Environmental Influences on Diseases in Later Life

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Introduction

Over the last century, there has been a rapid decrease in the incidence of many infectious diseases. Over the same period, the prevalence of several noninfectious diseases, e.g. obesity, type-2 diabetes, and coronary heart disease, has increased dramatically to the point that we are facing an epidemic of non-communicable diseases. These diseases are clearly observed more frequently in ‘rich’ countries: they are favored by the availability of abundant foods, motorized transportation and other riches and can be denominated ‘diseases of affluence’ [1].

Prominent among these diseases of affluence is a constellation of pathological findings, including obesity, type-2 diabetes mellitus, dyslipidemia, high blood pressure and other related metabolic or vascular abnormalities, which has been called successively the syndrome X, the insulin resistance syndrome or, more recently, the metabolic syndrome [2]. Although the pathogenesis of this syndrome remains debated, it is recognized that insulin resistance is one of its central components and might indeed be instrumental in the development of several of the associated metabolic alterations [3].

Genetic factors are generally thought to be involved in the pathogenesis of obesity, type-2 diabetes, and dyslipidemia. Genetic factors may directly intervene in the pathogenesis of insulin resistance. The recent epidemiological development of these disorders, which showed a several-fold increase in their rates of prevalence over only a few decades, i.e. during which it is unlikely that major changes in the genetic background occurred, clearly indicates that other factors play a prominent role. It is likely that these factors are to be searched for in the important environmental changes which have occurred in the recent history of the world.
Which Environmental Factors?

How does our environment affect the functions of our organism? In particular, how does it get involved in the pathogenesis of disease? What we eat is obviously part of our environment and changes in nutrient intake, whether qualitative or quantitative, may contribute to the development of diseases of affluence. More specifically, consumption of diets rich in saturated fats and refined sugar has been associated with the development of the metabolic syndrome [4]. Our environment also conditions our way of life, and living in an industrialized world where technical developments enable efficient ways of transportation and work automation certainly determines the extent to which we are physically active. There is no doubt that our present environment reduces our physical activity dramatically, and as such contributes to the development of insulin resistance and to the metabolic syndrome.

The living creatures we encounter in our everyday life represent a prominent part of our environment. Among such creatures, microorganisms can cause infectious diseases. There is little evidence presently to support the hypothesis that microorganisms are primarily involved in the pathogenesis of metabolic disorders. Recently, however, a large body of experimental work has shown that inflammation is closely linked to insulin resistance [5], and hence this view might possibly be revisited in a near future.

Contact with wild animals and potential predators was permanent in prehistorical times but it has become virtually inexistent nowadays in most affluent countries. In contrast, contact with other humans, whether in a familial context, at work or on social occasions, is an important part of our environment. These complex interactions might at times generate a significant ‘stress’.

How can environment have an impact on health on a long-term basis? There is evidence that environmental factors have a highly significant impact on diseases, even at quite distant times. As proposed by Barker et al. [6], poor nutrition during fetal development has important consequences in adult life. Epidemiological studies indicate that low birth weight is associated with type-2 diabetes, high blood pressure, lipid disorders, and obesity. Low birth weight is associated with insulin resistance in adolescents and young adults, i.e. at a time when food restriction had long disappeared. These observations can be reproduced in animal models. Energy or protein restriction during fetal development leads to permanent alterations of β-cell function and to reduced insulin sensitivity in later life [7]. Such permanent effects of nutrition during fetal development obviously do not involve genetic factors, but so-called epigenetic factors. Permanent silencing or overexpression of specific genes might be involved [8]. Permanent structural changes at the organs level may also intervene.
Regarding obesity, there is evidence that not only fetal nutrition but also nutrition in the early postnatal period is predictive of future weight status [9]. This large increase in body weight during the early postnatal life is closely associated with obesity in adolescents and adults. A low birth weight associated with a rapid weight gain in the first postnatal year is associated with impaired glucose tolerance [10]. Although such studies are still scarce, they strongly suggest that environmental factors might play a prominent role at various key periods of human lifespan. The fetal period, the early postnatal period, puberty, pregnancy and senescence might be such periods when the human body reorganizes to face novel demands, and hence may be especially prone to permanent effects of the environment. Hypothetically, such permanent effects may be secondary to modulation of gene expression, or to structural changes in various organs and systems [8]. In particular, reorganization of brain circuitry (brain plasticity) may occur at any time during life span, but may possibly be facilitated at specific periods.

The Metabolic Syndrome: A Stress-Related Disorder?

The human body has developed an intricate set of neural and endocrine mechanisms which aim at maintaining a constant ‘internal milieu’, a process called ‘homeostasis’. In order to be able to cope with special situations, however, the organism has to alter the ‘internal milieu’. This occurs during physical exercise when endogenous substrates are mobilized from the adipose tissue, the liver, and skeletal muscles to ensure sufficient energy provision to the working muscle. It has been recognized for more than 50 years that an organism, when facing a threatening condition, develops a set of rather stereotyped neuroendocrine responses. This set of responses is elicited by infection, trauma, and also fear or psychological stress. It involves activation of the sympathetic nervous system and secretion of epinephrine from the adrenal medulla, and activation of the hypothalamo-pituitary-adrenal axis, the latter resulting in secretion of glucocorticoids from the adrenal cortex. The combined effects of these neuroendocrine alterations is the mobilization of lipids from the adipose tissue and glucose from hepatic glycogen to ensure ample energy availability, the development of an acute state of insulin resistance which diverts glucose away from skeletal muscle to ensure glucose supply to the brain. Simultaneously, vasoconstriction occurs in the splanchnic area while vasodilation takes place in skeletal muscle, allowing an ample supply of oxygen and energy substrate to allow locomotion. These coordinate responses allow the flight and/or fight responses essential to avoid or survive predators. These responses to threat or stress constitute a controlled deviation from homeostasis, which has been called allostasis [11, 12].

In industrialized societies, the threat of predators has virtually disappeared. The same stress response can, however, be elicited by other stimuli.
such as professional stress or social stress (family problems, interpersonal conflicts, etc.). Such stressful stimuli, when present, may be long lasting and lead to continuous stimulation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. This will result in a sympathetic overactivity, and in increased epinephrine and glucocorticoid secretion. All these factors, taken individually, may induce insulin resistance. In addition, high glucocorticoid levels are thought to favor fat redistribution from the subcutaneous to visceral depots, leading to the development of central rather than peripheral obesity if excess energy is ingested [13].

Metabolic and Hemodynamic Effects of Acute Stress in Lean and Obese Humans

Several stimuli are known to elicit ‘stress responses’. Although relatively stereotyped, the neural structure and pathways activated, and the neuroendocrine, metabolic, and hemodynamic responses may differ to some extent from one stimulus to the other [14]. In humans, the hemodynamic responses to mental stress appear to match relatively closely the ‘flight or fight’ reaction described in animals. Mental stress can be elicited by various procedures, such as color-word conflict tests, complex mental arithmetics, or asking the subject to deliver a talk in front of an audience. Such procedures increase the sympathetic nervous system activity and epinephrine secretion, resulting in an increased heart rate and cardiac output. In addition, it induces a vasodilation in skeletal muscle which, by decreasing the cardiac post-load, contributes to increase cardiac output (table 1). This vasodilation in skeletal muscle is triggered by activation of β-adrenergic receptors and involves local nitric oxide production. Sympathoadrenal activation also increases resting energy expenditure, an effect mediated by β-adrenoceptors. In addition, mental stress activates the hypothalamic-pituitary-adrenal axis, resulting in increased plasma cortisol concentrations. When insulin sensitivity is quantified by means of a hyperinsulinemic clamp, mental stress does not reduce insulin-mediated glucose disposal in spite of the increased plasma catecholamine and cortisol concentrations. On the contrary, insulin-mediated glucose disposal is acutely enhanced in relation to the increased muscle blood flow which allows enhanced glucose and insulin delivery to skeletal muscle (table 1) [15]. These effects of mental stress are significantly altered in obese, insulin-resistant subjects. When obese female patients were compared to normal weight females, mental stress elicited similar increases in plasma catecholamine concentrations and heart rate, indicating that the sympathetic nervous system was activated to the same extent in both groups. Energy expenditure was also stimulated to the same extent in lean and obese subjects. In contrast, mental stress failed to increase cardiac output or reduce systemic vascular resistance in obese
### Table 1. Metabolic and hemodynamic effects of mental stress

<table>
<thead>
<tr>
<th></th>
<th>Lean females</th>
<th>Obese females</th>
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<tbody>
<tr>
<td></td>
<td>hyperinsulinemia</td>
<td>hyperinsulinemia + mental stress</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>58 ± 3</td>
<td>86 ± 3 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>77 ± 2</td>
<td>85 ± 2 (p &lt; 0.001)</td>
</tr>
<tr>
<td>Cardiac index, liters/min/m²</td>
<td>3.6 ± 0.3</td>
<td>5.2 ± 0.5 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Systemic vascular resistances, U</td>
<td>21 ± 2</td>
<td>15 ± 2 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Insulin-mediated glucose disposal, μmol/kg/min</td>
<td>24 ± 2</td>
<td>31 ± 3</td>
</tr>
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From Seematter et al. [15].
patients. As a consequence, insulin-mediated glucose disposal failed to increase during mental stress but blood pressure response was increased (table 1) [15]. These two alterations are presumably secondary to the absence of vasodilation in response to mental stress in obese patients. Interestingly, the alterations observed in obese patients during mental stress could be reproduced in healthy lean female patients by an infusion of a lipid emulsion [16]. This suggests that lipids induce vascular alterations which impair the vasodilatory response induced by mental stress. This lipid-induced vascular dysfunction in turn prevents the increase in insulin-mediated glucose disposal, and leads to a substantially higher elevation in blood pressure.

Put together, these observations indicate that mental stress significantly enhances plasma catecholamines and cortisol concentrations. This does not appear to acutely impair insulin sensitivity, but it can be postulated that repeated mental stress may lead to chronic alterations in cortisol and catecholamines concentrations, and insulin resistance. Furthermore, chronically elevated cortisol concentrations may favor the development of abdominal obesity and the metabolic syndrome [13, 17]. While mental stress does not acutely impair glucose homeostasis in healthy individuals, it leads clearly to deleterious hemodynamic (and possibly metabolic) effects in obese insulin-resistant patients. Again, it can be postulated that repeated mental stress in obese patients can contribute to increase blood pressure and to increase plasma glucose concentrations due to failure to induce an appropriate muscle vasodilation.

The Metabolic Syndrome: An Inflammatory Disorder?

It is well known that insulin resistance is a prominent finding in patients with severe infection or inflammation. An increase in stress hormones (epinephrine, cortisol, glucagon, growth hormone) and proinflammatory cytokines (tumor necrosis factor-α (TNFα), interleukin (IL) 2) contributes to a decrease in insulin-mediated glucose disposal in skeletal muscle under such conditions [5].

Over the past 10 years, it has been increasingly recognized that adipose tissue produces many metabolic and endocrine mediators, e.g. TNFα and ILs. Indeed it has been proposed that production by adipocytes of inflammatory mediators may be directly involved in the pathogenesis of insulin resistance in obese patients. Furthermore, it is now well established that increased levels of inflammatory mediators (C-reactive protein, TNFα, IL6) are positively associated with the risk to develop coronary heart disease on type-2 diabetes [18]. These observations raise the possibility that a low-grade inflammation may be responsible for the development of insulin resistance and the metabolic syndrome. Such chronic inflammation may be
produced by chronic infections, tissue injury induced by reactive oxygen species, etc.

Nutritional factors may also be responsible for the development of a low-grade inflammatory response. It has been observed for instance that feeding rats a high-fat diet leads to activation of the nuclear factor IkB in adipocytes which in turn increase TNFα expression, thus leading to insulin resistance [19].

**Mental Stress as a Proinflammatory Trigger?**

Inflammation always involves the production of cytokines such as TNFα and ILs, which in turn exert effects at the level of the central nervous system. The consequences are not only changes in body temperature set points, but also an activation of the neuroendocrine stress responses. This may be part of an intricate and finely regulated system which balances inflammatory reactions, since both the increased plasma glucocorticoids and the autonomic (parasympathetic and sympathetic) nervous system contribute to downregulation of inflammation [20]. There is, however, recent evidence that mental stress may also act as a proinflammatory factor by directly triggering peripheral inflammatory responses. Thus, healthy individuals subjected to acute mental stress (delivering a talk in front of an audience) had a stimulation of TNFα expression in circulating monocytes, an effect which involved activation of α- and β-adrenergic receptors [21, 22]. Chronic stress may well have such proinflammatory effects: a recent study indicated that the spouses of demented subjects living at home (a condition likely to bring a considerable stress on the non-demented spouse) had increased plasma IL6 levels (as well as increased morbidity and mortality) [23]. The proinflammatory effects of chronic stress may therefore well be clinically relevant!

**Future Perspectives**

The research work outlined above strongly suggests that stress may play a significant role in the pathogenesis of the metabolic syndrome (fig. 1). Stress hormones, if chronically elevated as a result of stressful stimuli, may induce insulin resistance and favor abdominal obesity. Once insulin resistance and obesity are present, the deleterious effects of stress on blood pressure and glucose homeostasis may be enhanced due to lipid-induced insulin dysfunction. Stress may thus create a vicious circle by inducing insulin resistance which would in turn increase the deleterious effects of stress on blood pressure.
This scheme is quite preliminary at this stage and several major issues remain to be evaluated.

Experimental data and clinical experience indicate that there are interindividual variations in the neuroendocrine and overall responses to stressfull stimuli. Some individuals adapt rapidly to repeated stressfull events while other may build up a long-lasting stimulation of the sympathetic nervous system and the hypothalamo-pituitary-adrenal axis [24]. The basis for these interindividual variations remains to be explored. Some recent observations may provide valuable hints. It was shown that, in individuals suffering from post-traumatic stress after the terrorist nerve gas attacks in the Tokyo subway, the size of the cingulate gyrus had decreased [25]. Similar previous observations indicated that survivors of Vietnam War had hypotrophy of the hippocampus [26]. Since this neuronal structure is involved not only in memory but also in the control of emotions, and hence stress responses, these observations raise important questions: does stress lead to permanent alterations in neural structures within the limbic system which may lead to persistent stress reactions and allostatic responses? Alternatively, do innate or acquired alterations in limbic structure predispose some individuals to pathological stress responses?
It is well established that chronic stress produces deleterious effects in the brain just as it does in other body organs [27]. For instance, repeated stress or high levels of glucocorticoids decrease the number of apical dendrite branch points and produce cell loss in the CA3 pyramidal layer of the hippocampus [28]. There is also evidence that acute and chronic stress decreases levels of brain-derived neurotrophic factor (BDNF) in the dentate gyrus and pyramidal cell layer of the hippocampus in rodents [29]. BDNF, one of the most prevalent neurotrophic factors in the brain, regulates the survival and differentiation of selective populations of neurons in the peripheral and central nervous systems [30]. There is also ample evidence that BDNF regulates synaptic plasticity. These observations suggest that decreased levels of BDNF in response to stress could

![Figure 2](https://example.com/fig2.png)

**Fig. 2.** Effect of fish oil supplementation on the neuroendocrine and metabolic responses to mental stress. Healthy volunteers were submitted to a mental stress before and after 3–4 weeks supplementation with fish oil. The average peak responses observed during mental stress are shown in this figure. Fish oil significantly blunted the stimulation of epinephrine and cortisol secretion, the increase in plasma free fatty acids, and the stimulation of energy expenditure. Redrawn from data of Delarue et al. [35].
contribute to impairments in neuronal survival/atrophy and synaptic plasticity in the hippocampus [29]. In contrast to stress, environmental enrichment and physical activity increase BDNF expression in the hippocampus, suggesting that they may represent important issues to improve anti-stress treatment [31, 32].

The environment has a significant impact on brain neurochemistry and synaptic plasticity. In rodents, high-fat diets cause a state of insulin resistance which can be prevented by intracisternal administration of BDNF [33]. In addition, dietary restriction increases neurogenesis and induces BDNF expression in the dentate gyrus of rats providing insight into the mechanisms whereby diet impacts on brain plasticity [34].

Modulation of stress responses by various environmental factors clearly constitute research avenues to be explored. A recent study has shown that fish oil supplementation significantly blunts the metabolic and neuroendocrine responses to smental stress [35]. Mental stress-induced increases in plasma catecholamines, cortisol and free fatty acids, and stimulation of energy expenditure were all significantly blunted in healthy males after a 3-week supplementation with fish oil (fig. 2). Another study indicated that fish oil supplementation decreased the anxiety of a group of students while preparing for their graduation examination [36]. These observations suggest that fish oil exert effects at the level of the central nervous system. Studies aimed at assessing the mode of action of fish oils in the brain may provide valuable hints regarding the mechanisms by which nutrients may alter these stress responses.

Moreover, it appears essential to evaluate whether environmental factors applied at specific periods of life may affect brain function and lead to permanent alterations in stress responses. One study indicated that intrauterine growth retardation led to a reduction in levels of some neurotrophic factors, including BDNF [37]. Whether this translates into altered allostatic processes later in life and whether similar changes can be induced at other key periods of human development of senescence are only a few of several important questions which remain to be addressed.

References

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Discussion

*Dr. Basu:* Those are fascinating data, Prof. Tappy. In your fish oil studies, how much fish oil did you use as supplement? Is it similar to the trials that have been done before for cardiovascular prevention?

*Dr. Tappy:* We used relatively high doses, i.e. 7.2 g fish oil, corresponding to 0.7 g docosahexaenoic acid and 1.1 g eicosapentaenoic acid.

*Dr. Basu:* Did that alter the lipid levels in these individuals?

*Dr. Tappy:* Not in these healthy subjects. We didn't see any change in basal lipid levels. We also assessed insulin sensitivity and didn't see any change.

*Dr. James:* I think that I should probably speak on Yajnik's [1] behalf again. You highlighted the importance of mental stress associated with cytokines and that is extremely interesting. As you know cytokine production increases as people put on weight by virtue of the increase in adipose tissue mass. The adipose tissue essentially becomes a massive hormone factory, pushing out the cytokines. Now Yajnik et al. [2] have looked at cytokines in Indian villages. There was no mental stress analysis done on these individuals, but they looked at 3 groups of people: people in the village; people in the slums, and then middle-class affluent city dwellers. They showed that there is an astonishing increase in cytokine production among the slum dwellers which they assume is not so much related to the small increase in body weight even though abdominal adiposity increases, but that this is a sanitation infective, a phenomenon that actually reflects the environment. They didn't talk about mental stress, whereas by the time you get into the middle class in India then the cytokines drop again but not as low as in the villages. Do you know of any studies that have attempted to discriminate environmental adiposity first of all, and sanitation on the general infective load secondly, from mental stress in a society?

*Dr. Tappy:* The data you mentioned are really very interesting. I am not aware of any studies that tried to address the effects of mental stress on a population basis, and even on an individual basis. As you mentioned there might be some important interaction between mental stress and the degree of adiposity. It has been documented that mental stress activates inflammatory cytokines in monocytes and the question is: does it also activate it in fat cells or skeletal muscle? I am not aware of any data addressing that now.

*Dr. James:* Can I come back on that, linking this to the development of insulin resistance. If there is local cellular activation of tumor necrosis factor-α (TNF-α), then Matsuzawa et al. [3] in Osaka presented beautiful data showing that diabetes seems to be fundamentally linked to the activity of a newly discovered hormone called adiponectin which is put out by adipose tissue. They also discovered that adiponectin and TNF-α operate against each other, so that if you add TNF-α, adiponectin goes down, and adiponectin looks as though it is fundamentally involved in preserving
insulin sensitivity. So people with diabetes have low adiponectin, and if they have cardiovascular disease with diabetes they have an even lower adiponectin level. If there is an abnormality of adiponectin activity through a gene, a single gene change that doesn't allow it to operate, then those individuals almost universally have glucose intolerance or already frank diabetes and atherosclerosis. There is a fundamental link in adiponectin in terms of endothelial function. So if you are right about the genetic impact of mental stress, you can now actually produce a hormonal sequence that looks as though it is fundamentally locked in with the diabetic tendency.

**Dr. Tantibhaedhyangkul:** When TNF-α is infused in cancer patients, food intake decreases. Cancer patients are cachectic, they lose weight, they have increased TNF-α and poor appetite, but in obesity TNF-α and insulin resistance are also increased. What is the difference between the two responses? There must be something else; it is not just that simple.

**Dr. Biolo:** I would like to comment on one fascinating hypothesis that you put forward, Prof. Tappy. The possibility that visceral obesity can derive from the combination of a chronic stress response and hypercortisolism combined with overnutrition is really fascinating. However, we have a real experimental model to test this hypothesis in human diseases. For example, cancer patients have a very high chronic stress response and sometimes they may be overnourished by doctors. Do we have evidence that in this condition there is accumulation of adipose tissue in these patients? Another comment I would like to make is that the stress response does not only involve cortisol secretion but also activation of the sympathetic system, and the two hormones have an opposite effect on fat deposition in visceral tissues.

**Dr. Tappy:** Yes I agree that cortisol and the sympathoadrenal system might have different effects on visceral versus subcutaneous adipose tissue. I am not aware of any data. Also I am not a cancer specialist, but regarding stress and visceral adipose tissue in cancer patients, cancer is characterized by a catabolic response and in fact it differs markedly from obese individuals.

**Dr. Tantibhaedhyangkul:** We are talking about insulin resistance. What happens with leptin resistance?

**Dr. Tappy:** I am not sure that the concept of leptin resistance is well documented. By saying leptin resistance, one assumes that leptin must be responsible for the development of obesity, which has not been documented so far. The concept of insulin resistance is very well documented because a low insulin-mediated glucose disposal has been seen in some individuals, but by increasing insulin levels a full response can be recovered. For leptin this is not the case. I think there are not enough data to accept the hypothesis of leptin resistance.

**Dr. Tantibhaedhyangkul:** Corticotropin-releasing hormone can be increased, the sympathetic system can be increased, and cortisol can be increased, similar to insulin resistance. Are the two related or not?

**Dr. Tappy:** There are marked differences between rodents and humans regarding the effects of leptin. In rodents there is no question that leptin administration increases the sympathetic nervous system and increases energy expenditure, and that it alters adrenocortical secretions. In humans there is very limited evidence that these effects are present.

**Dr. James:** I would just add that I agree with this analysis. The concept of leptin resistance was an early concept, and when a special conference on leptin was held with the originators of all the data you have just been hearing about, they came up with the view that we have to be careful before we automatically assume that there is an intrinsic leptin resistance. It looks as though leptin is a marvelous signal to the brain when it drops and amplifies the urge to eat. We have just heard the evidence that came from the Cambridge group on what happens if there is total leptin deficiency.
and small amounts of leptin are added. But it looks as though the receptors in the brain for leptin are very soon completely occupied by leptin; so it is almost as though we have an artificial concept of leptin resistance in that case. So as adipose tissue increases, there is a secondary response with leptin increasing, but the receptor system in the brain is already then totally occupied. So then there is a further increase in leptin but it is not doing anything, therefore it is resistant and it may simply be that leptin is a prime signal when it is at a low level rather than at a high level. At least that is the concept that emerged and was published in *Nutrition Reviews* a couple of years ago.

*Dr. Kopelman:* Could I ask about sex steroids because they are very important with this stressed state in fat/adipose deposition. I wonder whether there were dramatic changes in circulating sex steroids during your test?

*Dr. Tappy:* We did not measure sex steroids.

*Dr. Go:* That is a very important question since adipose tissue itself is an endocrine organ: it can release leptin, it can release estrogen, and it can also release TNF-α, and there are two other hormones. So the question then is what is the sympathetic control mechanism on adipose tissue in obesity and how much of that is interfering with the corticotropin-releasing factor (CRF) mechanism that you have elucidated?

*Dr. Tappy:* I don’t know how to answer this question. There are very few data regarding the effect of stress on the sympathetic nervous system and adipose tissue. There is evidence that the subcutaneous white adipose tissue is much more richly innervated than previously thought. So I agree that we need to have much more comprehensive data regarding the effect of sympathetic activation on adipose tissue secretions.

*Dr. Go:* CRF stress mechanisms in irritable bowel syndrome can now be tested in humans given the CRF antagonist. So, in fact, one should be able to study whether or not an alteration can be seen in insulin resistance using CRF blockade. I want to ask Dr. Basu if he has been looking at CRF antagonists?

*Dr. Basu:* Not CRF antagonists, but we are looking more at the expression on the visceral fat of 11β-dihydroxysteroid hydrogenase types 1 or 2, and we are in the process of designing studies to look at that in humans. We have no data yet, we are still doing the studies.

*Dr. Shenkin:* I wonder if I can get back to the question of stress and the acuteness or chronicity of stress. Of course both kinds of stress can increase the proinflammatory cytokine response, but my understanding is that acute stress, especially if it is infective or traumatic, would increase the cytokine response to a very much higher level than either chronic stress or psychological stress which you mentioned here. Acute stress and the responses to acute stress are usually beneficial; this is part of how we cope with a disturbance in homeostasis. What we would really like to explore further is the point at which responses to acute stress become harmful. How long do these responses have to go on before we start to develop complications of the response to inflammation? What are the situations where a chronic, very low level of proinflammatory response actually causes harm, as opposed to these much higher levels of response which in fact are beneficial?

*Dr. Tappy:* Obviously acute mental stress may have some beneficial effects: an increase in insulin sensitivity and an enhanced muscle blood flow probably contribute to an appropriate response. I don’t know of any studies that have specifically addressed chronic stress. I think what is important is that in wild life the stress response probably occurs when animals are in contact with predators but it very rapidly fades away when the predators are gone. In our Westernized way of life we do not have predators, but have developed the ability to raise stress responses by thinking of possible threats or unpleasant things. Furthermore these responses may be inappropriately long-lasting.
Dr. Allison: Perhaps Dr. Biolo could comment on this. Is there a real dividing line between acute and chronic stress? If, for example, we look at convalescent burn patients who are somewhere in between, we know from Wells et al. [4] that insulin resistance goes on for a long, long time, weeks, months, and that these people put on fat much more easily than they do lean mass. So perhaps there isn't quite as much a distinction as we would imagine. Is this a permanent feature; do these people remain with a greater tendency to obesity and a lower lean mass? Perhaps Dr. Biolo would answer that question because he is in the middle of that work.

Dr. Biolo: Basically the cytokine response is qualitatively very similar. However, I think that the hormonal response is very different. In our acutely ill patients we have a huge increase in stress hormones, cortisol and catecholamines, and also a huge increase in cytokines. But in chronic disease states like chronic uremia or liver cirrhosis we don't observe a very high increase in hormones. When a lot of calories are given to burn patients, we very rapidly observe a huge infiltration in the liver, but we don't see as much in dialysis patients for example. It is very common to overnourish dialysis patients, but we don't see so much fat accumulation in the liver. Then I think that the hormonal response should make a lot of difference in the two experimental models.

Dr. Tan: In your graph you showed that a high-fat diet leads to increased synaptic plasticity which leads to a decreasing stress response. We all know about the radical diet proponents who question the high-carbohydrate low-fat diet of the American Diabetes Association and other institutions. Considering that this radical low-carbohydrate and high-fat diet has really been shown to be very successful in decreasing obesity among our patients, you are trying to elucidate whether this kind of diet may actually be beneficial in terms of decreasing insulin resistance by hopefully decreasing the stress response.

Dr. Tappy: A high fat diet decreases the expression of brain-derived neurotropic factor and so it would be expected to increase stress responses. That is a deleterious effect of a high-fat diet on insulin sensitivity.

Dr. Steenhout: About the high-fat diet: if it is increasing as you say, how can the stress response work with the famous Atkins diet to reduce obesity?

Dr. Tappy: The Atkins diet is very controversial, but if it works and people actually lose weight, it means that they have a negative energy and fat balance. In that, it is quite different from an isocaloric high-fat diet. I guess that explains the difference.

Dr. Steenhout: Just recently I saw trials with different diets [5–7]. I agree with you with regard to the reduced caloric intake, but some are only based on carbohydrate and some on carbohydrate and fat. The reduction in weight was higher when there was some fat. I think also that there is always confusion about fat intake and fat metabolism. It reminds me of an article by Willett [8] who concluding that, within the US, a substantial decline in the percentage of energy from fat consumed during the past two decades has corresponded with a massive increase in obesity. So we have to be careful when we blame fat all the time because there is one thing in the body and one thing in the absorption of fat and in the diet. Would you comment on that?

Dr. Tappy: Regarding the fact that we blame everything on high fat, high-fat diets are a nice experimental model in rodents but there is limited information available in humans showing that a high-saturated fat diet leads to deleterious effects in terms of cardiovascular risk factors and insulin sensitivity, but that it is not the case with high-monounsaturated fat diets. There is nothing such as simply a high-fat diet, you still have to specify what are the specific fats included in the diet.

Dr. James: The Atkins diet is a very clever technique for inducing a programmed specific diet to lower calories so people lose weight. It is particularly conducive to that
because by virtue of being low in carbohydrate it allows one to become relatively ketotic which therefore reduces appetite and so you get this short-term effect. But looking at the integrated data, people went through that whole process years ago. It could be argued that there was another error in the 1960s when originally Yudkin [9] said that sugar was the cause of heart disease and everybody went on these high-fat diets, and the epidemic of heart disease was extraordinary. The evidence is overwhelming in terms of the propensity to coronary heart disease if the saturated fat intake is increased. But this Atkins diet is a very clever gimmick; there are other gimmicks which sometimes operate with the same mechanism. The worry is that when you stabilize, as has been suggested on an isocaloric high-fat diet, then you have real problems. The only group that I know of in the world that did not have problems on high-fat diets was when it came from olive oil. These were the Cretan data where you must remember that these shepherds were walking between 15 and 30 km/day up the Cretan mountains, and therefore if everybody would run every day they could have as much olive oil as they like. There is very little evidence of any society in the world where one is on an over 30% fat diet of any description where they are not obese, unless they are extremely physically active as in Crete in the 1960s. The Institute of Medicine did an analysis of why the low-fat diet in America hasn’t worked. We have to give the food industry huge credit in one way because they altered the fatty acid composition of their diets to help cholesterol, but the nutritionists did not tell them that when you are on a low-fat diet you should not then replace it with refined sugars. So the refined sugar intake absolutely rocketed. The Institute of Medicine said if you have a package of food of the same energy density then people spontaneously eat the same number of calories whether it is from condensed carbohydrate or condensed high-energy fat. So I think that is one of the problems that the nutritional world is not being clear enough in thinking through these strategies and that may be one element in the American epidemic. From the point of view of stress I think we just ought to put on record another intriguing observation about long-term chronic stress, and that is Mamot’s analysis of the propensity to heart disease. He noticed that if you do only classic cholesterol, high-density lipoprotein, smoking, blood pressure analysis and so on, you cannot explain why people in the low socioeconomic classes tend to be much more prone, in fact have double the risk of heart disease even when you take this into account. His proposition is that the most clear-cut relationship in that group is what he calls work-related stress factors. In other words, if a person working in a company essentially considers that he has no control over his future and that his boss can make his life terrible one minute or determine how many hours are to be worked and so on, if he completes a very detailed questionnaire, which is actually being used now throughout the world, then it will systematically be found that this feature is linked to coronary heart disease. Now it certainly occurred to me as I listen to you that if in fact you take this as evidence of stress, and I gather that the psychometric people found that this is a pretty reliable index, how much do you feel you can control your personal life, then in fact you might say that we could think of the same mechanism than you certainly brought out actually having an implication for Mamot’s work too because again the insulin resistance adiponectin story relates fundamentally to endothelial function. So I think you are opening up a totally fascinating world which I have frankly never thought of before.

Dr. Basu: I have to comment on the Atkins diet. In the New England Journal of Medicine sometime in May, some data were published about the Atkins diet [10]. In that 1-year study the people on the low-carbohydrate diet did lose some weight initially for the first 3 months, but at the end of the 12-month study period there was no difference between the low-carbohydrate and the high-carbohydrate diet. Secondly, also one important thing about the Atkins diet is that almost 50% of the people could
not tolerate or continue on the Atkins diet for the whole duration of time. So the attrition rate was very high indeed. If you look at the choices of food in the Atkins diet, they are very little; there is not much you can take and the calorie intake decreases substantially on the Atkins diet.

References
