

# Scientists battle obesity overload

It sounds amusing: government officials are patrolling the streets of Philadelphia with weighing scales in an effort to persuade locals to lose weight after their city was voted fattest in America by a men's fitness magazine. But fat isn't fun and obesity is on the increase the world over.

A new report by the UK's National Audit Office (NAO), NAO's "Tackling Obesity in England" is one of many to call attention to the alarming increase in obesity rates worldwide. According to the report, most people in England are either fat or obese. It reveals that 58% of adults are overweight or obese, having a body mass index (BMI) greater than 25 (BMI is calculated by dividing the weight of a person in kilograms by the square of the height in meters). And 20% are obese, having a BMI over 30.

Figures in other developed countries look similar. According to the WorldWatch Institute in Washington DC, 61% of adults in the US and 54% in Russia are overweight. The number of people in developing countries who are overweight is also rising.

Perhaps even more worrisome are the rates at which obesity figures are increasing. According to NAO the number of people who are obese in England has tripled over the last 20 years and, if the trend continues, one in four will be obese by 2010. The Centers for Disease Control and Prevention (CDC) has reported a 57% increase in obesity in the US since 1991. As many as 300,000 Americans now die each year from obesity-related illnesses—a figure approaching the 400,000 who die prematurely from cigarette smoking.

The accepted wisdom seems to be that the increasing rates of obesity are due to inactivity and fat-rich diets and to address the problem, the CDC has launched a major study to examine the connection between urban sprawl and obesity among Americans. CDC estimates that 75% of Americans don't achieve the recommended standard for

physical activity—30 minutes of moderately intense physical activity five days a week.

Current medical options for dealing with the epidemic are limited. Drugs result in a relatively small weight loss which patients may regain. "We are at the stage now with obesity drugs that we were in the 50s with hypertension," says Frank Greenway of the clinical department of Pennington Biomedical Research Center.

The encouraging news is that following the discovery of leptin around

orlistat (Xenical) made by Hoffmann-LaRoche, which inhibits the absorption of dietary fat. Last month, the UK body that advises the government on which medications should be available through the National Health Service, the National Institute for Clinical Excellence, recommended that orlistat be used for the management of obesity for certain adults.

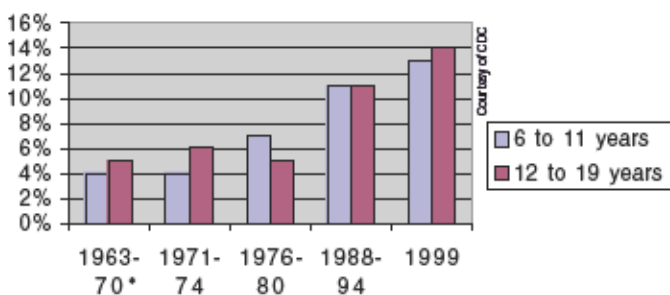
In addition to pharmacological targets which, like leptin, are involved in pathways controlling appetite and satiety, new approaches target the metabolism of fat cells. One area of active commercial research is beta-3 agonists, which stimulate the beta-3 adrenoreceptors found primarily on brown fat cells in rodents. Stimulation of these receptors increases thermogenesis in brown fat cells, causing the fat stores in the white fat cells to be broken down.

A derivative of the ciliary neurotrophic factor (CNTF), a hormone that regulates body weight by leptin-like mechanisms, is due to enter late stage clinical testing. In Phase II trials, patients who took the optimal dose averaged around 10 pounds more weight loss than patients on placebo over a 12-week period. However, the reported weight loss was no greater than that obtained with orlistat; furthermore, axokine has to be given by injection.

In February of this year Metabolic Pharmaceuticals, an Australian company, began clinical trials in Britain of a synthetic form of a small region of the human growth hormone. The drug called AOD9604 (advanced obesity drug 9604) speeds up the use of stored fat cells, increasing the energy expenditure.

And a completely new approach may come from a recent study that mice given a cleaved product of a natural hormone produced by adipocytes, lost weight even when they ingested as much high-fat, high-calorie rich food as they could eat because the compound stimulates muscle oxidation of free fatty acids (*Nature Med*, 7, 296; 2001).

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Prevalence of overweight in children and adolescents in the US. \*Data for 1963-65 are for children 6-11 years of age; data for 1966-70 are for adolescents 12-17 years of age.

six years ago, obesity research has entered a new phase. When leptin, a hormone secreted by fat cells, is injected into obese, leptin-deficient mice it curbs appetite and boosts metabolic rates. Within a month the mice lose half their excess weight. "Leptin made people start to view obesity as a chronic disease with regulatory disturbances in hormonal systems," says Greenway. However, in October 1999, Amgen, the company that bought commercial rights to leptin, reported that it performed poorly in its first clinical trial, and it is now thought that it might work to "maintain" rather than induce weight loss in humans.

But as the physiology and molecular biology of obesity become better understood, pharmaceutical companies have invested in fat research. "There are now agents on the horizon that will be useful for treating the disease," says Greenway.

Weight loss medications that have been approved so far by the Food and Drug Administration are appetite suppressants and a lipase inhibitor called