Submission No. 13
(Inq into Obesity)

15/05/08

THE UNIVERSITY OF MELBOURNE

The University of Melbourne Obesity Consortium

Submission to

HOUSE OF REPRESENTATIVE STANDING COMMITTEE ON HEALTH AND AGEING

INQUIRY INTO OBESITY IN AUSTRALIA

Executive Summary:

Undertaking therapy for any metabolic disorder without knowledge of its cause is likely to lead to failure.

Scientific evidence points to several conclusions:

1. **The brain regulates body weight.**
2. **Body weight is defended.**
3. **Obesity can be caused by either genetic mutation but, more commonly, by sustained change in the expression of normal genes.**
4. **Obesity once established, tends to become a permanent state.**
5. **There are likely to be dietary factors that can trigger obesity in susceptible people.**
6. **Obesity cannot be successfully treated long term by a lifestyle change model alone.**
7. **More research is needed to understand the causes of obesity to provide better evidence-based strategies to prevent and treat it.**

We recommend the following:

1. **Recognize and accept obesity as a medical condition.**

2. **Increase funding resources for research into the biological mechanisms of obesity and its prevention, to an extent commensurate with the health care significance of the problem.**

3. **Focus public health interventions on evidence based programs to prevent obesity rather than attempting to achieve weight loss in those that are already obese.**

4. **Ensure that all public health interventions have sufficient resources to audit outcomes, as even the most apparently logical interventions need to be shown to work.**

5. **Provide targeted funding for the management of obesity using integrated programs run in public hospitals and in the primary care setting.**

6. **Evaluate the potential impact of pharmaceutical developments that are on the horizon and the potential for Australia to participate in these developments.**

BACKGROUND

The Impact of Obesity on Health: Obesity is recognised as a major problem in modern society. In Australia, data from the 2000 AusDiab Study show that the majority of adults (~61% of males and ~52% of females) are overweight and/or obese (Cameron AJ et al 2003). This epidemic is of grave concern because obesity is associated with multiple disorders including cardiovascular disease, diabetes, cancer, hypertension, dyslipidaemia, sleep apnoea and polycystic ovarian syndrome and social and psychological problems (Table 1). Clearly this disease has major economic implications for Australia that include hospitalisation and surgery costs due the condition and its complications, lost working time, as well as PBS costs associated with treatment of its complications such as type 2 diabetes. Because of these consequences of obesity, understanding ways of preventing and treating it needs to become a major goal of our health care system.

Failure to Stem the Epidemic: Weight loss is highly beneficial to health (Avenell A et al 2004) but long-term weight loss has proven to be almost impossible to maintain by the majority of people (Rossner S et al: NHMRC 2003). There is evidence that neither public health measures (Jeffery RW et al 1995), nor individual therapies (Rossner S) work in the long term (with the exception of bariatric surgery) (Albrecht Ret al 1999). **Why is it that despite being powerfully motivated to maintain a lower weight for social and medical reasons, the dieters almost always regain all the weight they have lost within one to two years?**

We consider that the biology of body weight regulation and the biological reasons for weight regain must be first understood if we are to make any progress in the prevention and successful treatment of this serious condition. Failure to take into account the recent and emerging scientific evidence on body weight regulation could result in the failure of programs designed to stem the obesity epidemic.

There is scientific evidence that weight is regulated and that once established, excess weight is defended. In addition, emerging evidence suggests that environmental factors can trigger genetic obesity in some susceptible individuals.

Central Control of Hunger and Satiety: Feelings of hunger and satiety are important determinants of energy intake and hence of body weight. While humans can modulate food intake by voluntary control in the short term, the almost invariable weight regain that occurs in obese individuals after weight loss suggests that in the long term, biologically-determined feelings of hunger and satiety may be more important than voluntary control of food intake. (PLEASE SEE APPENDIX 1 FOR DETAILS).

Hormonal regulation of body weight

A key regulator of hunger is the fat cell-derived hormone leptin. The role of leptin in the brain is to inhibit food intake and increase energy expenditure and it does so by altering the level of expression of hypothalamic neurotransmitters (Schwartz MW et al 1996). It reduces food intake by decreasing the levels of Neuropeptide Y (NPY) and increasing the levels of Melanocyte Stimulating Hormone (MSH) (Sahu A et al 2003) (APPENDIX 2). Leptin deficiency is a rare cause of obesity. In most obese people leptin levels are high, in proportion to fat mass. In obesity leptin action is impaired due to receptor insensitivity analogous to insulin insensitivity in type 2

diabetes (Considine RV et al 1996). For this reason leptin therapy does not cause weight loss in obese people.

Leptin Levels Following Weight Loss: One possible reason for weight regain following dieting is that leptin levels profoundly decrease with weight loss (Geldszuz R et al 1996; Keim NL et al 1998; Wisse BE et al 1999). It appears that fat cells (adipocytes) can sense the reduction in energy intake and reduce leptin production. A dieting individual then experiences effects of leptin deficiency, namely insatiable hunger and lethargy. This effect was clearly illustrated in two children born with the inability to produce leptin who became hyperphagic from birth and were never satiated (Montague CT et al 1997).

Role of Other Hormones in Body Weight Regulation: While of key importance, leptin is not the only circulating signal that can influence food intake. A number of different gut peptide hormones such as CCK and PYY are known to be anorexigenic, promoting early termination of a meal, while ghrelin and adiponectin are so far the only appetite-stimulating hormones described (APPENDIX 2).

The recent increase in the prevalence of overweight and obesity is clearly due to the continuous availability of high-energy foods, together with a major reduction in the obligatory need for physical activity. However not everyone becomes obese when placed in our obesogenic environment. Thus a genetic predisposition is required for the environment to produce obesity. Studies on monozygotic and dizygotic twin pairs either reared together or reared apart suggest that ~ 70% of the influence on body weight is genetic while ~ 30% is environmental (Stunkard AJ et al 1990, Bouchard C et al 1990). The dominance of genetic influences has been confirmed with adoption studies in which it was shown that adoptee's body size resembles their biological parents with very little resemblance to their adopted parents (Sorensen TI et al 1992). Some of the genes that could predispose to obesity have been identified (Clement K et al 2002) but there are likely to be many more as yet undiscovered.

Possible Epigenetic triggers to obesity.

Rare cases of monogenic obesity have been reported. These include defects in leptin and the leptin receptor genes and mutations in the melanocortin system especially the melanocortin 4 receptor (Dubern B et al 2007). However it is possible that in most individuals obesity may be caused by epigenetic change caused by the environment. [Epigenetic change results in the sustained silencing or over-expression of a gene with no change in its sequence]. The first evidence that obesity could be an epigenetic phenomenon came from the realization that starvation of the mother during the first trimester led to obesity and hypertension in the adult offspring (Ravelli GP et al 1976). This finding has been reproduced by inducing starvation early in pregnancy in animals and thus mechanisms are beginning to be discovered (Chadio SE., et al 2007). There is now also rat data showing that a high-energy-rich palatable diet early in life can trigger permanent obesity that is then vigorously defended even when the animals have only low fat food available (Levin BE et al 2000). These studies demonstrate that early prevention must be our primary target.

This scientific evidence points to several conclusions:

1. **The brain regulates body weight.**
2. **Body weight is defended.**
3. **Obesity can be caused by either genetic mutation but, more commonly, by sustained change in the expression of normal genes.**
4. **Obesity once established, tends to become a permanent state.**
5. **There are likely to be dietary factors that can trigger obesity in susceptible people.**
6. **Obesity cannot be successfully treated long term by a lifestyle change model alone.**
7. **More research is needed to understand the causes of obesity to provide better evidence-based strategies to prevent and treat it.**

We recommend the following:

1. **RECOGNIZE AND ACCEPT OBESITY AS A MEDICAL CONDITION.**

2. **INCREASE FUNDING RESOURCES FOR RESEARCH INTO THE BIOLOGICAL MECHANISMS OF OBESITY AND ITS PREVENTION TO AN EXTENT COMMENSURATE WITH THE HEALTH CARE SIGNIFICANCE OF THE PROBLEM.**

3. **FOCUS PUBLIC HEALTH INTERVENTIONS ON EVIDENCE BASED PROGRAMS TO PREVENT OBESITY RATHER THAN ATTEMPTING TO ACHIEVE WEIGHT LOSS IN THOSE THAT ARE ALREADY OBESE.**

4. **ENSURE THAT ALL PUBLIC HEALTH INTERVENTIONS HAVE SUFFICIENT RESOURCES TO AUDIT OUTCOMES, AS EVEN THE MOST APPARENTLY LOGICAL INTERVENTIONS NEED TO BE SHOWN TO WORK.**

5. **PROVIDE TARGETED FUNDING FOR THE MANAGEMENT OF OBESITY USING INTEGRATED PROGRAMS RUN IN PUBLIC HOSPITALS AND IN THE PRIMARY CARE SETTING.**

6. **EVALUATE THE POTENTIAL IMPACT OF PHARMACEUTICAL DEVELOPMENTS THAT ARE ON THE HORIZON AND THE POTENTIAL FOR AUSTRALIA TO PARTICIPATE IN THESE DEVELOPMENTS.**

Table 1 – Complications of obesity

System	Health Problem
Cardiovascular	Hypertension, dyslipidaemia, increased risk of coronary heart disease and stroke (Goran MI et al 2003)
Respiratory	Obstructive sleep apnoea, asthma (Resta et al 2001)
Endocrine	Insulin resistance, type 2 diabetes, polycystic ovary syndrome (Moran LJ et al 2002), Male infertility and lower testosterone levels (Pritchard J et al 1998).
Orthopaedic	Back pain, osteoarthritis (Manek NJ et al 2003)
Dermatological	Acanthosis nigricans, skin tags (Garcia Hidalgo L 2002)
Gastrointestinal	Non-Alcoholic Steato Hepatitis (NASH) (Shen L et al 2003) , reflux oesophagitis (El-Serag HB et al 2002), gall stones (Nakeeb A et al 2002.
Psycho-social	Social isolation and discrimination, decreased self-esteem (Sarlio-Lahteenkorva S et al 1999), binge-eating disorder and bulimia (Branson R et al 2003)
Other	Increased risk of breast and other cancers (Calle EE et al 2003), increased intracranial pressure (Sugerman HJ et al 1995) and proteinuria (Bonnet, F et al 2001)

APPENDICES

APPENDIX 1 Body Weight Regulation

There is a complex central mechanism emerging with powerful influence on hunger and satiety. Circulating peripheral signals that are responsive to the nutritional state, modulate this central regulator. It is known from animal studies that in the hypothalamus, multiple neurotransmitters alter feeding behaviour. These include (among others) the appetite stimulators, neuropeptide Y (NPY), agouti-related peptide (AGRP) and melanin concentrating hormone (MCH), and the appetite suppressants melanocyte stimulating hormone (MSH) and cocaine and amphetamine regulated transcript (CART) (Inui A 1999). In turn, the levels of these neurotransmitters are controlled by peripheral signals that are sensitive to nutritional intake. The known circulating modulators of hunger and satiety include nutrients such as glucose, ketone bodies and Free Fatty Acids, and hormones such as ghrelin, leptin, adiponectin, insulin, Cholecystokinin, Glucagon-like peptide-1 and PYY, with others possibly yet to be described (Zhang Y 1994; Nakazato M 2001; Murphy KG et al 2004; Burton-Freeman B et al 2002; Romon M et al 1999).

APPENDIX 2 – Circulating Signals Controlling Hunger

Leptin was first described in 1994 as the product of the obese (*ob*) gene and is a protein secreted primarily by adipocytes (Zhang Y 1994). Leptin circulates throughout the body and is transported into the brain by an active saturable mechanism (Wong ML et al 2004). Genetic leptin deficiency in rodents (Caro JR et al 1996) and humans (Montague CT et al 1997) results in hyperphagia and marked obesity.

Ghrelin is a 28 amino acid, acylated peptide secreted by oxyntic cells in the stomach fundus. Circulating ghrelin concentrations increase before eating (pre-prandially) and decrease after eating (post-prandially). Ghrelin increases food intake through the stimulation of ghrelin receptors on hypothalamic NPY-expressing neurons and agouti-related protein-expressing neurons (Cummings DE et al 2003).

After a meal, CCK is released into the bloodstream from endocrine I cells of the duodenum and the jejunum, leading to inhibition of food intake (for review see Geary N et al 2004). Exogenous administration of CCK shortens the duration of a meal, and CCK receptor antagonism increases food intake, reverses the inhibitory effects of exogenous CCK, and has been shown to reverse the inhibitory effects of intestinal fat infusion on food intake and feeding behaviour (Moran TH et al 1998).

PYY is released primarily from the distal GI tract, ie, the colon, and acts as an agonist (stimulator) with the Y2 receptor in the hypothalamus. In two recent studies, intravenous infusion of exogenous PYY(3-36) (the biologically active form of PYY) was shown to suppress 24-h food intake in humans (Batterham RL et al 2002, 2003). Subjective ratings of hunger and satiety were in line with the lower food intake (Batterham RL et al 2002, 2003). In both obese and lean subjects, food intake during a buffet lunch was decreased by ~30% (Batterham RL et al 2003). Other satiety factors include GLP-1, glucose-dependent insulinotropic polypeptide (GIP), amylin, PP, bombesin, somatostatin, and enterostatin.

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Australian Centre for Science, Innovation and Society

Austin Health Weight Control Clinic

Bariatric Surgery - Austin and Western Hospitals

Centre for Adolescent Health

Centre for Community Child Health

Department of Economics

Department of Medicine,
St. Vincent's Hospital

Department of Physiology

Eating Disorders Foundation of Victoria

Faculty of Land and Food Resources

Institute for Breathing and Sleep - Austin Health

Key Centre for Women's Health/Public Health

Metabolic Disorders Centre, Austin Health

Metabolic Disorders Clinic, Royal Melbourne Hospital

National Centre of Excellence for Functional Foods

Obesity Clinic, Royal Children's Hospital

Obesity Clinic, Western Hospital

Pregnancy Research Centre,
Royal Women's Hospital

School of Behavioural Science

School of Nursing

St. Vincent's Institute of Medical Research

Victoria Centre of Excellence for Eating Disorders

Walter & Eliza Hall Institute of Medical Research

Contact details:

Professor Joseph Proietto
Dept of Medicine
Repatriation Hospital
300 Waterdale Rd
Heidelberg 3081

Telephone 9496 2250
Fascimile 9497 4554
Email: j.proietto@unimelb.edu.au

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National Centre of Excellence for Functional Foods

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Obesity Clinic, Western Hospital

Pregnancy Research Centre, Royal Women's Hospital

Royal Women's Hospital

School of Behavioural Science

School of Nursing

St. Vincent's Institute

Victoria Centre of Excellence for Eating Disorders

Walter & Eliza Hall Institute of Medical Research

ontact details:
rof J. Proietto
ept of Medicine
epatriation Hospitlal
)0 Waterdale Rd Heidelberg
elephone 9496 2250
ascimile 9497 4554
mail: j.proietto@unimelb.edu.au

THE UNIVERSITY OF MELBOURNE

12 May 2008

Mr James Catchpole
Committee Secretary
Inquiry into Obesity in Australia
PO Box 6021
Parliament House
Canberra ACT

Dear Mr Catchpole,

Please find included a submission from the University of Melbourne Obesity Consortium to the Inquiry into Obesity in Australia.

Do not hesitate to contact me for any clarification.

Regards,

Joseph Proietto
Professor of Medicine

Department of Medicine
Repatriation Hospital
Heidelberg 3081

TEL: (03) 9496 2250
FAX: (03) 9497 4554
Email: j.proietto@uimelb.edu.au