The adrenal gland sits on top of the kidneys and the pituitary gland sits in the centre of the brain. The pituitary controls various organs such as the reproductive organs, the thyroid and the adrenals. ACTH (adrenocorticotrophic hormone) was isolated by Collip who was instrumental in the story of the discovery of insulin! ACTH drives the excess cortisone production in the adrenal. Removal of the adrenal glands or the pituitary tumour will return the patient to normal good health and the patient will lose their obesity. So this is a well-defined disease that changes the apatite centre and causes obesity. There are other known causes of obesity such as leptin excess.

An attractive American girl came to live with a widow who lived beside us and served as a link between Irish neurosurgery and Harvey Cushing. The American stayed and married the local Vicar who became an Archbishop. Her Father, William Sharpe, was a pupil of Cushing and became a very eminent neurosurgeon in the USA. Indeed, he was one of the father's of paediatric neurosurgery. He wrote many neurosurgery text books [1]. Her son is a very successful neurosurgeon in Dublin. When he was my student we went up to Coleraine in Northern Ireland to a meeting where he was presenting a paper. We stopped in Belfast for a delightful meal with wine and conversation which became funnier with each glass of wine. At last we got into the car for another hour and a half's drive to the conference hotel. We started off, probably about 11pm so hurried on. Sometime later the engine developed a noise. I was persuaded to stop. We got out and opened the bonnet. It was dark so we saw little. I turned to the son of the Archbishop and suggested a prayer and the laying on of hands, but his response when he realised I was serious, was to suggest I drive more slowly. I was very disappointed.

We limped into the hotel very late. Next day after the meeting I was still hoping he had phoned his father to get advice about the laying on of hands etc but to my dismay he arranged a lift in another car back to Dublin and I was left to admit defeat somewhere near Newry, hire a car and go back a week later with a trailer to haul the poor car home and thence to the dump. I no longer believe in prayer but do have a better car! Now we have to describe mice, because the mice unravelled the leptin story of obesity and its treatment. Leptin (Leptos in Greek meaning thin) was discovered Some success but hunger made it unacceptable to many. by Douglas Coleman and Jeffrey Friedman. 'The elation of peering into the depths of nature and being the first to see something new is impossible to describe'. This discovery opened the doors to a major new understanding of obesity, fat cells (adipocytes) and apatite control. Their study demonstrated beyond doubt that body weight is tightly controlled by the endocrine system. The hormone leptin is secreted by the adipocyte. Leptin has a profound inhibitory effect on apatite Min-Dian Li [2]. Previously it was known that disturbance of the hypothalamus in the brain resulted in obesity.

The signalling system was unknown. Hippocrates observed that weight can be controlled by deciding to eat less and exercise more. This is, of course, still true and is now thought of as the behavioural concept of obesity but so many people cannot manage to change behaviour! the apatite centre is so strong. Is there an obesity gene.? In 1949 a colony of mice showing severe obesity was identified in The Jackson Laboratory. The gene was located on chromosome 6 and was designated obese (ob). Friedman and colleagues finally cloned the ob gene in 1994. They showed that the gene was expressed only in the adipose tissue. A second mouse strain with genetic obesity and diabetes syndrome was identified by Coleman in 1966, It was designated diabetes (db) by Hummel et al. [3]. The animals showed dramatic early onset obesity, diabetes, insulin resistance, hyperphagia (overeating), and physical inactivity. Coleman proposed that the db mice lacked a circulatory saiety factor that controls weight through the hypothalamus. Now we know so much more about the hypothalamus and how leptin regulates the apatite centre. There are a few people with leptin deficiencies who are very obese and respond to leptin therapy, but the majority of obese people have excess leptin and do not respond to leptin injections. The control mechanism seems to be broken or reset. Reset because most obese patients stabilise at a high weight and then stay at that weight. Surprisingly if a patient diets and loses weight very often when they stop the diet, the weight returns to their original high weight and stabilises again at that weight.

There are so many other hormones in the digestive tract that also control apatite making the story so complex and the research field so exciting. The idea that obesity is a behavioural abnormality has now been abandoned, at least to a large extent.

The stomach, as a repository of food is it seems a good place to start in the attack against obesity. A balloon is put into the stomach to give a feeling of fullness and therefore reduce apatite and lead to weight reduction. This has been tested. There was some success, but complications and hunger were the main obstacles to uptake. Gastric banding was another approach. The bands slipped and with persistence in eating the bands stretched. Another problem was that to alleviate the hunger sugar drinks could be taken with ease.

There are hormones in the stomach and, particularly in the duodenum, the first part of the intestine, which control saiety. What is amazing is that putting a plastic tube into the duodenum stops the food coming in contact with the lining of the duodenum and suddenly hunger is switched off and weight loss ensues. The tube is still under research. Another approach is an operation to bypass the duodenum. The Roux en Y operation, where the duodenum is by passed, is highly effective in causing weight reduction and reducing hunger. What is surprising is that a simpler operation, the sleeve gastrectomy, where a sleeve is made of the stomach, has almost the same effect as the Roux en Y but is simpler to perform with less complications and also has a remarkable metabolic effect. The benefits include reversal of diabetes in Type 2 Diabetes, reduction in hypertension (high blood pressure), reduction in disturbances in cholesterol metabolism, reduction in complications of diabetes, reduction in heart attacks and strokes.

In one study, Courcoulas AP et al [4], after 5 years Roux en Y surgery resulted in 23% weight loss and 56 % of patients still had remission of their diabetes Glucagon like peptide -1 (GLP-1) is a hormone that stimulates insulin secretion. It was discovered following on the observation that oral glucose stimulated more insulin secretion than when given intravenously. GIP (glucose dependent insulinotrophic polypeptide) was discovered as being a gut hormone that stimulated insulin secretion in the seventies by John Brown. GLP-1 was discovered to have insulin stimulating properties by Druker and colleagues in 1987. The hormone had significant insulin stimulating effects but only when the blood sugars were high. An ideal drug for a diabetic patient as hypoglycaemia (abnormally low blood sugars) would not be a hazard. The problem was that it was broken down in the body very rapidly, so it had to be given intravenously. The hormone had other effects, it supressed apatite and slowed gastric emptying leading to a feeling of fullness (Satiety) The Gila monster lizard now enters the story.

The lizard became very famous because his saliva contained a form of GLP-1 which was not rapidly degraded. Dr John Eng was a diabetologist working in the Va Hospital in the Bronx in New York. He was a pupil of Rosalyn Yallow who with Solomen Berson discovered how to measure insulin using radio isotopes. She won the Nobel Prize. Eng discovered that the lizard had a venom which was very toxic but also lowered glucose and was very similar to GLP-1. The drug exenatide was isolated and known as Byetta. the first GLP1 agonist on the market with twice a day injections. Other agonists followed made by changes in formula so that the drug was not rapidly broken down and therefore given by injection daily and

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then weekly as new methods of delivery were discovered. Once a week injection has been shown to reduce weight by almost 15% in a year's trial as compared to 2.4 % weight loss in the control group who were advised on exercise and diet. However, 4.5% discontinued treatment on the semaglutide as compared to 0.8% in the placebo group. The discontinuation mostly due to nausea and diarrhoea Wilding J P H et al. [5].

Oral semaglutide has been developed. In a 26-week trial reduction in body weight and glucose were similar to the injectable form Davies M et al. [6] and more recently an amalgamation of various trials demonstrated that the oral formulation was as effective as the injection both in terms of weight reduction and blood sugar reduction. (Pratley et al Diabetes Therapeutics) [7] One of the very worrying side effects of obesity is an increase in risk of cancers. Obesity is associated with increased chronic inflammation which changes the immune system response. T Cell function and numbers are reduced in various cancers. The T cell is one of the main cells involved in immunity and the immune system is central to surveillance and destruction of cancer cells at their earliest appearance. Cancer is a failure of this surveillance system. Rathmell JC & Ringle AE et al. [8,9] No paper on obesity would be complete without a section on diet. For so many years I tried to persuade patients that obesity was due to eating more food than they needed and therefore eating less food than they needed would result in weight loss. Among the many patients I failed to impress was a very overweigh friend/patient who was very successful in business, in his family life and in his good humour and sensitivity. When he invited me to dinner, he demonstrated his ability to consume vast quantities of delicious food his wife had made. Our conversations about food and weight loss continued over the years until one day he told me he had cracked the problem. He was going to see a nutritionist. By his tone he was accusing me of not having referred him sooner. The conversation was much like when he took himself off to a personal trainer. A few weeks later I met him and asked how he got on. 'Gerald' he said, she wanted me to eat less so I of course did not go back'.

The Steno study many years ago demonstrated, in a small group of diabetic patients, wonderful results in terms of hypertension, dyslipidaemia and blood sugar control by careful management. Weight reduction was not on their agenda. They explained that only 5% of patients could manage weight reduction by diet and 95% felt a failure if they did not succeed, so they decided to ignore weight. They obtained very impressive results in suppression of both macrovascular, such as myocardial infarction, and microvascular events, such as retinopathy. Their study demonstrated that taking care of patients in a meticulous manner really matters. I did try weight reduction by admission to hospital to start a patient on calorie restriction and was very upset some years later to listen to a radio talk show where it was related by one of my Ex-students that an obese lady said that she would throw herself out the window if I continued the low calorie diet. I responded by saying that she would not fit through the window!

My memory of the incident was that the chat was all banter but on replay on the radio I sounded unfeeling and that I did not recognise her anxiety and depressed state. I did not remember her name so many years later and therefore was unable to ask her if I had misunderstood the situation and that hers was a cry for help. I would be so upset if she thought I had been less than sympathetic and empathetic, but perhaps I was mistaken and that indeed she was crying for help. Depression is a major part of obesity and it is not possible to even try to lose weight if depressed. A zero calorie diet had a following some years ago but resulted in some suicides when done as an outpatient. Bariatric surgery is associated with suicide. A recent paper on bariatric surgery had seven suicide deaths reported Lagerros et al. [10] People with depression are not suitable candidates for surgery,

Prof Roy Taylor and his group were researching weight loss and improvement in diabetes, blood pressure, insulin resistance and fat in liver and pancreas. Their seminal work showed that weight reduction by starvation or rather semi-starvation resulted in the same metabolic changes as found in bariatric surgery. They then went on to try weight reduction by very low-calorie diet in a structured way. They had support from general practices in the North of England and Scotland. They had a nurse or dietician in each practice to instruct patients and support them in their endeavour to lose weight. The cost was minimal.

They wrote to about 1500 patients with type 2 diabetes about their trial, inviting them to take part. 800 did not bother to reply. 306 participants eventually took part their results were impressive and exciting. Lean et al. [11,12] 24% lost more than 15kg. 46% of patients had remission of their diabetes. Follow up of this group after 2 years showed that 36% still had remission of their diabetes. The maintenance of weight loss is even more difficult than losing weight. An interesting trial has just been published Lundgren et al. [13]. Obese patients, in a randomised trial, went on a low-calorie diet for 8 weeks (800calories). This was accompanied by an exercise programme (Minimum aerobic physical activity of 150, min a week of moderate intensity aerobic physical activity or 75 min of vigorous intensity a week). During the 8 weeks weight loss of 13kg occurred. Some of the patients then went on to Liraglutide (A GLP-1 agonist) daily injections. The patients on the Liraglutide lost another 3.4 kg but weight increased in the placebo group by 6.1 Kg. This very encouraging trial demonstrated a robust way to stop weight regain after a short weight loss programme with an 800 calorie diet.

Conclusion

In 2021 obesity is considered a disease and has many causes. The hormonal disturbances leading to obesity are still to be unravelled but enough is known to be hopeful that drugs will be developed to improve on the GLP-1 agonists which have the common side effect of nausea. Bariatric surgery, now called metabolic surgery, has a place to play but hopefully in the near future will become redundant.

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References

1. Rehder R, Cohen AR (2015) Neurosurg Focus 39: 1-12.
2. Min-Dian Li (2011) Leptin and beyond: an odyssey to the central control of body weight. Yale J Biol Med 84: 1-7.
3. K P Hummel, M M Dickie, D L Coleman (1966) Diabetes, a new mutation in the mouse. Science 153(3740): 1127-1128.
4. Courcoulas AP, James W Gallagher, Rebecca H Neiberg, Emily B Eagleton, James P DeLany, et al. (2020) Bariatric Surgery vs Lifestyle Intervention for Diabetes Treatment: 5-Year Outcomes From a Randomized Trial. Clin Endocrinol Metab 105(3): 866-876.
5. Wilding J P H (2021) New Eng J Med 384: 986-1002.
6. Davies M, Thomas R. Pieber, Marie-Louise Hartoft-Nielsen (2017) Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes A Randomized Clinical Trial. JAMA 318(15): 1460-1470.
7. Pratley RE, Matthew J Crowley, Mette Gislum, Christin L Hertz, Thomas B Jensen, et al. (2021) Oral Semaglutide Reduces HbA1c and Body Weight in Patients with Type 2 Diabetes Regardless of Background Glucose-Lowering Medication: PIONEER Subgroup Analyses. Diabetes therapeutics 12: 1099-1116.
8. Rathmell JC (2021) Obesity, Immunity, and Cancer. New Eng J Med 384(12): 1160-1162.
9. Ringle AE, Jefte M Drijvers, Gregory J Baker, Alessia Catozzi, Juan C García-Cañaveras (2020) Obesity Shapes Metabolism in the Tumor Microenvironment to Suppress Anti-Tumor Immunity. Cell 183(7): 1848-1866.
10. Ylva Trolle Lagerros, Lena Brandt, Jakob Hedberg, Magnus Sundbom, Robert Bodén (2017) Suicide, Self-harm, and Depression After Gastric Bypass Surgery: A Nationwide Cohort Study. Ann Surg 265(2): 235-246.
11. Michael Ej Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, et al. (2018) Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Randomized Controlled Trial 391: 541-551.
12. Michael E J Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, et al. (2019) Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes and Endocrinology 7(5): 344-355.
13. Julie R Lundgren, Charlotte Janus, Simon B K Jensen, Christian R Juhl, Lisa M Olsen, et al. (2021) Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined. N Engl J Med 384(18): 1719-1730.

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