Chapter 8

Other adverse effects of weight control and physical activity

Health effects

Human studies

Weight control and weight loss

Data on effects of weight control in humans have been considered mainly in Chapter 6, in which risk modification due to BMI status and weight change was reviewed for all-cause mortality, other chronic diseases and surrogate markers. Keeping BMI within the normal range and weight stability over lifetime seem to constitute the optimal approach.

Adverse effects need to be considered in relation to various aspects of weight control, such as weight stability, small constant losses over time and heavy losses due to energy restriction. Not all of these aspects are relevant to each of the following sections. The induction of weight cycling deserves particular attention in connection with unsuccessful weight reduction. Long-term weight cycling has often been found to be associated with increased risk (Chapter 6). However, neither the reasons for increased risk in connection with weight cycling in the observational setting nor the underlying biological mechanisms are well understood.

Osteoporosis and fractures

Many studies have examined relationships of BMI or other measures of fatness in adult life to bone mineral density (Holbrook & Barrett-Connor, 1993; Mussolino *et al.*, 1998; Kroke *et al.*, 2000) and subsequent risk of fractures (Meyer *et al.*, 1995; Ensrud *et al.*, 1997a; Joakimsen *et al.*, 1998; Owusu *et al.*, 1998; Kato *et al.*, 2000; Margolis *et al.*, 2000). Increased BMI has usually been found to be associated with improved bone mineral density and decreased risk of fracture. Of particular interest are studies that looked at the effect of weight change in adult life on risk of osteoporosis and fractures. Most of these found that weight gain is associated with a decreased risk of hip fracture (Grisso *et al.*, 1994; Cummings *et al.*, 1995; Meyer *et al.*, 1995; Langlois *et al.*, 1996; Ensrud *et al.*, 1997b; French *et al.*, 1997; Joakimsen *et al.*, 1998; Langlois *et al.*, 1998; Meyer *et al.*, 1998) and that weight loss increases risk for hip fracture. However, further evaluation is needed of whether the increased fracture risk affects all bone sites similarly, whether mild weight losses and intentional weight reduction are associated with a substantial risk for fracture and whether exercise-induced weight reduction has effects different from those achieved by dietary weight reduction. For example, Ensrud *et al.* (1997b) found in a cohort study of 6754 non-black women that weight loss of more than 10% in the preceding six years induced higher risk of frailty fractures such as those of the proximal femur, pelvis and proximal humerus among thin women and those with unintentional weight loss. Intentional loss and mild losses were not linked with higher fracture risk in this study. However, intervention studies for weight reduction with middle-aged and older women have also showed a decrease in bone mineral density (Compston *et al.*, 1992; Jensen *et al.*, 1994; Chao *et al.*, 2000). In connection with weight reduction, the beneficial effect of exercise as a means to reduce weight also needs to be taken into account.

Weight cycling is also linked to increased risk for hip fracture (Meyer *et al.*, 1998: RR = 2.1 (95% CI 1.2–3.5) in Norwegian women and 2.7 (95% CI 1.2–5.9) in men; French *et al.*, 1997: 1.6 (95% CI 0.96–2.8) in Iowa women). This observation from prospective cohort studies is supported by results of a cross-sectional survey of 169 premenopausal women in Finland (Fogelholm *et al.*, 1997), which indicated that lower bone mineral density after weight cycling significantly affects the lumbar spine and distal radius (data adjusted for weight and age at menarche). Other bones such as the femoral neck and trochanter were not significantly affected in this study. These observations are consistent with those from another cross-sectional study on 1043 older white men and women, with particular emphasis on site-specific effects (Holbrook & Barrett-Connor, 1993). There is currently no plausible biological explanation for the lowering effect of weight cycling on weight-adjusted bone mineral density. This association contrasts with the fact that weight cycling is often linked with subsequent increase in weight, a well established protective factor.

Eating disorders

Epidemiological studies of anorexia nervosa, bulimia nervosa, binge-eating disorder and other eating disorders in different populations are hampered by

inadequate reporting and case definition. Anorexia nervosa seems to affect 0.5% of young women and bulimia nervosa 2% in western societies (Hsu, 1996). The male-to-female ratio of anorexia nervosa is one to ten. Although anorexia and bulimia nervosa are still uncommon disorders, they are among the most common psychiatric disorders affecting young women in developed countries. In these societies, a preoccupation with thinness and sociocultural pressures to diet have often been regarded as playing an etiological role in the pathogenesis of anorexia nervosa (Hsu, 1997). However, even in developing countries where obesity is socially acceptable, the prevalence of anorexia nervosa has been reported to be within the range seen in western countries (Hoek *et al.*, 1998). Severe dieting in adolescents is a predictor of anorexia nervosa and should be discouraged (Patton *et al.*, 1999). There are no indications that recommendations to maintain BMI within the range of 18.5 and 25 kg/m^2 and moderate and gradual weight gain in adults who are already overweight induce the onset of eating disorders.

Sarcopenia

In the context of weight control and particular weight-reduction programmes addressed to the general population, the effect of age on body composition needs to be considered. The ratio of body fat mass to lean body mass gradually changes with age and fat is redistributed towards the abdominal cavity (Seidell & Visscher, 2000). At older ages, weight loss often particularly involves lean body mass, so that the percentage of fat increases (Poehlmann *et al.*, 1995). While the reason for such changes is poorly understood, nutritional inadequacy and sarcopenia (loss of muscle) are clearly a problem in the oldest age groups (Baumgartner, 2000). Older adults with inadequate energy intake are more likely to develop acute illness and chronic disease (Mowe *et al.*, 1994; Naber *et al.*, 1997). There is also evidence that unintentional weight loss in elderly subjects is often caused by acute or chronic diseases (Fischer & Johnson, 1990). It is not known whether such changes of body composition with age may be responsible for the finding in some prospective observational studies, often comprising older age groups, that weight loss was associated with increased all-cause mortality and disease risk.

Gallstones

Obesity is a risk factor for gallstones in women (less so in men) and this risk increases with weight loss and weight cycling. It is unclear what mechanisms in gallstone formation are responsible for the increased risk associated with weight changes; the fat and total energy contents of a weight-loss diet seem to have an important role. In the Nurses' Health Study I (Syngal *et al.*, 1999) including 47 153 women, the relative risk for cholecystectomy was 1.2 (95% CI 0.96–1.5) among light weight cyclers (5–9 lb [2.3–4.1 kg] weight loss and gain within a 16-year period), 1.3 (95% CI 1.0–1.6) among moderate cyclers (10–19 lb [4.5–8.6 kg] weight gain and loss) and 1.7 (95% CI 1.3–2.1) among severe cyclers (≥20 lb [9.1 kg] weight loss and gain). Weight gainers had an increased risk for cholecystectomy (RR = 1.1; 95% CI 0.92–1.4), as did weight losers (RR = 1.6; 95% CI 1.2–2.1), compared with weight maintainers (who comprised only 11% of the population). Several clinical studies of obese individuals who achieved rapid weight loss with very low-energy diets have shown that up to one fourth of weight losers develop new gallstones after beginning a supervised very low-energy diet (Everhart, 1993). A third of these were symptomatic. In about half of the asymptomatic individuals, gallstones spontaneously disappeared within 1–2 years. The main risk factors for gallstone development were high BMI and high rate of weight loss (caused by a very low-energy diet). One study compared two different very low-energy diets (with 3.0 g and 12.2 g of fat/day) and reported that new (asymptomatic) gallstones developed in 55% of subjects following the lower-fat diet, but in none with the higher-fat diet (Festi *et al.*, 1998). Relatively high fat content of very low-energy diets may prevent gallstone formation by maintaining adequate gallbladder emptying, which counterbalances possible lithogenic mechanisms during weight loss.

Nutritional deficiencies

Dietary changes to lose weight can be associated with nutrient deficiencies. Elderly persons are particularly vulnerable to this (Mowe *et al.*, 1994; Naber *et al.*, 1997). Older versions of very low-energy diets have resulted in extreme malnutrition with some deaths reported. Modern very low-energy diets include sufficient amounts of nutrients during weight reduction under supervised conditions.

Drug treatment of obesity

Some drugs can help to promote weight loss and prevent weight regain in obese patients The most frequent adverse effects of orlistat are gastrointestinal (for example, oily stools, faecal urgency and faecal spotting) (Sjöström *et al.*, 1998). These side-effects usually appear early during treatment and are mild and transient. Consumption of a diet rich in fat markedly increases the risk of these side-effects. Mean plasma levels of vitamins A, D, E and K and β-carotene are reduced, but remain within the reference range during prolonged orlistat treatment. Sibutramine may increase heart rate and blood pressure. Other common adverse effects are dry mouth, nausea and insomnia (Lean, 1997; James *et al.*, 2000). Fenfluramine and dexfenfluramine have been reported to be associated with heart valve abnormalities, and these drugs were withdrawn from the market in 1997. One *post hoc* study

suggests that prior use of dexfenfluramine or phentermine/fenfluramine may be associated with higher prevalence of aortic regurgitation compared with untreated matched controls (Gardin *et al.*, 2000).

Weight loss and cigarette smoking

The weight loss that is often associated with cigarette smoking is accompanied by increased risk for all of the many tobacco-related diseases including cardiovascular disease and cancer, although this cannot be regarded as an adverse effect of weight loss per se.

Conclusion

Weight loss can have adverse effects on bone that may be counteracted by increased physical activity. Other adverse effects of weight loss include eating disorders, loss of muscle mass (if physical activity is not sufficient), nutritional deficiencies and gallstones. For the few individuals for whom drug therapy is indicated, there are adverse effects that range from mild to severe or even life-threatening.

Physical activity

Ordinary physical activities, for example walking for personal transportation or climbing stairs, are seldom associated with adverse effects (at least in persons of 'healthy', 'normal' or 'acceptable' weight) (Figure 32). Adverse effects are mainly incurred during participation in structured exercise to improve fitness or through sports participation.

Cardiovascular risks

Although the absolute level of risk is small (for example, one sudden death per 1.5 million episodes of vigorous exercise in the US Physicians' Health Study (Albert *et al.*, 2000)), the risk of heart attack or sudden cardiac death is increased during exercise. Specifically, the risk during vigorous exercise (≥ 6 METs) (or up to one hour after it) is between two times greater (Willich *et al.*, 1993) and six times greater (Mittleman *et al.*, 1993) than during less strenuous activities or no activity. In these studies, both with around 1200 subjects, of whom some 70% were men, the excess risk was, however, mostly limited to persons who did not exercise regularly. Among those who exercised at least four or five times per week, there was little or no excess risk during exercise, compared with all other times. As reviewed in Chapter 6, however, the protective effect of regular exercise is very strong and appears to outweigh the transient increase during vigorous exercise.

Exercise, even strenuous exercise, is not harmful to the healthy cardiovascular system. Studies of young persons (< 30 years) dying during exercise have invariably found structural, usually congenital, cardiovascular disease (Maron *et al.*, 1996). Among older persons, severe atherosclerotic coronary artery disease is found in the majority of cases of exercise-related sudden death (Waller & Roberts, 1980). The increases in heart rate and blood pressure during exercise may give rise to haemodynamic shear stresses that disrupt a vulnerable plaque, setting in motion a chain of events (including platelet activation) culminating in acute infarction. An important factor may be the intensity of exercise, because moderate levels do not increase platelet adhesion and coagulability (Wang *et al.*, 1994; Weiss *et al.*, 1998). To minimize the risks of acute exercise, sedentary people should progress gradually from light to moderate exercise and avoid sudden, unaccustomed heavy exertion (US Department of Health and Human Services, 1996).

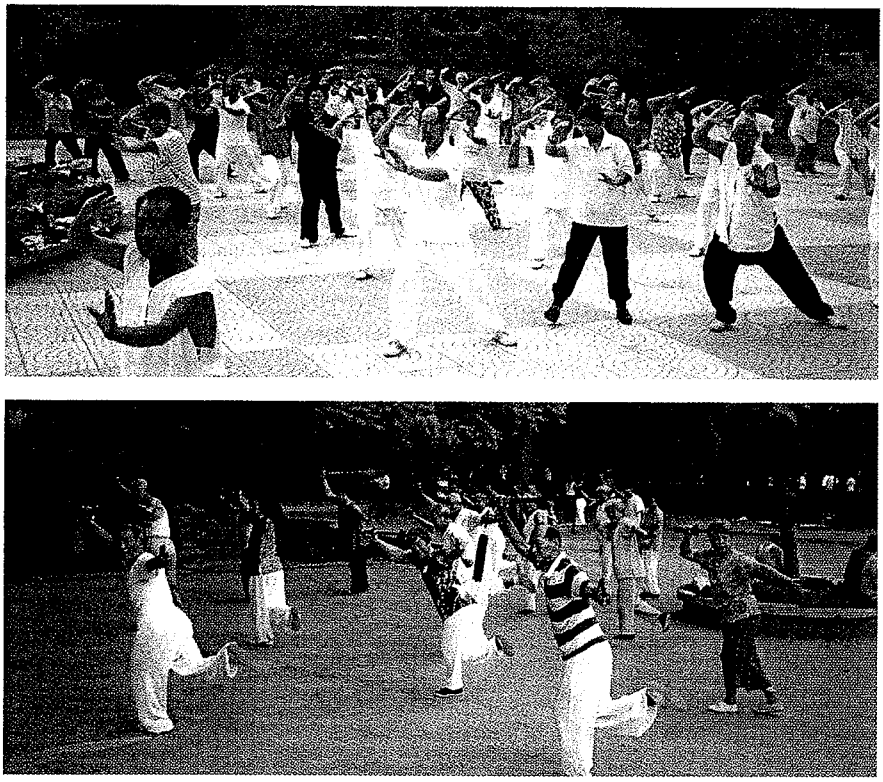

Figure 32 Older adults can benefit from regular physical activity, which needs not to be strenuous to achieve health benefits

Injuries

Injuries associated with exercise fall into two categories, overuse and acute traumatic. Incidence rates for acute sport and exercise-related injuries are probably rather low in the general population. For example, about 5% of adults who participated in a telephone survey reported an injury in the previous month (Uitenbroek, 1996). Rates are higher, of course, among sportsmen and women. For example, about half of 1391 surveyed participants in sports (Australian football, field hockey, basketball, netball) reported sustaining one or more injuries over a five-month winter season (Stevenson *et al.*, 2000). At Groningen University Hospital in the Netherlands, sports injuries comprised about one fifth of all injuries treated over a seven-year period, making these the second highest cause of accidental injuries after home and leisure accidents (Dekker *et al.*, 2000).

The majority of sports injuries are of low severity (Stevenson *et al.*, 2000), but a minority (9% in the Groningen study (Dekker *et al.*, 2000)) require hospitalization. Injuries are mainly musculoskeletal, the majority to the lower limb (e.g., ligament sprains, meniscus tear) (Baquie & Brukner, 1997), but cervical spinal injuries are occasionally incurred in sports such as rugby, trampolining, gymnastics and horse-riding (Silver, 1993). Two out of three sports injuries occur during team sports (Ytterstad, 1996), with soccer/football giving rise to a high number of injuries, even when corrected for exposure (Ytterstad, 1996; Stevenson *et al.*, 2000).

Injuries to a lower limb are common in runners. Based on a review of 10 surveys, between 24% and 65% of runners sustained one or more injuries during a year (Hoeberigs, 1992). Fifty to 75% of injuries appear to be due to overuse, i.e., constant repetition of the same movement (van Mechelen, 1992). Weekly distance run is the most important determinant of these injuries, for women as well as for men (Hoeberigs, 1992). Other predisposing factors are probably high intensity, a rapid increase in training distance or intensity (impact forces increase with running speed), running on hard surfaces and in poor shoes. In beginners, the frequency of injuries increases when the duration of running sessions exceeds 30 minutes (Colbert *et al.*, 2000b). Impact forces are much lower during walking, so the risk of injury is lower for walking than running (Colbert *et al.*, 2000b). Even among older persons, walking for exercise carries a low risk for injury; among 21 men and women aged 70–79 years walking briskly for three sessions per week, increasing to 45 min per session, only one injury was sustained over 13 weeks (4.8%) (Pollock *et al.*, 1991).

Bicycling (including on-road and off-road cycling) is associated with significant morbidity and mortality. Head injuries account for three quarters of deaths related to bicycling (Rivara *et al.*, 1997a). Injuries during swimming – another common aerobic activity – are few, but deaths do occur from drowning in swimming pools, mainly among young children (Rivara *et al.*, 1997b).

There is considerable inter-individual variation in predisposition to exercise-related illnesses such as hypothermia or hyperthermia and these may be exacerbated by environmental conditions, according to the fitness level of the individual. For example, slow runners and swimmers may experience net heat loss in conditions where those who can achieve a faster pace maintain thermal balance. Increased ventilation of the lungs during exercise increases the risk of exposure to environmental pollutants and can trigger environmentally-induced asthma (Utell & Looney, 1995). Exercise in a cold environment, particularly running, can also provoke asthma in susceptible individuals (Giesbrecht, 1995).

Osteoarthritis

The risk of articular surface damage or degeneration associated with repetitive stresses during exercise depends largely on the rate of loading and the number of loading cycles. The prevalence of osteoarthritis is increased among athletes in a number of sports disciplines, mainly those involving high loading (most ball games and competitive running) (Buckwalter & Lane, 1997). Performing more than three to four hours per day of heavy physical activity significantly increases the risk of developing osteoarthritis of the knee and running at least 20 miles per week increases the risk of osteoarthritis of the hip or knee (Vuori, 2001). Moderate levels of physical activity have not been found to be associated with risk.

Prior sports-related injuries may predispose to osteoarthritis. One study of 1321 former medical students with 36-year follow-up found that the risks of developing osteoarthritis of the knee or hip were > 5-fold and 3.5-fold higher in those reporting injury on the corresponding joint at entry or during follow-up, compared with those not reporting injury (Gelber *et al.*, 2000).

Athletic amenorrhoea and low bone mineral density

Menstrual dysfunction can be induced by strenuous aerobic exercise, particularly in individuals with low levels of body fatness who undergo a rather sudden increase in training load. There is no evidence to suggest adverse effects on fertility in the long term.

However, young women with athletic amenorrhoea have been reported to have lower vertebral bone mineral density than their normally-menstruating peers (Cann *et al.*, 1984). It was subsequently reported that this effect is not limited to the vertebra, but is evident at many skeletal sites (Rencken *et al.*, 1996). Cross-sectional studies suggest an inverse relationship between lumbar

spine mineral density and the degree of menstrual disorder (Drinkwater *et al.*, 1990). As 64% of 97 young female athletes studied experienced one or more episodes of amenorrhoea lasting for more than six months (Drinkwater *et al.*, 1990), many individuals may be at increased risk for running-related stress fractures and subsequent osteoporosis.

It is not known whether vertebral bone loss is reversible. Vertebral bone mineral density has been observed to remain low in formerly oligo/amenorrhoeic athletes despite several years of normal menses or use of oral contraceptives (Keen & Drinkwater, 1997). Amenorrhoeic athletes exhibit higher bone mineral density than anorexics, however (Marcus *et al.*, 1985), presumably because the osteogenic effect of the exercise offsets the adverse effects of low estrogen levels.

Upper respiratory tract infection

Unusually high incidence rates for upper respiratory tract infections have been reported among individuals participating in large volumes of vigorous exercise (Nieman, 1994), as reviewed in Chapter 4.

Experimental studies

Weight control

In general, overnutrition resulting in obesity and undernutrition resulting in malnutrition are associated with increased morbidity and mortality. However, some investigators have coined the phrase 'undernutrition without malnutrition' to describe a degree of energy restriction associated with health benefits, including a reduction in the risk for cancer.

While such an eating pattern has many potential health benefits, there are some possible drawbacks, such as the potential toxicity of glucocorticoids that are elevated with underfeeding and with administered micronutrient intake in dietary restriction protocols that reduce intake of all constituents.

Several studies have suggested that elevated glucocorticoid hormone levels in underfed rodents may contribute to the effect of underfeeding on cancer prevention (see Chapter 5). Elevated levels of primary glucocorticoid hormones in mice (Yaktine *et al.*, 1998), rats (Morimoto *et al.*, 1977) and humans (Chiappelli *et al.*, 1991; Kennedy *et al.*, 1991) have been reported and many studies have suggested that glucocorticoid hormones may have cancer-preventive potential. However, they also have well known toxic effects, including reduced bone mineral content (Weiler *et al.*, 1995) and blockage of cell cycle (Rhee *et al.*, 1995). The blockage of cell cycle may be beneficial in relation to the prevention of cancer, but cell cycle blockage of normal cells could be detrimental.

Other effects of dietary restriction with uncertain health impacts include smaller heart, (Oscai & Holloszy, 1970), bradycardia, decreased rate of cardiac contraction and relaxation (Hilderman *et al.*, 1996) and impaired cold thermoregulation (Banu *et al.*, 1999). Dietary restriction can also lead to reduced cortical bone mass and mineralization (Banu *et al.*, 1999).

Reducing food intake has the potential to reduce consumption of health-promoting dietary constituents. Evidence that diet restriction by reducing all dietary components may not optimize cancer prevention, reported by Birt *et al.* (1991), is presented in Chapter 5.

Physical activity

Studies in humans have indicated various potential adverse effects of excessive exercise training programmes, as reviewed above, but none of these effects have been studied in animal models under conditions of exercise that have been shown to prevent the development of cancer in an experimental tumour model system. [The Working Group noted that the available data from experimental studies do not permit generalizable conclusions about conditions of exercise (duration, intensity, and frequency) that are clearly protective against cancer in most model systems used to study the genesis of cancer and its prevention.]

Reproductive and developmental effects

Human studies

Excessive leanness (as indicated by a very low BMI, i.e., below 18.5 kg/m^2) and large weight loss have been associated with increased likelihood of anovulatory menstrual cycles or a shortened luteal phase. Women with very low or high BMI have been found to have reduced conception rates under controlled circumstances (Zaadstra *et al.*, 1993). These disruptions are due to hypothalamic dysfunction. Frisch (1987) proposed that a minimum ratio of fat to lean mass is normally necessary for menarche, fitness and fertility. Weight gain usually restores fertility in underweight women.

Weight

Severe weight loss can result in functional hypogonadotropic hypogonadism, which plays a major part in the amenorrhoea that is characteristic of anorexia nervosa. The plasma levels of follicle-stimulating hormone, luteinizing hormone (LH), estradiol and urinary gonadotropins are low, as is the plasma level of leptin. Adult women can develop pubertal and even pre-pubertal patterns of LH secretion (Marshall & Kelch, 1979). In addition, the gonadal response to gonadotropin-releasing hormone (GnRH) is a function of body-weight loss (Beumont *et al.*, 1976). In men with anorexia nervosa, LH and testosterone levels are low and can be in the pre-pubertal range. Fasting reduces LH pulse amplitude (Veldhuis *et al.*, 1993) and increases response to exogenous GnRH. This may indicate a decrease in this pituitary hormone (Rojdmark, 1987).

Physical activity

Amenorrhoea in marathon runners and delayed menarche in ballet dancers, figure skaters and gymnasts have been reported (Constantini & Warren, 1994). When the activity is interrupted (e.g., by an injury), menarche may occur even before body composition changes significantly (Warren, 1990).

Heavy training before puberty can lead to blunted growth velocity and stunted leg length growth, suggesting that it can decrease ultimate height (Lindholm *et al.*, 1994). Although in the general population scoliosis is associated with earlier menarche, in a study of ballet dancers, there were both delayed puberty and scoliosis (Goldberg *et al.*, 1993).

Experimental studies

Weight

The effect of dietary restriction in blocking the ability of female mice to breed has long been known (Nelson *et al.*, 1982). The major effect is on GnRH, with attendant decreases in circulating levels of LH and estrogen. When body weight in mice was lowered by 10–30% compared with controls, there was a decrease in numbers of pups per male and of implants per female in a dose-related manner (Chapin *et al.*, 1993). Female Sprague-Dawley rats had a 20% decrease in the number of corpora lutea at 30% dietary restriction and had lower ovarian weight. The percentage of motile sperm in males was decreased by dietary restriction of approximately 10%.

Physical activity (exercise)

Given the level of interest in the effects of exercise on reproductive end-points in humans, surprisingly little work has been done in animal models.

Moderate exercise reduced ovarian steroid levels and disrupted vaginal cycles in rats (Axelson, 1987). Also in rats, plasma testosterone levels were reduced by exhausting acute exercise, with little change in LH. In chronic treadmill training, there were inconsistent effects on testosterone levels, but the capacity of interstitial cell suspensions *in vitro* to produce testosterone after stimulation by gonadotropin increased by 20% (Harkonen *et al.*, 1990).

Genetic effects

There have been no studies on induction of heritable damage by dietary restriction or weight loss. A few studies have examined the reduction of DNA damage resulting from dietary restriction. However, if there is an increase in formation of oxidative radicals, it may be presumed that this will lead to increased potential to attack the genome (Marnett, 2000).

Human studies

Treadmill exercise to exhaustion increased measurable DNA damage in human lymphocytes (Hartmann *et al.*, 1994).

Experimental studies

Weight

A few studies have indicated that either dietary or energy restriction decreases the amount of oxidative damage products in organs such as the liver or heart of rodents (see the discussion of mechanisms in Chapter 5). This effect appears to be reversible with feeding *ad libitum* (Forster *et al.*, 2000). Additionally, long-term dietary restriction appears to lead to lower levels of oxidative products in muscle in old monkeys (Zainal *et al.*, 2000).

However, little is known on the total amount of damage in diet-restricted animals. Taylor *et al.* (1995) found significantly increased levels of oxidative damage (8-hydroxydeoxyguanosine and 8-hydroxyguanine) in the urine of diet-restricted mice compared with mice fed *ad libitum*. There is evidence that enzymes which protect against free radical damage, such as superoxide dismutase, glutathione peroxidase, catalase and haem oxygenase are induced and the activities of these enzymes appear to increase (Feuers *et al.*, 1995; Taylor *et al.*, 1995; and Chapter 5). Inducible DNA repair is also elevated in rodents (see Chapter 5). Some endogenous factors, such as increased oxidative damage, are possibly inducing these enzymes.

Studies of spontaneous mutation rates in transgenic mice (presumably driven by oxidative processes) showed little change due to dietary restriction (Stuart *et al.*, 2000). However mutation rate is a result of both genetic damage and the fixation of that damage through replication and 40% dietary restriction (with supplementation) significantly inhibits cellular replication (Lu *et al.*, 1993). Diet-restricted animals increase their level of activity by more than 50% around feeding time (Duffy *et al.*, 1989, 1990a, b). This increased activity (see below) may be important in the generation of increased oxidative damage.

Physical activity

Exercise results in increased oxygen utilization and it is not unexpected that it also leads to increased oxygen-related damage, especially in the mitochondria (Radak *et al.*, 2000).

With forced training, elevated mitochondrial reactive species (i.e., oxidative damage) and increased lipid peroxidation were found in rat muscle (Bejma & Ji, 1999), consistent with the elevated glutathione levels found earlier (Kim *et al.*, 1996). Increased carbonyl derivatives were found in rat mitochondria, compared with cytosol, after swimming (Radak *et al.*, 2000).

Since muscle is considered non-replicative, a focus on muscle provides little information on heritable effects. However, with increased metabolism and oxidation throughout the body, the effects of oxygen-related damage on tissues that replicate remain an open question.