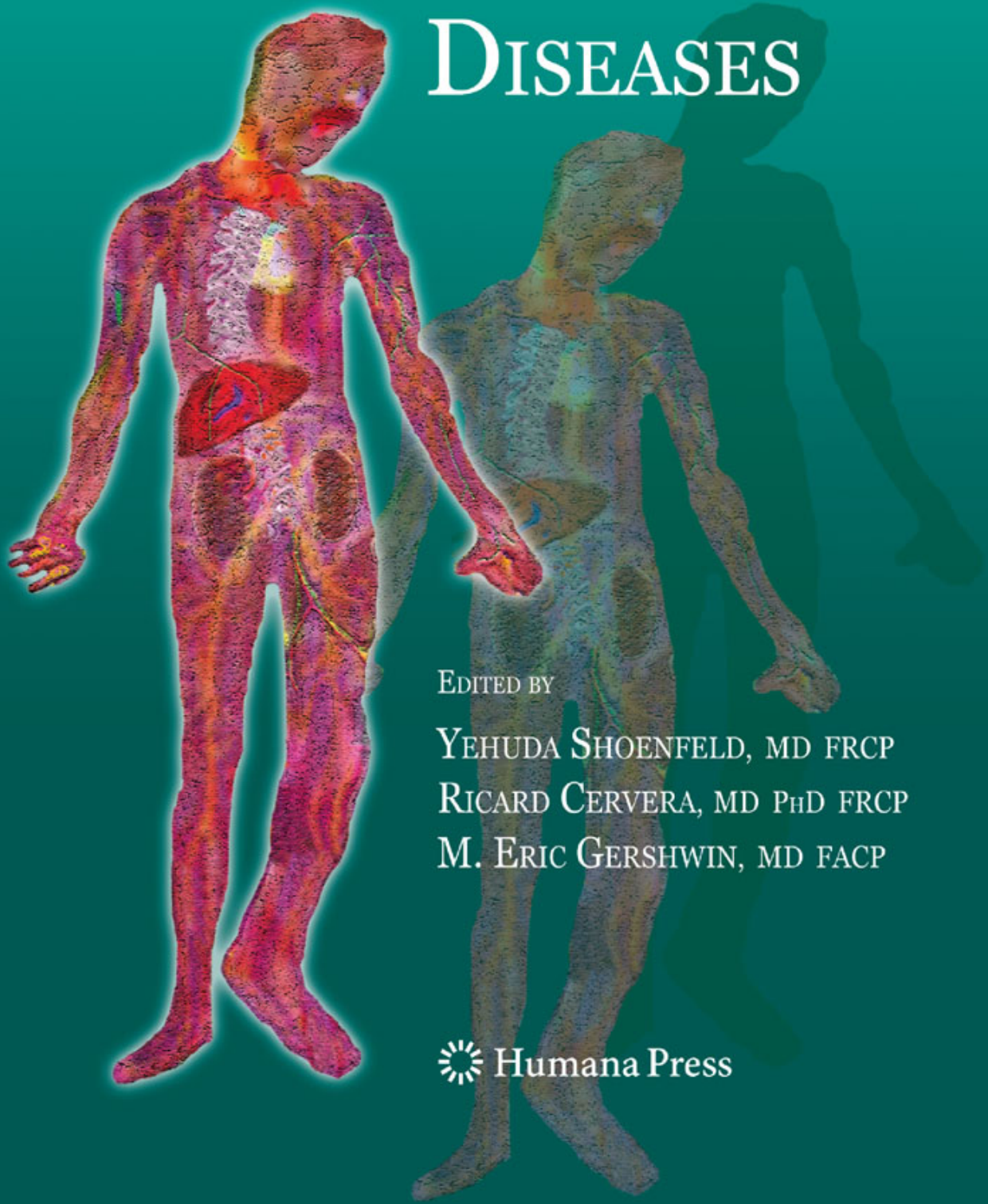
Diagnostic Criteria in Autoimmune Diseases



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Preface

Autoimmune diseases are a family of more than 100 illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. While many of these diseases are rare, collectively they affect, according to the Autoimmune Diseases Coordinating Committee (ADCC) of the U.S. National Institutes of Health, between 14.7 and 23.5 million people in the USA – up to 8% of the population – and their prevalence is rising. Because a complete cure is not available for nearly every one of these 100 autoimmune diseases, patients face a lifetime of illness and treatment. And, because most of these diseases disproportionately afflict women, and are among the leading causes of death for young and middle-aged women, they impose a heavy burden on patients' families and on society.

For these reasons, major efforts in autoimmune disease research and development must be directed toward reducing the impact of these conditions. These efforts should include, among other goals and again according to the ADCC, the generation of more accurate epidemiologic profiles of autoimmune diseases, the development of a greater understanding of the fundamental biologic principles underlying disease onset and progression, the provision of improved diagnostic tools to permit preclinical or presymptomatic diagnosis, the creation of more effective interventions, and the production of public and professional education and training programs.

For instance, the development of biomarkers can enable earlier diagnosis as well as aid physicians in selecting and monitoring treatment. New technologies, such as genomics and proteomics, can provide scientists with the tools to study gene and protein patterns in tissue samples, providing vital insights into the onset and progression of disease. However, we also need to gain a better understanding of the distribution of these diseases through epidemiologic studies, and of the environmental triggers that contribute to their onset. As we learn more about the genetic and environmental factors contributing to these diseases, we will be able to develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body, as also the ADCC points out.

But the first and most essential step in the management of autoimmune diseases is, no doubt, the recognition of the autoimmune disease itself by the attending physician. Autoimmune diseases can affect any part of the body, and have a myriad of clinical manifestations that make diagnosis an extremely difficult task. At the same time, autoimmune diseases share many features both at their onset and during follow-up. In addition, overlapping genetic traits enhance susceptibility to many of the diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family.

Conversely, despite the diversity in their presentation and natural history, autoimmune diseases share a number of underlying mechanisms, and thus have the potential to respond to treatment with the same or related therapies. More selective and less toxic immunosuppressive and immunomodulatory agents are currently being used to treat these disorders, and promising immune tolerance approaches are emerging. However, several factors limit our ability to conduct the most efficient clinical trials. For example, we lack standardized classification and diagnostic criteria for many autoimmune diseases.

These problems have prompted us to gather in a comprehensive book a critical review of 103 autoimmune diseases, dividing them into two main groups, namely systemic and organ-specific autoimmune diseases. We hope to offer a contemporary overview of these conditions with special emphasis on diagnosis. Each chapter contains the essential information required by attending physicians as well as bench scientists to understand the definition of a specific autoimmune disease, the diagnostic criteria, and the treatment. Moreover, established classification and diagnostic criteria have been quoted when available and, if not, authors have been asked to propose such criteria. *Diagnostic Criteria in Autoimmune Diseases* was conceived

for publication and debut on the occasion of the Sixth International Congress of Autoimmunity to be held in Porto, Portugal, on September 2008.

We have tried to produce a book of considerable intellectual caliber and this would not have occurred without the enthusiastic support of the authors. We wish to thank Richard Lansing and his staff at Springer for their hard work. The editors and all the contributors also extend special thanks to Kathy Wisdom for her devotion and zeal in helping us to put this volume together.

Finally, and most importantly, this text is dedicated to the sufferers of autoimmune diseases in the hope that they some day will be cured.

Yehuda Shoenfeld
Ricard Cervera
M. Eric Gershwin

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Pernicious Anemia

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Abstract Pernicious anemia (PA) is the most common manifestation of vitamin B_{12} deficiency, in which an autoimmune pathogenesis is supported by (a) the presence of mononuclear-cell infiltration into gastric mucosa with loss of parietal cells, (b) autoantibodies to parietal cells and intrinsic factor, (c) autoreactive T cells, (d) regeneration of parietal cells after therapy with corticosteroids or immunosuppressive drugs, (e) familial predisposition and (f) association with other autoimmune diseases. The progression of the chronic atrophic gastritis to gastric atrophy and clinical anemia is likely to span 20 to 30 years. The presence of serum antibodies to gastric parietal-cells predicts autoimmune gastritis. Immune suppression with corticosteroids or azathioprine appears to be the best treatment in early stages of the disease.

Keywords Pernicious anemia · vitamin B_{12} deficiency · type A gastritis

Pernicious anemia (PA) also known as *Biermer's anaemia, Addison's anaemia* or *Addison-Biermer anaemia,* is a form of megaloblastic anemia due to vitamin B_{12} (Cbl) deficiency; it is an autoimmune disease resulting from antibodies against intrinsic factor (IF) and gastric parietal cells (1); gastric atrophy probably resulting from immune destruction of the acid and pepsin-secreting portion of the gastric mucosa.; PA is considered as a chronic illness in which there is impaired absorption of vitamin B_{12} in the terminal ileum because of a lack of IF (secreted by the parietal cells of the gastric mucosa) (2); its usual course is slowly progressive and is the most common cause of vitamin B_{12} deficiency and, at the end stage, of the type A atrophic gastritis influencing the fundus and body of the stomach (3).

Epidemiology

Traditionally, pernicious anemia was believed to occur predominantly in people of northern European descent as well as in older populations because multiple epidemiological studies have shown that the average age of onset of pernicious anemia is greater than 60 years, with an increasing frequency with advancing age. Moreover, Carmel et al. (4) in a population survey found that 1.9% of persons more than 60 years of age have undiagnosed pernicious anemia. Nowadays, it has become apparent that the occurrence of PA in all racial and ethnic groups is more common than was previously recognized. Accordingly, reports of small case series of Chinese PA patients have emerged: Wun Chan et al. (5) recently found that 224 of 296 (76%) Chinese with megaloblastic anemia had PA. In fact the incidence is increasing in women and older adults because the diagnosis is unusual before 35 years of age, although typical pernicious anemia can be seen in children under 10 years of age (juvenile pernicious anemia) (3) and the overall prevalence of undiagnosed PA over age 60 years of age is 1.9% (4). In general, the prevalence is 80 cases per 100,000 individuals and the prevalence is highest in women (2.7%), particularly in black women (4.3%) and is less common in southern Europeans and Asians (6).

History

Pernicious anemia was first described in 1849 by the English physician Thomas Addison; later on, Austin Flint in 1869 linked the anemia with alterations of the stomach. (7) The name "pernicious anemia" was coined in 1872 by the German physician Anton Biermer. The studies of George H. Whipple on the effects of feeding liver in anemia followed by those of George R. Minot and William P. Murphy on the effects of feeding liver specifically in pernicious anemia led to the cure of pernicious anemia and to their receiving the Nobel Prize in 1934. As a result, it was suggested that the anemia was caused by lack of an

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extrinsic factor found in liver that was vitamin B-12 and an intrinsic factor in gastric secretion. Afterward, a serum inhibitor factor of intrinsic factor and autoantibodies to parietal cells were discovered (8) giving an immunological explanation of the underlying gastritis that caused pernicious anemia. Also in the 1950 s and 1960 s, the Schilling test became established.

Pathogenesis

A genetic predisposition to PA is suggested by clustering of the disease and of gastric autoantibodies in families, and by the association of the disease and gastric autoantibodies with the autoimmune endocrinopathies. About 20% of the relatives of patients with PA have PA. These relatives, especially first-degree female relatives, also have a higher frequency of gastric autoantibodies than normal. Recently, Junca et al. (8) detected early abnormalities in gastric function in first-degree relatives of patients with PA. About 23% of these relatives had parietal-cell antibodies. The disease is associated with HLA types A2, A3, A7, and B12 and with blood group A (9). The pathological process associated with type A gastritis appears to be directed toward the gastric parietal cells, shown by pathologic lesions restricted to parietal cells and the presence of autoantibodies to parietal cells and to their secretory product, intrinsic factor, in the serum and gastric juice. Evidence has shown that H^+/K^+-ATPase is the antigen recognized by parietal-cell autoantibodies (10). This enzyme has a highly conserved catalytic (α) subunit that is phosphorylated during reaction cycles. Gastric H^+/K^+-ATPase is responsible for secretion of hydrogen ions by parietal cells in exchange for potassium ions. Autoantibodies to parietal cells bind to both the 100-kd catalytic (α) subunit and the 60-to-90-kd glycoprotein (β) subunit of gastric H^+/K^+-ATPase. Although parietal-cell autoantibodies can fix complement and lyse parietal cells in vitro, it is unlikely that these autoantibodies are pathogenic in vivo, because gastric H^+/K^+-ATPase is not accessible to circulating antibodies. The importance, if any, of an early observation that passive transfer of parietal cell autoantibodies to rats resulted in reduction in parietal-cell mass without an inflammatory response is therefore uncertain. This particular finding could reflect that cell loss is due to antibody-triggered apoptosis, as has been forwarded for other pathophysiological conditions (11). A report describing autoantibodies that bind to the gastrin receptor was not confirmed. The results of studies showing reactivity of parietal-cell autoantibodies with the surface membranes of parietal cell in vitro may be explained by the loss of cell polarity after cellular dissociation (12). Pathogenic CD4+ T cells are reactive to the parietal cell autoantigen, H^+/K^+ ATPase, and are controlled by CD4+CD25+ T cells in an immunosuppressive cytokine-independent manner. Comparison of CD4+CD25+ T cell-mediated suppression in other autoimmune models shows inconsistencies with respect to requirements of cytokines for immunosupression. More recent data, however, indicate that the evidence for requirement of IL-10 and TGF-β could be due to the complex nature of the T cells causing the disease, as well as the role of induced regulatory T-cell populations. Evidence from this model indicates that immune responses must be initiated and then CD4+CD25+ T cells are recruited to control the quality of the immune response (10, 12). Finally, anemia, the principal feature of PA is caused by malabsorption of vitamin B_{12} in the terminal ileum due to intrinsic-factor deficiency.

Clinical Manifestations

The classic triad of weakness, sore tongue, and paresthesias may be elicited but usually is not the chief symptom complex, because the onset of PA is insidious and unclear and progresses slowly. Generally, the anemia is often well tolerated in this disease and many patients are ambulatory. The median age at diagnosis is 60 years; however, childhood PA has been reported associated with genetic failure to secret intrinsic factor or the secretion of a defective intrinsic factor (13). Symptoms of anemia are the usual presentation, but asymptomatic patients can be identified by routine hematologic investigation. Generally, the presentation of pernicious anemia resembles that of any other form of anemia. Mainly, neurological complications secondary vitamin B_{12} deficiency are developed which may cause peripheral neuropathy (paresthesias and numbness) and lesions in the posterior (loss of vibration and position sense, sensory ataxia) and lateral columns (limbs weakness, spasticity, and extensor plantar response) of the spinal cord and in the cerebrum. These lesions progress from desmyelination to axonal degeneration and eventual neuronal death (14). Megaloblastic madness is less common and can be manifested by delusions, hallucinations, outbursts, and paranoid schizophrenic ideation. Identifying the cause is important because significant reversal of these symptoms and findings can occur with vitamin B-12 administration. Also, patients with PA may develop several abnormalities of the digestive tract such as atrophic glossitis characterized by smooth and beefy, tongue megaloblastosis of the epithelial cells of the small intestine that results in diarrhea and malabsorption. Instestinal metaplasia is a risk factor for adenocarcinoma (15). Achlorhydria and bacterial overgrowth may also lead to the formation of carcinogenic nitrosoamines. The cardiovascular system is also affected; cardiac output is usually increased with hematocrit less than 20%, and the heart rate accelerates; therefore, in patients with preexisting heart disease, coronary insufficiency and congestive heart failure can occur. On the contrary, PA has been associated with common

TABLE 94.1. Clinical manifestation of PA.

Clinical Manifestation	Prevalence %
Anemia	30–60
Neurological complications	10–28
Peripheral neuropathy	0.6
Degeneration of cord	2.8
Dementia	5
Gastrointestinal complication	15
Glositis	1–3
Gastric carcinoma	

variable immunodeficiency and low serum immunoglobulin concentrations. Prevalence of clinical manifestations is shown in Table 94.1. PA may be associated with other autoimmune diseases such as autoimmune thyroiditis, insulin-dependent diabetes mellitus, Addison's disease, primary ovarian failure, primary hypoparathyroidism, Grave's disease, vitiligo, myasthenia gravis, and the Lambert-Eaton syndrome.

Pathological Features

Chronic atrophic gastritis is recognized macroscopically by loss of gastric mucosal folds and thinning of the gastric mucosa. It can be classified into two types according to whether the lesion affects the gastric antrum. Type A (autoimmune) gastritis involves the fundus and the body of the stomach and spares the antrum. It is associated with PA, autoantibodies to gastric parietal cells and to intrinsic factor, achlorhydria, initial low serum gastrin concentrations, that later result in hyperplasia of gastrin-producing cells. Type B gastritis is usually associated with *Helicobacter pylori* infection (10). The most common lesion in gastric-biopsy specimens from PA patients are mononuclear cellular infiltrates in the submucosa extending into the lamina propria between the gastric glands; extension of the cellular infiltrate into the mucosa is accompanied by degenerative changes in parietal cells and zymogenic cells. The cellular infiltrate includes plasma cells and T cells (16). Thereafter, the mucosa becomes atrophic, containing few pepsin-secreting and parietal cells, and then intestinal metaplasia is established. The chronic atrophic gastritis in PA is also associated with an increased risk of intestinal-type gastric cancer and gastric carcinoid tumors. The latter are presumably due to prolonged achlorhydria resulting from parietal-cell loss, compensatory hypergastrinemia, and argyrophilic cell hyperplasia. The bone marrow biopsy and aspirate usually shows that erythroid precursors are large and often oval. The nucleus is large and contains course motley chromatin clumps, having a checkerboard appearance. Nucleoli are visible in the more immature erythroid precursors. Giant metamyelocytes and bands are present, and the mature neutrophils and eosinophils are hypersegmented. The bone marrow histology is similar in both folic acid and Cbl deficiency. The megaloblastic changes due to Cbl deficiency can be reversed by pharmacological doses of folic acid but not otherwise. (17).

Hematologic Features

Laboratory abnormalities found in PA with established megaloblastic anemia are summarized in Table 94.2. The most important laboratory finding observed in PA is erythrocytic macrocytosis which is obvious when the mean cell volume (MCV) is greater than 100 fL (1, 17). The MCV and mean corpuscular hemoglobin (MCH) are increased, with a mean corpuscular hemoglobin concentration (MCHC) within the reference range. In addition, the peripheral blood usually shows a mild leukopenia and thrombocytopenia or pancytopenia, which parallel the severity of the anemia because vitamin B12 deficiency affects all hematopoietic cell lineages (10). Examination of the marrow is not indicated if the diagnosis is unequivocal; the earliest sign of megaloblastosis reflected in the peripheral blood smear is hypersegmentation of the polymorphonuclear leukocytes followed by the appearance of oval macrocytes, and anisopoikilocytosis (17).

Serological and Biochemical Features

Diagnosis of PA is supported by measuring blood levels of Cobalamin (Cbl) and folate; Cbl is low in most but not all patients with cobalamin deficiency. Patients with vitamin B12 deficiency will have serum levels <170 pg/mL, with symptomatic patients usually having levels <100 pg/mL. The diagnosis is best confirmed by finding an elevated level of serum methylmalonic acid (>1000 nmol/L); in fact, two metabolic markers, plasma methylmalonic acid (MMA) and plasma total homocysteine (tHC), are generally considered as more sensitive indicators of vitamin B12 status than plasma cobalamin levels. MMA and tHC are elevated in vitamin B12 deficiency (17). Normal MMA and

TABLE 94.2. Hematological findings in PA patients.

Peripheral blood
Macrocytosis with hypersegmented polymorphonuclear leucocytes.
Anemia
Leukopenia
Thrombocytopenia or
Pancytopenia
Bone marrow
Megaloblasts
Large myeloid precursors ("gyant metamyelocytes")
Low serum vitamin B_{12} concentrations
Normal serum folate concentrations
Positive Schilling test
Low serum holotranscobalamin concentrations

TABLE 94.3. Prevalence of autoantibodies to gastric parietal cells in several situations.

Patients with pernicious anemia	90%
Patients with simple atrophic gastritis	60%
Nonanemic first-degree relatives of patients with PA	30%
Normal subjects in the third decade	2.5%
Normal subjects in the eight decade	9.6%

homocysteine levels rule out cobalamin deficiency with 100% confidence, and normal homocysteine levels suggest that megaloblastic anemia is not caused by folate deficiency, since only tHC is elevated in folic acid deficiency (18). However an increased concentration of plasma methylmalonic acid (P-MMA) does not predict clinical manifestations of vitamin B_{12} deficiency and should not be used as the only marker for diagnosis of B_{12} deficiency. A Schilling test will confirm that vitamin B_{12} deficiency is the results of intestinal malabsorption due to intrinsic-factor deficiency. The Shilling test assay for cobalamin absorption consists of measuring urinary radioactivity after an oral dose of radioactive cobalamin is given: Absorption is low in PA, and it increases if radioactive vitamin B_{12} is administrated along with intrinsic factor (17). In patients with PA, serum antibodies that recognize the H^+/K^+-ATPase occur. Table 94.3 shows the prevalence of autoantibodies in PA. Antiparietal cell antibodies also occur in a significant percentage of patients with thyroid disease (1), and conversely, patients with PA have a higher than expected prevalence of antibodies against thyroid epithelium, lymphocytes, and renal collecting duct cells. Serum antibodies to gastric parietal cells can be detected by indirect immunofluorescence with unfixed, air-dried, frozen sections of mouse stomach in which the antibodies stain parietal cells. Antibodies to intrinsic factor ("type I" or "blocking," antibodies) or the intrinsic factor–cobalamin complex ("type II" or "binding," antibodies) are highly specific to PA patients. Type I autoantibodies are demonstrable in the serum of about 70% of patients with PA. Type II autoantibodies are found in the serum of about 35–40% of patients, and rarely occur in the absence of type I antibodies. Both types of autoantibodies can be detected more frequently in gastric juice than in serum (16).

Diagnostic Criteria

There are no diagnostic criteria for PA; however the presence of hematologic disorders, such as megaloblastic anemia, with positive Schilling test and type A chronic atrophic gastritis with loss of gastric parietal cells can support the diagnosis.

Prognosis

PA is a silent disease until its advanced or end stage. The prognosis depends of the stage of the disease when the diagnosis is made. Neurological complications may not be reversed even when the treatment is begun. On the contrary, if gastric cancer or gastric carcinoid tumors are developed, the prognosis will also depend on the early diagnosis and treatment. Because PA is associated with achlorhydria there is a 3-fold likelihood of developing gastric carcinoma; therefore periodic endoscopy is recommended approximately every 5 years, even in asymptomatic cases, to rule out gastric polyps or gastric carcinoma.

Predicting Role of Autoantibodies

The presence of serum gastric parietal cells predicts autoimmune gastritis. Anti parietal cells and anti-intrinsic factor antibodies are rarely measured in individuals with megaloblastic anemia, even though the anti-intrinsic factor antibodies in particular could be of considerable diagnostic value. Anti-intrinsic factor antibody is highly specific for PA (although its sensitivity is only modest), and its presence in megaloblastic anemia makes the diagnosis of PA almost certain.

Therapeutic Management

The first standard treatment widely used was a regular monthly intramuscular injection of at least 1 mg of vitamin B12 to correct the vitamin deficiency (4). Therapeutic management is summarized in Table 94.4. However, nowadays there are different proposed schedules:

(a) Therapy consisting of five to six intramuscular injections of hydroxocobalamin (1 mg each) over a 3-week period. Patients are then given 1 mg intramuscularly every 3 months for life (19). This regimen corrects the hematological abnormalities and replaces B12 stores.
(b) Therapy consisting of intramuscular injection of hydroxocobalamin 1 mg three times a week for two weeks and then once every 3 months for life. Daily dosing is given initially if there is neurological involvement (20).

These two treatments correct the anemia and may correct the neurological complications if given soon after their onset.

There is little evidence of a satisfactory hematological, biochemical, and clinical short-term response for oral B12 replacement in some randomized controlled trials. The evidence derived from limited studies suggests that high oral doses of B12 (1000 and 2000 mg daily) could be as effective as intramuscular administration in achieving hematological and neurological responses (21). Accordingly, high doses of oral vitamin B12 (1000 mg) initially

TABLE 94.4. Pharmacological treatment of pernicious anemia.

	Acute treatment	Dose	Duration	Maintenance	Dose	Duration
A	Hydroxocobalamin	100 mcg IV every other day	3 weeks	Hydroxocobalamin	100 mcg IV	Every 3 months for life
B	Hydroxocobalamin	100 mcg IV 3 times a week	2 weeks	Hydroxocobalamin	100 mcg IV	once every 3 months for life
C	Hydroxocobalamin	1000–2000 mg VO daily	120 days	Not available data		
D	Hydroxocobalamin	1000 mg VO		Not available data		

daily, thereafter weekly, and then monthly, are as effective as intramuscular vitamin B12 (22).

In the meantime, for newly diagnosed patients with vitamin B12 deficiency secondary to pernicious anaemia, who have an intact terminal ileum, an initial intramuscular dose of vitamin B12 followed by a trial of oral replacement may be considered (21). This recommendation is based on the observation that about 1% of vitamin B12 is absorbed by mass action in the absence of intrinsic factor.

A further large, pragmatic trial in primary care is needed to determine whether oral vitamin B12 is effective in patients with pernicious anaemia in primary care settings, but this therapy should not be used in hospitalized/critical patients.

Precautions in the therapy replacement of B12 deficiency should be considered:

- Administration of folic acid in a patient with vitamin B12 deficiency may induce a hematological response but will worsen any neurological symptoms, and can actually precipitate subacute combined degeneration of the cord (19).
- Patients with pernicious anaemia should also be given oral iron, because most will soon exhaust their iron stores (20).

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Idiopathic Aplastic Anemia

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Abstract Aplastic anemia, an uncommon hematological disease, is the paradigm of the human bone marrow failure syndromes. The pathophysiology is immune mediated in most cases, with activated type 1 cytotoxic T cells implicated. The molecular basis of the aberrant immune response and deficiencies in hematopoietic cells is now being defined genetically; examples are telomere repair gene mutations in the target cells and dysregulated T-cell activation pathways. Almost universally fatal just a few decades ago, aplastic anemia can now be cured or ameliorated by stem-cell transplantation or immunosuppressive drug therapy. Immunosuppression with antithymocyte globulins (ATGs) and cyclosporine is effective at restoring blood-cell production in the majority of patients, but relapse and especially evolution of clonal hematologic diseases remain problematic. Allogeneic stem-cell transplant from histocompatible sibling donors is curative in the great majority of young patients with severe aplastic anemia; the major challenges are extending the benefits of transplantation to patients who are older or who lack family donors.

Keywords Aplastic anemia · pancytopenia · $CD34^+$

Definition

The term "aplastic anemia" was introduced by Vaquez and Aubertin in the year 1904. The word "aplastic" is derived from the Greek "a" and "plasso" meaning "without form." "Anemia" is a potentially misleading term, as patients with aplastic anemia fail to form blood cells from all three lineages. The combination of peripheral cytopenias with a decreased or absent bone marrow precursor cells characterizes aplastic anemia. Although there are many known etiologies (Table 95.1), the cause of aplastic anemia is generally difficult to determine in an individual patient, and in the vast majority of cases, no causal etiology can not be found. At times, multiple risk factors can be uncovered in a given patient (Table 95.1).

Epidemiology

A large, prospective study conducted in Europe and Israel between 1980 and 1984 that required stringent case definition and pathologic confirmation reported an annual incidence of aplastic anemia of 2 new cases per 1 million population per year (1). Aplastic anemia occurs two- to three-fold higher in the Far East than in the West. This geographic variation likely stems from environmental rather than genetic risk factors, because the Japanese population in Hawaii manifests similar rates of aplastic anemia as other Americans (2). Studies have not been able to attribute the increased risk of aplastic anemia in the Far East to specific agents, such as chloramphenicol, widely used in Asia (3).

The incidence of acquired aplastic anemia varies bimodally with age, with one peak between ages 15 and 25 years and another peak at older than 60 years of age (4). Aplastic anemia occurs with equal frequency in both genders (1, 2).

Pathophysiology

An immune mechanism was implied decades ago from the recovery of hematopoiesis in patients who failed to engraft after stem-cell transplantation, when renewal of autologous blood-cell production was credited to the conditioning regimen. Also suggestive was that the majority of syngeneic transplantations in which bone marrow was

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