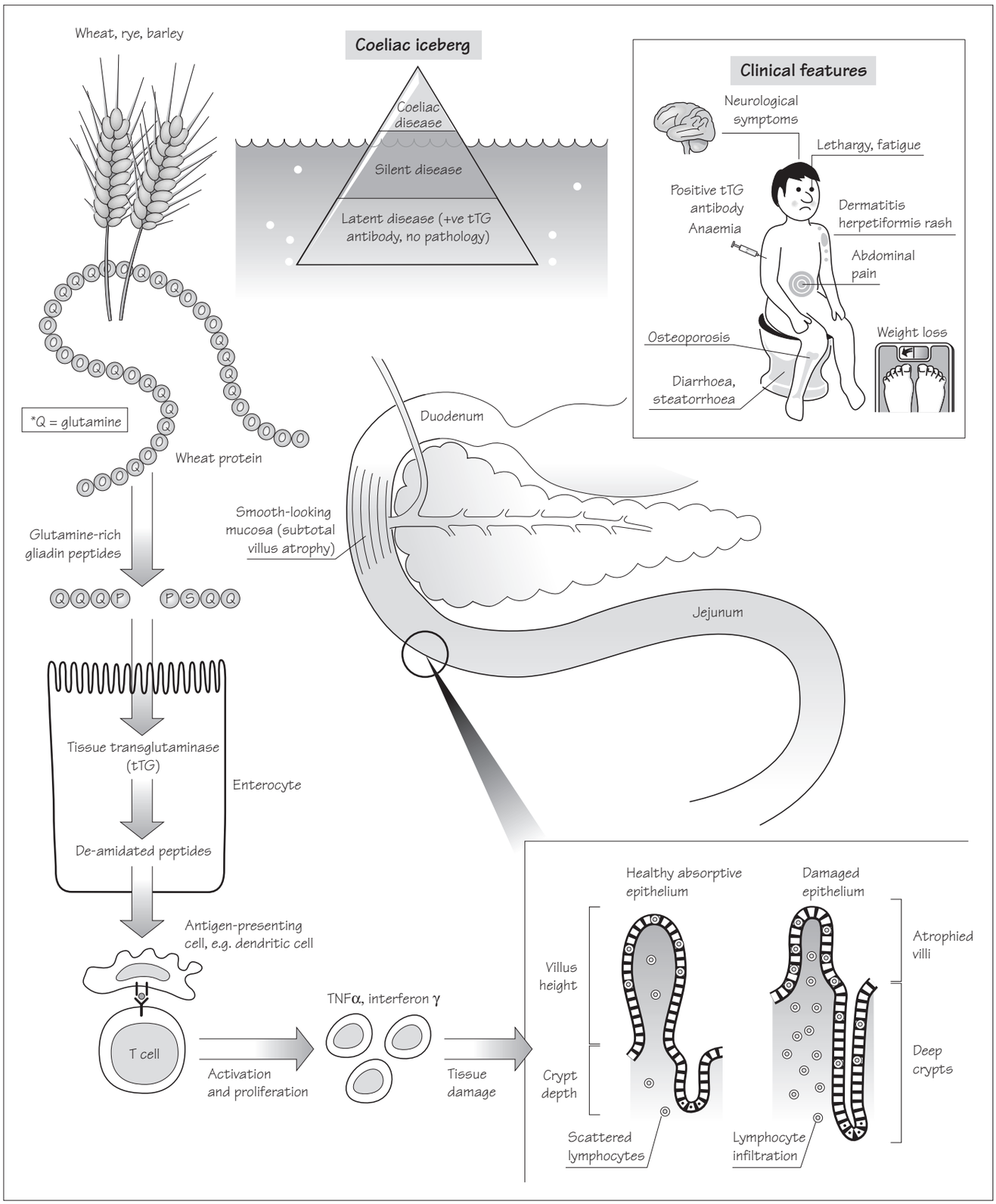
35 **Coeliac disease**



Coeliac disease is also known as **gluten enteropathy** because it is caused by immune reactivity triggered by glutamine- and proline-rich gluten proteins, found mainly in **wheat**, **rye**, **barley** and **oats**. The illness may become apparent at any age, from infancy to old age, may remain asymptomatic, and may be detected incidentally.

Aetiology and pathogenesis

The healthy small intestinal epithelium is maintained by constant cell turnover, and the balance between normal shedding of old epithelial cells at the tips of villi and the formation of new cells from **stem cells** in the crypts maintains a **2 : 1 ratio** between villus height and crypt depth. The **lamina propria** contains a small number of lymphocytes, macrophages, fibroblasts, capillary endothelial cells and other cells. The epithelium itself contains a population of resident **intraepithelial lymphocytes** that maintain **surveillance** against potential pathogens.

In **genetically susceptible** individuals, immunological reaction to gluten-derived **gliadin** peptides develops upon dietary exposure. The exact genes causing coeliac disease have not been identified but certain major histocompatibility complex (**MHC**) **class II** gene alleles are strongly associated with the condition. Early dietary exposure to gluten, particularly after **weaning** from milk, may increase the risk of developing the disease.

The ubiquitous cellular enzyme **tissue transglutaminase** (**tTG**), which normally cross-links glutamine residues with lysine in connective tissue proteins, plays an essential role in the pathogenesis, by converting glutamine residues in native gliadin peptides to glutamate, creating more immunogenic peptides. However no disease-associated polymorphisms in the *tTG* gene have been identified.

Lymphocytes react with the modified gliadin peptides on the surface of **antigen-presenting cells** and proliferate, increasing the number of intraepithelial and lamina propria lymphocytes. Activated lymphocytes secrete inflammatory mediators, including the **cytokines**, γ-interferon and tumour necrosis factor α (TNFα), **recruiting** and **activating** more inflammatory cells, altering the **proliferative rate** of intestinal epithelial **stem cells**, and increasing the rate of programmed cell death (**apoptosis**) in mature enterocytes. This creates an oedematous, swollen intestinal mucosa, with short, thick, blunt villi and deeper than normal crypts (**subtotal villus atrophy**), and the reduced epithelial surface area and compromised epithelial digestive and absorptive capacity leads to **malabsorption**.

The concentration of dietary gluten is highest proximally in the intestine and therefore coeliac disease affects the duodenum and proximal jejunum most severely.

Clinical features

Coeliac disease can become apparent at **any age**, although most cases are diagnosed in early childhood or in middle age. Coeliac disease may remain clinically silent and people with circulating antibodies to tTG, but no overt pathology, may be considered to have latent disease.

Malabsorption causes **diarrhoea** and **weight loss**. Inability to absorb fats results in **steatorrhoea**, with bulky, pale, foul-smelling stools that float in water, because of their high fat content. **Anaemia**, caused by iron deficiency is frequent. Malabsorption of calcium and vitamin D increases the risk of developing **osteoporosis**.

Nutrients that are mainly absorbed in the proximal small intestine, such as **iron** and **calcium**, are most affected by coeliac disease, while nutrients predominantly absorbed in the jejunum and ileum, such as **folic acid**, **vitamin C** and **vitamin B_{12}**, are affected only in more advanced disease.

Patients may complain of **abdominal pain** and **tiredness** and, for unknown reasons, **neurological complaints**, ranging from mild peripheral neuropathy to more severe central nervous system disturbance, occur in up to 10% of patients.

A small number of people develop a blistering rash called **dermatitis herpetiformis**, associated with antibodies to tTG reacting with a form of this enzyme in dermal cells.

Possibly as the result of chronic inflammation, people with uncontrolled coeliac disease are at increased risk of developing intestinal **neoplasms**, particularly intestinal **lymphoma**. This risk is substantially reduced by strict adherence to a gliadin-free diet (see Chapter 38).

All these signs and symptoms disappear when gliadin is omitted from the diet and reappear if it is reintroduced.

Diagnosis

Unexplained anaemia and vague abdominal and neurological symptoms should prompt the physician to check for coeliac disease, as it is often missed and is particularly common in some populations, such as people originating from western Ireland. Conversely, it remains rare among Africans.

Circulating **antibodies** to tTG offer an excellent serological marker of coeliac disease, with sensitivity and specificity approaching 100%. The test was first described as detecting an unknown antigen in the lining of oesophageal smooth muscle (endomysium), hence the term **anti-endomysial antibody**. This test replaces the **antigliadin** anti-body test that has lower sensitivity and specificity. Serological tests rely on detecting immunoglobulin A (**IgA**) antibodies and are unreliable in the 1 : 500 individuals with selective IgA deficiency (see Chapter 18).

Upper gastrointestinal **endoscopy** and duodenal **mucosal biopsy**, to confirm **subtotal villus atrophy** and lymphocytic infiltration, is performed before treatment, after initiating a gliadin-free diet, and again after reintroduction of a gliadin challenge diet, and is the gold standard of diagnosis. With the advent of reliable serological testing, it is now used less frequently.

Rare forms of small intestinal disease, such as Whipple's disease, Crohn's disease of the small intestine and **tropical sprue** may mimic coeliac disease and here a duodenal or jejunal biopsy may be particularly helpful in the diagnosis.

Treatment

The mainstay of treatment is for patients to follow a **gluten-free diet**. Wheat, rye and barley proteins are present in many ready-made meals and snacks, so the help of a professional dietician and a patients' association, such as the **Coeliac Society** in the UK, should be enlisted to maintain vigilance. In severe, uncontrolled coeliac disease, acute intestinal inflammation can be treated with corticosteroids, but this is hazardous and rarely indicated.