The objective of the present review is to provide an overview of the metabolic effects of pro-inflammatory cytokine production during infection and injury; to highlight the disadvantages of pro-inflammatory cytokine production and inflammatory stress on morbidity and mortality of patients; to identify the influence of genetics and adiposity on inflammatory stress in patients and to indicate how nutrients may modulate the inflammatory response in patients. Recent research has shown clearly that adipose tissue actively secretes a wide range of pro- and anti-inflammatory cytokines. Paradoxically, although inflammation is an essential part of the response of the body to infection, surgery and trauma, it can adversely affect patient outcome. The metabolic effects of inflammation are mediated by pro-inflammatory cytokines. Metabolic effects include insulin insensitivity, hyperlipidaemia, muscle protein loss and oxidant stress. These effects, as well as being present during infective disease, are also present in diseases with a covert inflammatory basis. These latter diseases include obesity and type 2 diabetes mellitus. Inflammatory stress also increases during aging. The level of cytokine production, within individuals, is influenced by single nucleotide polymorphisms (SNP) in cytokine genes. The combination of SNP controls the relative level of inflammatory stress in both overt and covert inflammatory diseases. The impact of cytokine genotype on the intensity of inflammatory stress derived from an obese state is unknown. While studies remain to be done in the latter context, evidence shows that these genomic characteristics influence morbidity and mortality in infectious disease and diseases with an underlying inflammatory basis and thereby influence the cost of in-patient obesity. Antioxidants and n-3 PUFA alter the intensity of the inflammatory process. Recent studies show that genotypic factors influence the effectiveness of immunonutrients. A better understanding of this aspect of nutrient–gene interactions and of the genomic factors that influence the intensity of inflammation during disease will help in the more effective targeting of nutritional therapy.

Obesity: Inflammation: Genotype: Chronic disease: Immunonutrition

The immune response to infection injury and inflammatory agents

The immune system has evolved to combat microorganisms and initiate repair of injured tissue. Its normal function is central to successful recovery of hospitalised patients. Likewise, in the community, the immune system supports a good quality of life and longevity. The system has a large capability for immobilising invading microbes, creating a hostile environment for them.
and bringing about their destruction\(^1\). The system also becomes activated by stimuli and conditions that do not directly involve pathogens (burns, penetrating and blunt injury, the presence of tumour cells and the presence of chronic inflammatory diseases). The broad spectrum of patients entering hospital will be experiencing these events to different extents. The response of the immune system to these diverse factors outlined above contains common elements. The elements of the response include activation of lymphocytes and macrophages, the production of immunomodulatory proteins (cytokines), oxidant molecules (\(\text{H}_2\text{O}_2\), superoxide, hypochlorous acid and NO), anti-inflammatory hormones (cortisol), natural antagonists (cytokine receptor antagonists), antioxidants (glutathione) and antioxidants enzymes (superoxide dismutase, catalase and glutathione peroxidase)\(^1\).

The cellular part of the response sets in train a dichotomous response. In general, lymphocytes produce a specific acquired immune response and macrophages initiate an inflammatory response. This latter part of the response is exemplified by the symptoms of ‘rubor, calor and dolor’ (redness, heat and pain) as described by Paracelsus. However, the inflammatory process may exist over a wide range from symptomless intensities to high and life threatening intensity, as seen in sepsis.

Inflammation is an essential part of the response to infection, surgery and trauma. Its prime purpose is to kill pathogens by creating a hostile tissue environment through production of oxidant molecules and activation of T and B lymphocytes. Substrate is released, from endogenous sources, by the inflammatory process to support the activity of T and B lymphocytes, and to enhance antioxidant defences so that healthy tissue may be protected from the potent mediators released during inflammation. Three pro-inflammatory cytokines, IL-1\(\beta\), IL-6 and TNF\(\alpha\), modulate these events. Under their influence blood lipids are elevated, muscle protein is lost, gluconeogenesis is enhanced, catabolic hormone production is increased and insulin insensitivity occurs. All of these cytokine-induced effects, however, may play a role in the pathology of a wide range of chronic diseases\(^2\).

**Function of pro-inflammatory cytokines during the normal response to infection and injury**

IL-1\(\beta\), IL-6 and TNF\(\alpha\) have widespread metabolic effects. Signs and symptoms experienced after infection and injury, such as fever, loss of appetite, weight loss, negative nitrogen, sulphur and mineral balance, and lethargy are caused directly or indirectly by pro-inflammatory cytokines. Indirect effects of cytokines are mediated by neural actions upon the adrenal glands and endocrine pancreas resulting in increased secretion of the catabolic hormones adrenalin, nor-adrenalin, glucocorticoids and glucagon. Insulin insensitivity occurs in addition to this ‘catabolic state’.

The biochemistry of an infected individual is thus fundamentally changed to ensure that the immune system receives nutrients from within the body (Fig. 1). Muscle protein is catabolised to provide amino acids for synthesising new cells, glutathione and proteins for executing and controlling the immune response. Amino acids are also converted to glucose (a preferred fuel, together with glutamine, for the immune system\(^1\)). The extent of the rearrangement in protein metabolism is evident from changes in urinary nitrogen and sulphur following infection and injury and the rearrangement of lipid and glucose metabolism by elevation of plasma lipids\(^3\).

**Adverse effects of pro-inflammatory cytokines and inflammatory stress**

Paradoxically pro-inflammatory cytokines, although essential for normal immune function, play a major role in tissue damage during inflammatory disease and may increase mortality from infections and mediate loss of muscle mass, following injury and surgery, in a wide range of infections. In conditions such as sepsis, pro-inflammatory cytokines are produced in excessive amounts and are an important factor in increased mortality\(^2\). Low-level inflammation has also been closely linked with poor clinical outcome and shortened lifespan. In 1989, data from the British Regional Heart Study showed that mortality rates from CVD and all causes were inversely related to serum albumin concentrations\(^3\). As albumin is a negative acute phase protein and is lowered during inflammation, the finding suggested that low-intensity, chronic inflammatory stress is inimical with health and avoidance of morbidity and mortality\(^2\). Subsequent studies clearly showed that atheromatous plaque growth and instability were due to pro-inflammatory cytokine production and inflammation within the plaque lumen. Thus the focus on the mechanistic basis of atherosclerosis shifted from one totally associated with aberrant cholesterol and TAG metabolism to a more complex scenario involving inflammatory stress.

**Influence of adipose tissue mass on inflammatory stress**

It is well known that obesity and smoking are strong risk factors in atherosclerosis and that obesity, insulin
insensitivity and diabetes mellitus form a triuriminate of disease. The recent finding that adipose tissue is an active endocrine organ and produces several inflammatory mediators provided a unifying mechanism for the linkage between the incidences of chronic diseases. The most abundant protein in adipose tissue is adiponectin, which stimulates immune cells to produce anti-inflammatory cytokines and may explain disturbed immune function in severely obese individuals(4,5); adipose tissue has also been shown to overproduce TNFα and IL-6 in obesity(6–9). Obesity is associated with a steady infiltration of macrophages into adipose tissue such that in grossly obese individuals, macrophages constitute up to 40% of the cellular population of the tissue(10). Apart from the relevance of these findings for the pathogenesis of the metabolic syndrome, the inflammatory state related to obesity may also interfere with recovery of injury(11). Similarly, dyslipidaemia, often encountered in obesity and an essential part of the metabolic syndrome, is also known to be an independent risk factor for the development of sepsis and increased mortality(12). Indeed the risk of death from multi-organ failure was shown to be greater in obese patients than in patients with normal weight(13,14).

A study on obese women clearly showed that a reduction in adipose tissue mass, achieved by consuming 2520 kJ/day for 10 weeks, substantially reduced the ability of adipose tissue to produce TNFα, IL-6, IL-8 and leptin(15).

### Influence of genotype on inflammation and disease

The explosion of new knowledge that followed the decoding of the human genome is helping to unify the understanding on the pathology of chronic disease.

Since the 1990s it has become clear that small, naturally occurring, variations (single nucleotide polymorphisms (SNP)), mostly in the promoter region of genes, influence the amount/bioactivity of product produced when the genes are activated. A large body of research has indicated that SNP occur in the upstream regulatory (promoter) regions of many pro- and anti-inflammatory cytokine genes that influence the level of cytokine production(16,17). Recent findings have also suggested that SNP modify the responsiveness of individuals to changes in nutrient intake. For example, SNP influence the lipaemic response to dietary lipid(18), alter the interrelationship between plasma vitamin B12, folate and homocysteine(19) and modulate the ability of fish oil to reduce TNFα production(20).

### Genetic effects on the intensity of the inflammatory process

SNP in the genes responsible for molecules involved in the inflammatory process modulate the intensity of inflammation. In vitro production of TNFα, by peripheral blood mononuclear cells from healthy and diseased subjects, stimulated with inflammatory agents, shows remarkable constancy in males and post-menopausal females(21). This constancy suggests that genetic factors exert a strong influence. SNP in the promoter regions for the TNFα and lymphotoxin-α (LT-α) genes are associated with differential TNF production(16,22). In addition to modifying the expression of LT-α itself, the TNFβ2 (A) alleles are linked to high TNF production, particularly in homozygous individuals. The TNFα –308 (A) allele is associated with enhanced TNFα expression in a number of studies(16,22). A number of SNP that have been implicated in the outcome to inflammatory stress are shown in Table 1.

### Table 1. Single nucleotide polymorphisms (SNP) in cytokine genes associated with altered levels of cytokine production

<table>
<thead>
<tr>
<th>Gene and location of polymorphism in the promoter region</th>
<th>Genotype associated with raised or lowered cytokine production and/or altered outcome to inflammation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-inflammatory SNP</td>
<td></td>
</tr>
<tr>
<td>TNFα –308</td>
<td>TNF2 (A) allele</td>
</tr>
<tr>
<td>LT-β + 252</td>
<td>LT-β + 252 AA (TNFβ2:2)</td>
</tr>
<tr>
<td>IL-1β – 511</td>
<td>CT or TT</td>
</tr>
<tr>
<td>IL-6 – 174</td>
<td>G allele</td>
</tr>
<tr>
<td>Anti-inflammatory SNP</td>
<td></td>
</tr>
<tr>
<td>IL-10 – 1082†</td>
<td>GG</td>
</tr>
<tr>
<td>TGF-1β + 915 (Arg-25-Pro)†</td>
<td>GG</td>
</tr>
</tbody>
</table>

LT, lymphotoxin; TGF, transforming growth factor.†Improved outcome for anti-inflammatory cytokines.‡Significantly different from females with the same genotype by multivariate analysis allowing for longer operation time and greater blood loss $P = 0.013$ and $P = 0.027$ for CRP and IL-6, respectively.

### Table 2. Influence of TNFα –308 polymorphism and gender on the inflammatory response to surgery in patients with gastrointestinal cancer

<table>
<thead>
<tr>
<th>Duration of operation (min)</th>
<th>Blood loss (ml)</th>
<th>Peak CRP concentration†</th>
<th>Peak IL-6 concentration†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Mean</td>
<td>Mean</td>
<td>sd</td>
<td>sd</td>
</tr>
<tr>
<td>n</td>
<td>n</td>
<td></td>
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</tr>
<tr>
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<td>65</td>
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<td>65</td>
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</tr>
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<td>402</td>
<td>24</td>
<td>362</td>
</tr>
<tr>
<td>676</td>
<td>544</td>
<td>7</td>
<td>315</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein.†pg/ml 1 d post-operatively.‡Significantly different from females with the same genotype by multivariate analysis allowing for longer operation time and greater blood loss $P = 0.013$ and $P = 0.027$ for CRP and IL-6, respectively.
levels of activity and differential sensitivity to stimulation by inflammatory agents. Alleles 1, 2 and 4 are poor promoters, while allele 3 causes high gene expression. A number of molecules suppress the production of pro-inflammatory cytokines and exert an anti-inflammatory influence. These include antioxidant defences and IL-10. There are at least three polymorphic sites in these genes, such as catalase, superoxide dismutase and glutathione peroxidase, which influence levels of activity.

Enhancement of antioxidant defences is important, in protecting healthy tissues and in preventing excessive activation of NF-kB by the oxidative cellular environment, during inflammation. SNP also occur in genes encoding enzymic components of antioxidant defences, such as catalase, superoxide dismutase and glutathione peroxidase, which influence levels of activity.

Thus each individual possesses combinations of SNP in the genes associated with inflammation, which bestow on them ‘inflammatory drives’ of differing intensities. At an individual level this may express itself as differing degrees of morbidity and mortality. Circumstantial evidence of this phenomenon has been reported in a number of studies. The strength of the genomic influence on the inflammatory process may affect the chances of an individual developing inflammatory disease, particularly if their antioxidant defences are poor. In intensive care patients, the 1082 G high-producing allele, for IL-10, was present in those who developed multi-organ failure, with a mortality for the two genotypes were 53 and 33%, respectively. In a study on patients undergoing surgery for gastrointestinal cancer, it was found that post-operative C-reactive protein and IL-6 concentrations were higher in men than women and that in multivariate analysis, in which greater operation duration and blood loss in males was allowed for, males possessing the TNF-α – 308 A allele had greater responses than men without this allele. The genomic influence was not seen in females (Table 2). In a study on hospitalised geriatric care patients, men possessing the ‘less inflammatory’ LT-α+252 AA or IL-1 − 511 CT or TT genotype had a shorter 3-year survival rate than men possessing the LT-α+252 GG or AG, or IL-1 − 511 CC genotype. Furthermore, possession of the IL-1 − 511 T allele was associated with a 48% greater length of stay in hospital in men (Table 3). Women were unaffected by these genetic influences.

**Gender gene effects**

In general, males are more sensitive to the genomic influences on the strength of the inflammatory process than females. In a study on LT-α+252 genotype and mortality from sepsis, it was found that males with an AA genotype had a mortality of 72% compared with men who were GG who had a 42% mortality rate. In female patients the mortalities for the two genotypes were 53 and 33%, respectively. In a study on patients undergoing surgery for gastrointestinal cancer, it was found that post-operative C-reactive protein and IL-6 concentrations were higher in men than women and that in multivariate analysis, in which greater operation duration and blood loss in males was allowed for, males possessing the TNF-α – 308 A allele had greater responses than men without this allele. The genomic influence was not seen in females (Table 2).

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**Genotype insulin sensitivity and body fat mass and distribution**

Paradoxically, insulin insensitivity may, at first, exert a beneficial effect on the response to infection and injury, but has an adverse influence on chronic disease processes. Glucose and glutamine are major fuels for cells of the immune system. An insulin-insensitive state will reduce glucose uptake by tissues in which the process is insulin dependent (muscle) thereby increasing availability for tissues in which the process is not insulin dependent (immune tissue). During inflammation, secretion of catabolic hormones, which enhances muscle protein breakdown and glutamine release, will, as a secondary effect, oppose insulin action.

Many studies, conducted on large uninfected populations, have shown a clear link between obesity, oxidant stress and inflammation. As indicated above, the link lies in the ability of adipose tissue to produce pro-inflammatory cytokines. There is also a positive relationship between adiposity and TNF production. A positive correlation has been noted between serum TNFα, TNFβ production and BMI in non-insulin dependent diabetes.
mellitus patients and healthy women\(^{(39,40)}\). Thus plasma TAG, body fat mass and inflammation may be loosely associated because of these endocrine relationships. We investigated cytokine production in 139 healthy males and found that while there were no statistically significant relationships between BMI, plasma fasting TAG and the ability of peripheral blood mononuclear cells to produce TNF\(_\alpha\) in the study population as a whole, individuals with the LT-\(\alpha+252\) AA genotype (associated with raised TNF production) showed significant positive relationships between TNF production, BMI and fasting TAG\(^{(41)}\). Thus, although the study population was composed of healthy subjects, within that population were individuals with a genotype that resulted in in an ‘aged’ phenotype as far as plasma lipids, BMI and inflammation were concerned. Furthermore, individuals with the ‘aged’ phenotype may be disadvantaged should they become hospitalised. It has become clear recently that adipose tissue at different sites around the body has differing propensity for inflammatory mediator production. Visceral adipose tissue has a greater potential for production of these molecules than subcutaneous adipose tissue. This difference in capacity explains the adverse influence of visceral obesity on CHD and insulin insensitivity\(^{(42,43)}\).

**Influence of genotype on anti-inflammatory responses to nutrients**

As can be seen from the earlier sections of this paper, oxidant stress and genetic factors are potent determinants of pro-inflammatory cytokine production. A reduction in inflammatory stress can be achieved by feeding nutrients that either suppress pro-inflammatory cytokine production or act as antioxidants. Fish oil is in the first category and vitamin E and N-acetyl cysteine are in the second category. Rheumatoid arthritis and inflammatory bowel disease have been most successfully treated with fish oil\(^{(44)}\). The anti-inflammatory mechanism may be by means of suppression of pro-inflammatory cytokine production. Endres et al. showed that a large dose (15 g/d for 6 weeks) of the oil, in nine healthy volunteers, gave a small reduction in TNF\(_\alpha\) and IL-1\(\beta\) production from peripheral blood mononuclear cells\(^{(45)}\). Subsequently, less than half of 11 similar small intervention studies were unable to demonstrate a statistically significant reduction in cytokine production\(^{(20,46)}\). We have shown, however, that healthy subjects with the LT-\(\alpha+252\) A allele and IL-6 – 174 GG genotype responded to fish oil with a decrease in TNF\(_\alpha\). Likewise phenotype influences responsiveness. A BMI >25 kg/m\(^2\) bestows sensitivity to the anti-inflammatory effects of fish oil. Clearly, while the level of inflammation determines whether fish oil will exert an anti-inflammatory influence or not, and is influenced by both LT-\(\alpha+252\) and IL-6 – 174 G alleles, the precise genomic mechanism for an anti-inflammatory effect is unclear at present\(^{(2)}\).

Antioxidant intake also modifies cytokine production. In a study on healthy men and women and smokers, dietary supplementation with \(\alpha\)-tocopherol (600 IU/d) for 1 month suppressed the ability of PBMC to produce TNF\(_\alpha\). Production was reduced by 22 and 33% in non-smokers and smokers, respectively\(^{(47)}\). In a dietary intervention study on normolipaemic and hypertriglyceridaemic subjects given 600 IU \(\alpha\)-tocopherol/d for 6 weeks, reduced TNF\(_\alpha\), IL-1\(\beta\) and IL-8 production by lipopolysaccharide-stimulated blood mononuclear cells occurred\(^{(47,48)}\). A similar effect of \(\alpha\)-tocopherol was noted in a study on normal subjects and type 2 diabetics\(^{(49)}\). However, there were large standard deviations in the data from these studies, indicating major inter-individual variability in the ability of vitamin E (and antioxidant status) to suppress the production of the cytokine. This phenomenon suggests a significant genomic influence.

While a number of studies have shown that \(\alpha\)-tocopherol suppresses superoxide production, the situation with regard to nitric oxide is less clear\(^{(47,48)}\). At present, it is not known whether antioxidants interact with SNP in the genes associated with oxidant stress and inflammation in a differential manner as may occur with the other anti-inflammatory nutrient, \(n-3\) PUFA\(^{(2)}\).

**Conclusions**

Inflammation is both an essential process for human survival and one that plays a disadvantageous role in a wide range of diseases. Many of these diseases are common associates with the current epidemic of obesity that is assailing both industrialised and non-industrialised countries. Furthermore, the biological cost of this interrelationship is impacting adversely on health budgets. In addition to infective agents, inflammation can be induced by oxidant stress and obesity. The pro- and anti-inflammatory cytokines, nuclear transcription factors and antioxidant defences influence the intensity of this latter response. The recent insights from the characterisation of the human genome have revealed individual differences in the degree to which the key proteins in this physiological matrix are expressed. The variability in protein expression induced by SNP in the genes associated with the inflammatory process is being shown to be an important determinant of the strength of, and outcome from, the inflammatory process.

A number of studies have shown that these genomic factors impinge on a broad range of diseases. Studies are starting to show that individual responsiveness to nutrient therapy may be influenced by genomic factors. Thus individual responsiveness, to nutrients that can or might modulate inflammation, now has to be considered within the genomic framework that is currently unfolding during the post-genomic era. In this way the ‘cost’ of in-patient obesity may be reduced.

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