Centralization of Body Fat

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INTRODUCTION

Centralization of body fat stores has proven to be an index of several serious diseases and their precursor states, indicated by risk factors. Historically this is an observation which originates from anthropologists in the early twentieth century. Kretschmer (1) noticed the difference in disease associations with different body build, mainly from the aspect of his own specialty, which was psychiatry. He observed that the pychnic type frequently suffered from gout, atherosclerotic disease and stroke, and he saw early signs of glucose intolerance as well as abnormal pharmacological reactions of the autonomic nervous system in comparison with, particularly, the leptosomic body build type. Both these types were also different from the aspect of food intake, where the pychnic type increased more readily in body weight. Kretschmer made anthropometric measurements from which the waist-to-hip circumference ratio (WHR) can be calculated. Such calculations show that the pychnic type had a WHR which is well within the risk zone for disease, as recently suggested by the WHO (2). The pychnic type was also more prone to develop depressive symptoms while the leptosomic type often had a schizoid personality.

Jean Vague in Marseille (3) is another pioneer who already 50 years ago saw the differences between gynoid and android obesity and the risk for complications in the latter. Vague was focusing mainly on adipose tissue distribution but also made observations on other diseases than obesity.

All these sharp-sighted clinical observations have been confirmed and extended in modern science with more refined methods, as will be briefly reviewed in this chapter.

Centralization of body fat stores can be measured in a number of ways. The gold standard methods for obtaining absolute masses of various body fat stores are the imaging techniques. These methods are, however, complicated and expensive to use in epidemiological work, where simpler surrogate measurements have to be employed. Such methods include skinfolds, which, however, do not measure intra-abdominal fat masses. Various circumference measurements such as waist circumference or the WHR provide an estimate of internal fat masses. The WHR has probably been somewhat better anchored in prospective studies of disease than the waist circumference, although the latter is slightly easier to measure. The abdominal sagittal diameter seems to provide the most accurate estimation of the important visceral, intra-abdominal fat masses (4).

Utilizing such measurements, it has now become increasingly clear that body fat centralization is a powerful index of prevailing previously established risk factors for disease such as insulin resistance, dyslipidaemia and hypertension, is found with high prevalence in already established disease, and is a powerful independent risk factor for disease in prospective studies. The abnormalities associated with body fat centralization span a wide range of somatic diseases in metabolism and energy intake, such as obesity, cardiovascular and cerebrovascular diseases. Furthermore, respiratory, haematological
and psychiatric diseases as well as cancer show associations with centralization of body fat. This is also the case for personality characteristics, alcohol abuse, socioeconomic and psychosocial handicaps. It is thus apparent that centralization of body fat embraces a large cluster of human life conditions, health and disease.

Only from this wide array of conditions does it seem unlikely that central fat distribution could be a causative factor. It seems more likely that centralization of body fat is an index of perturbations in profound, central regulation of several vital systems in the body. Such regulations usually have their origin in the hypothalamic–limbic areas of the brain, which regulate vital functions in endocrine, metabolic and haemodynamic systems via neuroendocrine and autonomic signals to the periphery. This is orchestrated by the central nervous system into appropriate reactions to maintain homeostasis or allostasis. When various factors challenging these counterbalancing mechanisms become too severe, homeostasis or allostasis can no longer be maintained, and disease and disease symptoms will appear in the long run.

In this chapter certain new developments within this area will be overviewed. The input into this research emanated originally from the obesity field, where Jean Vague’s pioneering work has attracted too little attention. Obesity will, however, only be briefly touched upon here, primarily with emphasis on novel findings. Instead an outlook into other diseases and conditions will be offered. Some, but not all, of these fields are related to obesity, suggesting that body fat centralization has a much more fundamental significance for human disease than only in the obesity field.

By approaching various problems in biomedical research with epidemiological techniques on a population basis, it is possible to obtain a wide view on several diseases and their development, provided that a sufficient number of well-selected variables are examined. With this method many conditions can be analysed to search for potential pathogenetic pathways and generate hypotheses for further research. Selecting out only one phylogenetic characteristic for examination in case control studies limits the focus on the particular selected variable, for example obesity. In our research we have therefore frequently based observations on epidemiological studies to obtain a wider outlook on health problems.

It must now be considered established that central, abdominal obesity is the malignant form of obesity. This condition seems to be associated with various perturbations of the function of the HPA axis. About one-quarter of a male population, selected at random, and all 52 years of age, have signs of an elevated diurnal cortisol secretion, associated with abdominally localized excess of body fat, measured with the sagittal, abdominal diameter, as well as signs of metabolic derangements, characteristic of the metabolic syndrome (5). It seems possible to explain the central fat accumulation as well as the metabolic derangements via effects of cortisol (6,7). The elevated cortisol secretion is seen most clearly when the endogenous activity of the HPA axis is most pronounced, that is before noon (Figure 16.1). During this period reports of perceived stress were also most prevalent (unpublished). This observation is in agreement with results of controlled animal experiments, where chronic stress facilitates this particularly active phase of HPA axis activity (8), and indicates that the men examined were exposed to a stressful environment not only during the day in their ordinary life when their cortisol secretion was measured, but also during a period preceding the examination.

In about 10% of the population the HPA axis displays a depressed activity with less diurnal variation, a ‘burn-out’ condition (see Figure 16.1). The cortisol secretion is about 75% of controls, and the secretion is again most perturbed during the high activity phase of the HPA axis. This is also in agreement with controlled animal experiments of chronic stress (9), and might be the end result of a development in stages from repeated stress challenges, as in the group of men mentioned above, to eventual burn-out.

In spite of not being elevated, cortisol secretion in this condition is associated with central obesity and its well-known associated risk factors, including hypertension and elevated pulse rate. Interestingly, in this group secretions of testosterone and growth hormone are depressed (5), probably a consequence of the challenges on their central regulation by the HPA axis perturbations (10).

Such a burned-out HPA axis has been observed
previously in conditions of severe stress such as in war veterans, holocaust victims, chronic pain, and ‘vital exhaustion’ (9), but it can apparently also be found in the general population. It appears that psychosocial and socioeconomic handicaps as well as alcohol abuse might be involved, but there are most likely other factors involved, yet to be identified, some of which probably have a genetic background (11,12). This condition should have a high priority for further research because of its serious endocrine abnormalities with associated malignant risk factor pattern.

In this condition the pathogenetic factors at play are unlikely to include cortisol secretion, because total cortisol secretion is low. It seems possible that the diminished secretions of sex steroid and growth hormones are involved. Deficiencies in these hormones would be expected to be followed by similar consequences as elevated cortisol, because these hormones counteract and balance the effects of cortisol in both the regulation of visceral fat mass and insulin resistance (6,7).

Another putative pathogenetic pathway might be via elevation of central sympathetic nervous activity, as indicated by the elevations of blood pressure and heart rate in this condition (5). Animal experiments clearly show that when the activity of the HPA axis is insufficient or burned out the sympathetic nervous system is activated in compensation to maintain homeostatic conditions (13). This would also be expected to be followed by increased mobilization of free fatty acids with hepatic and muscular insulin resistance (14,15) as well as dyslipidaemia and perhaps diminished hepatic clearance of insulin as consequences (16). Free fatty acids are clearly elevated in abdominal obesity (16).

It should be observed at this point that although it seems possible to understand the pathogenetic pathways to centralization of body fat with associated risk factors via elevated cortisol secretion (5), as seen in the group of men with elevated stress-related cortisol secretion, the evidence suggests that the kinetics of diurnal cortisol secretion are at least of equal importance. In the men with elevated stress-related cortisol secretion the increase in diurnal cortisol is limited, about 20% in comparison with controls. The nocturnal cortisol secretion was not measured, and might have been elevated also to add to the total increase in cortisol secretion. It is noteworthy, however, that this group of men had significantly lower cortisol secretion in the earliest measurement after waking up (Figure 16.1). One might speculate that this is a sign of progression towards the low secretion of the group with the burned-out axis.

The burned-out condition is by itself the most powerful evidence suggesting that the perturbed regulation of the HPA axis rather than elevated cortisol secretion might be the crux of the matter in attempts to understand how cortisol secretion is associated with metabolic abnormalities.

The men in the group examined who had a normal HPA axis function with little or no exposure to perceived stress (see Figure 16.1) also had normal secretions of testosterone and growth hormone as well as normal blood pressures and heart rate. This is an apparent picture of normally regulated neuroendocrine and autonomic functions in several axes. Here cortisol secretion was negatively correlated to various risk factors. This means that, for example, absence of body fat centralization was associated with high cortisol, particularly when measured during the physiological stimulation of cortisol by food intake (17). This is an unexpected finding; one would actually have expected the opposite correlation. We have interpreted this to mean that a normally functioning neuroendocrine system as indicated by a high plasticity of the HPA axis, and normally functioning gonadal and growth hormone secretions, is associated with signs of bodily health, a ‘mens sana in corpore sano’ (18).
Taken together these observations indicate that neuroendocrine regulations are of fundamental importance for somatic health. Regulation of HPA axis activity probably occupies a central role, where cortisol secretion might be considered both as an index of neuroendocrine health or abnormality, with cortisol itself as a trigger of somatic perturbations in some, but not all conditions. These considerations, based on observations, probably explain the complicated results in previous attempts to measure cortisol secretion in obesity. We have recently finalized a similar population study in women as that reported in men (5,11,17). The situation is different in several important aspects. Hyperandrogenic ejectivity (HA) is a prominent, important abnormality in women related to centralization of body fat. The highest quintile of free testosterone is strongly associated with abdominal obesity and conventional risk factors for cardiovascular disease, stroke and type 2 diabetes mellitus. We have previously shown that HA is a powerful, independent risk factor for these diseases, as well as certain cancers (19), and is therefore probably a major predisposing condition for disease in women. The mechanism of action is likely to be induction of insulin resistance in muscles, which then triggers metabolic disease (20).

The nature of this HA has been examined in the new population study. It seems highly likely that its origin is at least partly adrenal, because steroids secreted mainly by the adrenals such as dihydroepiandrosterone sulphate and cortisol are elevated in parallel. Furthermore, concentrations of free testosterone show associations with features of saliva cortisol concentrations, which have been shown in men to be particularly associated with risk factors, namely low morning cortisol and food-induced cortisol secretion (21). Associations between HA and depressive traits have been found, similar to the associations of cortisol secretion in this condition, previously disclosed in men (22). Further potential background factors are currently being examined.

There are, however, probably also other factors involved. First, the aromatase gene shows polymorphisms in microsatellite areas, associated with elevated androgens and decreased 17β oestradiol, which are the expected consequences of a defect function of the aromatase enzyme, which converts testosterone to 17β oestradiol. A poorly functioning aromatase would therefore be followed by elevated testosterone. This may add to HA.

Furthermore, the androgen receptor gene shows a diminished number of trinucleotide repeats (CAG, glutamine) in the first exon, which might be associated with increased androgen sensitivity.

The polymorphisms found are thus localized to microsatellites with tetra- or trinucleotide repeats in the genes examined. Such abnormalities have introduced a new dimension in the research of genetic abnormalities in polygenic diseases. Monogenic diseases with mutations in exons usually have an all or nothing phylogenetic consequence. The interesting feature with microsatellite polymorphisms is that they often express themselves as quantitative abnormalities of more or less importance (23). For example, we see in the example mentioned above a variation in the expression of HA depending on the number of or lack of nucleotide repeats.

In summary, the currently performed analyses in women suggest that not only adrenal cortisol but also adrenal androgens are associated with central obesity with its risk factors and diseases. Adrenal androgens might well be also elevated in men with central obesity, but would be expected to be followed by minor or no peripheral consequences, because they would add only a minor fraction to testosterone produced in the gonads. The insulin resistance following HA in women is probably the trigger for at least the metabolically related diseases. Additional factors seem to be involved as disease-generating triggers in women with HA, including androgen metabolism and sensitivity.

**OBESITY. CORTISOL METABOLISM**

Cortisol is subjected to metabolic transformations in the periphery, which are of importance for the impact of cortisol on peripheral target tissues. This area is reviewed in the chapter by Walker and Seckl (Chapter 18), where detailed references can be found, and is only discussed here in relation to the central perturbations of HPA axis activity, reviewed in the preceding section.

There are two main systems regulating cortisol metabolism. One is the 5α reductases which transfer cortisol to tetrahydrocortisone, which is an essentially inactive metabolite excreted in the urine. The other system is the 11β-hydroxysteroid dehyd-
rogenases (HSD), which consist of the HSD1, converting cortisone to cortisol, and the HSD2, converting cortisol to cortisone. In humans cortisone is a much less powerful glucocorticoid than cortisol.

There is evidence for an increased activity in obesity of 5α-reductase and HSD2, which inactivates cortisol. This would be expected to result in less active occupancy of the central glucocorticoid receptors (GR) which regulate cortisol secretion by a negative feedback mechanism (9), and an elevated cortisol secretion would be the expected outcome. In a recent study cortisol measurements have been adjusted for the body mass index (BMI), in an attempt to examine cortisol secretion without the influence of adipose tissue inactivation. This resulted in a visualization of elevated cortisol secretion in obesity (24). Consequently peripheral inactivation of cortisol might explain the elevated cortisol secretion in obesity.

It is, however, apparently not possible to explain why cortisol secretion is particularly elevated in centrally localized obesity, since an elevated cortisol secretion along this mechanism would be expected to be dependent on total mass of adipose tissue irrespective of its localization. Furthermore, if cortisol is rapidly inactivated in the periphery, this would not be expected to result in peripheral consequences of hypercortisolism, as seen in central obesity.

Local elevations of the HSD1, which has been reported to occur in visceral fat depots, might have local effects but it seems difficult to imagine that a secretion of cortisol from visceral fat would have systemic effects, due to the small mass of this tissue. Cortisol from such elevated secretion would presumably also be inactivated peripherally. It is also difficult to understand the relationships, if any, between mechanisms, working on the regulatory centres of the HPA axis, described in the preceding section, and peripheral metabolism of cortisol. It might be considered that the peripheral enzymes involved in cortisol metabolism are secondarily modified by obesity-related factors such as cortisol itself, insulin and other hormone secretions which are abnormal.

These peripheral conversions of cortisol add to the complexity of this field, but are clearly important for the understanding of the problems involved. Parallel studies of both the central and peripheral mechanisms, regulating the net concentration of circulating glucocorticoids and their interaction with peripheral target tissues, would be needed to understand potential interactions and the resulting outcome.

**OBESITY. PERINATAL FACTORS**

Perinatal factors are likely to be involved in the problem of centralization of body fat stores. This idea originates from studies by Barker (25), who found that children born small for gestational age frequently develop centralization of body fat and associated metabolic syndrome, ‘the small baby syndrome’. Although originally based on statistical observations from populations where intrauterine undernutrition was suspected, this hypothesis has gained considerable support from the results of recent studies.

Subjects with the small baby syndrome and abdominal preponderance of body fat stores have recently been reported to have elevated cortisol secretion (26). This might correspond to the group of men we have studied with elevated stress-related cortisol and centralization of body fat (8,17).

There are experimental studies which indicate potential mechanisms. The HPA axis can be sensitized by intrauterine exposure to immune stress or cytokine exposure or to lipopolysaccharides (27,28), and the handling of newborns has also been shown to be of importance (29). Recent studies have provided further interesting information, probably explaining the effects of prenatal exposure to lipopolysaccharides. These bacterial endotoxins stimulate the secretion of cytokines. Prenatal exposure to interleukin-6, tumour necrosis factor α or dexamethasone, a synthetic glucocorticoid which passes the placental barrier, is followed by permanent sensitization of the HPA axis, leptin-resistant obesity and insulin resistance (30). It seems likely that leptin-resistant obesity is caused by the increased corticosterone secretion from the HPA axis, because a similar condition develops after elevated corticosterone exposure in adult rats (31). This is probably applicable also to humans because it is well known from clinical experience that patients treated with glucocorticoids overeat and become obese. Furthermore, in recent experiments we have been able to show that women taking 25 mg prednisolone daily for a week increase their food intake in spite of elevated leptin concentrations (32).
These interesting developments suggest that centralization of body fat and also the development of obesity might be affected not only by cortisol in adulthood, but also by prenatal factors. Infections during pregnancy might speculatively be involved in such developments.

It is thus apparent that perinatal factors are critical for the development of obesity and centralization of body fat stores with its metabolic associates in adult life. Evidence suggests that this might at least partly be mediated via programming of the regulation of the HPA axis. It will be of interest in the future to find out to what extent 'the small baby syndrome' is involved in the overall prevalence of centralization of body fat and the metabolic syndrome in adult life.

**HYPERTENSION**

There is now considerable evidence indicating that primary hypertension is frequently associated with centralization of body fat mass (33) and the metabolic syndrome (34,35). From the statistical correspondence between elevated blood pressure and insulin arose the suggestion that elevated blood pressure might be caused by hyperinsulinaemia or its precursor, insulin resistance. This contention is supported by experimental work showing that the central sympathetic nervous system is activated by insulin (36).

New evidence is, however, not in agreement with this chain of events (37). In statistical calculations with blood pressure as the independent variable, HPA axis perturbations take over all statistical power, and blood pressure is no longer dependent on insulin. This suggests that some factor related to HPA axis activity is a major determinant of blood pressure. This is probably the activity of the sympathetic nervous system, which shows signs of parallel activation when the HPA axis is not functioning normally (38). This is a well-described phenomenon with interactions between the central regulation of the HPA axis and the sympathetic nervous system at several levels. In fact, it is difficult to activate one of these axes without interfering with the other, due to this tight coupling of their regulatory centres (10).

It therefore seems likely that the relationship between insulin levels and blood pressure is due to a parallel activation of the HPA axis and the sympathetic nervous system at central levels. It seems likely that the sympathetic nervous system is responsible for blood pressure elevation and the HPA axis for insulin resistance with hyperinsulinaemia following as described above. The HPA axis is presumably also responsible for the centralization of body fat as also discussed above.

In the case of primary hypertension; centralization of body fat stores seems to be a sign of central neuroendocrine disturbances where elevated blood pressure is probably due to a parallel activation of the sympathetic nervous system, also occurring at a central level. It may well be, however, that insulin amplifies this autonomic activation. For further discussion of this problem, see review in Björntorp *et al.* (35).

**MENTAL DEPRESSION**

Much to our initial surprise we found in population studies that subjects with traits of depression and anxiety often had centralized fat depots (39). This has also been found in our most recent studies in both men and women (22, and data in preparation). These traits are depressed moods, frequent use of antidepressant drugs and anxiolytics as well as various sleeping difficulties (39–41). This has now also been confirmed from other laboratories (42). As is almost invariably the case, this centralization of body fat is followed by the metabolic syndrome, as well as frequently, by hypertension.

These findings are of interest from at least two aspects. Full-blown melancholic depression is a condition with severe perturbations of several neuroendocrine axes, including activation of the HPA axis with poor suppression of cortisol secretion by dexamethasone, elevated activity of the sympathetic nervous system and inhibition of the hypothalamic-gonadal axis and growth hormone secretion (43). These are exactly the same neuroendocrine perturbations that occur in people with centralization of body fat (see above). Consequently, we believe that depressive traits might be a significant pathogenetic factor which via the neuroendocrine perturbations will lead to body fat centralization and the metabolic syndrome.

Another aspect of interest is that depression is clearly followed by an increased risk for somatic
disease and premature mortality, also when suicide is taken into account. Prospective studies have demonstrated that the risk for cardiovascular disease and type 2 diabetes mellitus is clearly increased in subjects with frequent episodes of depression, and the risk power is comparable to that of conventional somatic metabolic risk factors such as dyslipidaemia, insulin resistance and hypertension (44,45). Unfortunately, such risk factors have not been extensively followed in these prospective studies of depression. A very recent study has, however, clearly shown that visceral fat masses are elevated in patients with repeated depressive periods (46).

Taken together this evidence strongly suggests that depressive traits or clinically manifest melancholic depression are associated already at early stages with centralization of body fat masses, and metabolic and circulatory risk factors for prevalent, serious, somatic disease. This probably provides an explanation for the increased somatic morbidity and mortality in depression. The pathogenetic mechanisms are most likely provided by the central multiple neuroendocrine and autonomic perturbations, that occur in depression as well as in subjects who present with centralization of body fat. This field has recently been summarized, and the reader is referred to this review for detailed references and further discussion (47).

This has interesting therapeutic implications. Mental depression is improved or cured by modern pharmacological treatment. This is also followed by a correction of the neuroendocrine and autonomic abnormalities. If the proposed chain of pathogenetic events presented above is correct, then metabolic and haemodynamic abnormalities, following the neuroendocrine and autonomic aberrations, would also be expected to be improved. Unfortunately, this does not seem to have been systematically followed in psychiatric literature.

We have therefore recently finalized a pilot study with this problem in focus. Men with elevated WHR were treated with an antidepressant inhibiting serotonin reuptake, but without effects on energy balance. This was followed by an apparent normalization of the signs of a perturbed activity of the HPA axis as well as a decreased activity of the sympathetic nervous system, and signs of metabolic correction such as improved glucose tolerance and insulin sensitivity. Interestingly, these men did not show any pathological scores in several depression scales, and these scores did not change with treatment, perhaps suggesting that metabolic improvements may occur without parallel mental changes (48). In addition, these results suggest that the serotonergic system is involved in neuroendocrine regulation, which is an established phenomenon (10).

**ALCOHOL AND SMOKING**

There are several reports in the literature that tobacco smoking as well as elevated alcohol consumption is associated with centralization of body fat stores. This is dramatically apparent in the so-called pseudo-Cushing syndrome which is due to alcohol abuse. Both tobacco smoking and alcohol intake above a limit of a couple of drinks per day are followed by an activation of the HPA axis, providing a possible link to centralization of body fat stores (49).

**PSYCHOSOCIAL AND SOCIOECONOMIC FACTORS**

Psychosocial factors have been found to be associated with an elevated WHR in both men and women. The relationships seem stronger in men, with factors such as living alone and divorce. Socioeconomic handicaps are also involved, including poor education, physical type of work, low social class and low income (50,51). This has also recently been observed in the Whitehall studies with strong inverse relationships between socioeconomic status on the one hand and an elevated WHR associated with the metabolic syndrome on the other (52). In a similar treatment of our data we find the same relationships, which are associated with perturbations of the HPA axis. In addition, exposure time for such handicaps seems to worsen the symptoms (53).

It seems likely that exposure to such socioeconomic and psychosocial handicaps provides a background which would frequently expose such individuals to a stressful environment, and activate the stress systems in the lower part of the brain, followed by the neuroendocrine and autonomic cascade of events, eventually leading to central fat accumulation, the metabolic syndrome and disease.
This then might provide an explanation for the social inequality of disease.

PERSONALITY

Accumulating evidence now also suggests that body fat tends to be stored in central depots in certain types of personalities. This includes both normal variants and what has been defined as personality disorders (54,55). Men with an elevated WHR frequently score high on items of ‘novelty seeking’, and sometimes display antisocial, histrionic and explosive personalities. Personality disorders include schizoid and avoidant, dependent and passive, aggressive characteristics. Men with such personalities might be expected to react to their surroundings in a way that induces stress. Examinations also show that they have high values on various reported stress items such as difficulties in control of not only important things in life but also day to day problems and annoyances, and have a high total score in stress questionnaires. These findings are in concert with the reports of frequent perceived stress periods, associated with perturbed neuroendocrine functions, which supposedly are followed by centralization of body fat (5,17) as discussed in a preceding section.

ENDOCRINE DEFICIENCIES

Men with low testosterone, women after menopause and both men and women with growth hormone deficiency without involvement of HPA axis perturbations tend to have abdominal obesity (49). These hormones prevent accumulation of body fat in intra-abdominal depots, and deficiency would then be expected to be followed by enlargement of these depots. The mechanisms whereby this occurs have been largely elucidated, and substitution with the deficient hormone is followed by a specific decrease of visceral fat as well as improvement of the factors included in the metabolic syndrome (6). The prevalence of such conditions seem to be in the order of 10% in the middle-aged male population (56).

CANCER

Cancer is also predicted by increased proportions of the central fat stores. This was first reported in a small number of endometrial carcinomas (57), and has subsequently been reported also for breast carcinoma (58) and confirmed in a larger study of endometrial carcinomas (59). Since these reports seem to suggest that the carcinomas predicted are localized to tissues which are sensitive to sex steroid hormones, one might speculate that the abnormalities of steroid hormone secretion found in abdominal obesity are also involved in this problem. Elevated androgens are closely associated with centralization of fat in women (21,60) as discussed in a preceding section, and probably originate from the adrenals as a consequence of a central drive of the HPA axis. Such abnormalities indicate disturbed secretions of sex steroid hormones which in an unknown way might be associated with these endocrine dependent carcinomas.

GENETIC FACTORS

Genetic factors are clearly involved in the phenomenon of central accumulation of body fat. Such factors could be present locally in the adipose tissues in question, or in the regulatory mechanisms involved in adipose tissue distribution. A major factor in this regard is probably the activity of the HPA axis, which has been shown to be strongly dependent on genetic factors (61).

A first target for examining molecular genetic factors in men with elevated central body fat has been the gene locus of the glucocorticoid receptor (GR), because the men with perturbed diurnal cortisol secretion discussed in the section on obesity often show abnormalities in the suppression of the HPA axis by dexamethasone (5). We then found that a known polymorphism of the GR gene locus, situated in the first intron, was associated with centralization of body fat as well as insulin resistance and, furthermore, an exaggerated stimulated cortisol secretion (62). Furthermore, another polymorphism in the promoter region is associated with elevated basal cortisol secretion (63). There are thus genetic markers for centralization of fat depots in this gene, probably, if functionally significant, acting via regulation of the HPA axis.
In women additional polymorphisms, localized in microsatellites of genes involved in androgen metabolism and sensitivity seem to be involved (21), as discussed in a preceding section.

Other polymorphisms of potential general interest for the syndrome of elevated central fat are those involved in the regulation of the sympathetic nervous system. Such polymorphisms have been found in the beta-2-adrenergic receptor and in the dopamine-2 receptor, both associated with elevated blood pressure. Polymorphisms of the leptin receptor are, however, apparently protective for hypertension in obesity (64–66).

These early findings demonstrate that the syndrome of central fat accumulation is associated with several gene polymorphisms, indicating a complex genetic background of the syndrome.

**WHY DOES FAT ACCUMULATE PREDOMINANTLY IN CENTRAL DEPOTS?**

The mechanistic, mainly endocrine background to visceral fat accumulation has been reviewed elsewhere (6). One may wonder from a teleological viewpoint why humans in a wide variety of conditions store an excess fraction of body fat in central depots.

These depots are equipped with a very sensitive fat mobilization system, which becomes even more efficient by a dense innervation and a rich blood flow to remove mobilized free fatty acids to the portal circulation, and subsequently after hepatic extraction, to systemic circulation. Accumulation of depot fat in these portally drained depots thus serves as an easily available substrate for important liver and peripheral functions in, for example, muscles. The substrate delivery to the periphery is in the form of both free fatty acids and very low density lipoprotein triglycerides, synthesized in the liver (for review see Björntorp (16). The accumulation of central fat is more pronounced in men than women. Specific localization of fat accumulation seems to have a clear survival value, particularly in men, who were particularly dependent on their muscles for survival in ancient times.

One may also look upon this phenomenon as a reserve depot for periods when the surrounding milieu is threatening, and where much available energy is best stored in easily mobilizable depots, and not, for example, in the gluteo-femoral depot of women, which seems to be constructed for specific child-bearing purposes (6). Such a construction is, however, outdated in current urbanized societies. When this excess is not used for purposes of energy delivery to muscles after longer stressful periods with accumulation of central fat, these depots remain intact as a sign of long-term environmental pressures, which lead to disease by mechanisms involving neuroendocrine and autonomic mechanisms, as discussed above.

**GENERAL SUMMARY**

This overview has attempted to summarize briefly the multitude of conditions in which central, visceral fat is accumulated in excess. In all these situations there seems to be a neuroendocrine background affecting the HPA as well as other central hormonal axes, often coupled to the autonomic nervous system. This parallel activation is characteristic of an arousal reaction of centres in the lower parts of the brain, constructed for adaptation to surrounding pressures in order to maintain homeostasis or allostasis. The widespread occurrence of elevated central body fat masses suggests by itself that vital, common pathways are activated. The associations between central fat and such diverse conditions as heart disease, stroke, diabetes, obesity, hypertension, cancer, depression, anxiety, endocrine disturbances, personality aberrations, alcohol abuse, socioeconomic and psychosocial handicaps etc., suggest some kind of common pathogenetic denominator. It seems likely that this denominator is a central arousal, induced by factors in a competitive, hectic society. Central fat accumulation may be considered mainly as a conveniently observable indicator of a chronic exposure to such damaging factors, remaining as an outdated survival mechanism. Figure 16.2 illustrates a hypothesis of the putative pathways linking increased central fat mass to diseases and conditions which have been shown to be statistically associated with it.

**ACKNOWLEDGEMENT**

The studies from the author's laboratory referred to have been performed in collaboration with a large
Figure 16.2  Hypothetical explanation to the statistical associations between central fat depot enlargement and a large cluster of different factors. Various stress factors, including psychosocial and socioeconomic handicaps (psycho-soc, soc-ec), depression, anxiety, alcohol and smoking which, dependent on personality characteristics, via corticotrophin-releasing hormone (CRH) and endocrine perturbations, including cortisol, sex steroid and growth hormones (endocr) direct fat to central depots, and constitute risk factors for endocrine type of cancers. In addition, CRH, together with the functionally, tightly connected central sympathetic nervous system (SNS), generates metabolic and haemodynamic (hypertension) risk factors for disease.

number of international and Swedish researchers. Their names are found in the reference list.

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