Abstract. Myeloproliferative disorders (MPD) constitute a subset of hematological malignancies characterized by a stem cell-originated clonal proliferation of aberrant myeloid cells, one of which is polycythemia vera (PV). PV is the most common myeloproliferative disorder with an annual incidence of at least 23 cases per million in North America and Western Europe. PV patients suffer high risk of thrombotic and hemorrhagic complications and propensity to clonal evolution to acute leukemia and myelodysplastic syndrome. Current treatment involves reduction of whole blood erythrocytosis by phlebotomy to reduce blood viscosity and use of myelo-
suppressive therapy. On average, after 10 years of treatment, a significant portion of PV patients (5–15%) progress to postpolycythemic myeloid metaplasia and/or leukemia; the majority of these patients (70%) die within 3 years. Distinguishing PV from other polycythemic disorders can be very challenging and in this chapter PV will be discussed in the context of other polycythemic disorders. Recent research breakthroughs in the understanding of its molecular basis have improved our understanding of PV pathophysiology and open the possible vista of specific pharmaceutical intervention.

17.1 Introduction

Polycythemia means “too many cells in the blood” derived from the Greek for “many,” “cells,” and “blood.” Another term, erythrocytosis, derived from the Greek for “red” and “cells,” is also frequently used. For historical purposes, the two terms are loosely equivalent and no consensus on which term to use has been achieved. Because erythrocyte is the most abundant cell type, polycythemia actually means “too many red blood cells.”

True polycythemia is defined as an elevated erythrocyte mass in excess of 32 mL/kg for males and 28 mL/kg for females (Berlin 1975). Relative polycythemia can result from a decrease of plasma volume instead of an actual increase of erythrocyte mass and will not be discussed here.

17.2 Classifications of Polycythemia

Polycythemias can be classified according to their cellular and molecular basis (Prchal 2001b). Primary polycythemias are caused by inherited or acquired genetic defects affecting the primary cells (hematopoietic progenitors), leading to dysregulated proliferation. Biochemical parameters associated with this condition include:

1. Decreased or a low normal serum erythropoietin (Epo) levels, and
2. Excessive erythroid proliferation in response to cytokines [e.g., Epo, Insulin-like growth factor 1 (IGF-1)] (Prchal 2001b).

Clinical entities comprising primary polycythemias include:

1. Polycythemia vera (PV), a clonal precursor to malignant development,
2. Primary familial congenital polycythemia (PFCP),
3. Chuvash polycythemia (with features of both primary and secondary polycythemia).

Secondary polycythemias are caused by extrinsic factors such as elevated or inappropriately normal serum levels of Epo, IGF-1 or cobalt (Jacobson et al. 2000). These extrinsic factors (e.g., Epo) overstimulate erythropoiesis in the bone marrow in excess of the physiological needs “inappropriate polycythemias;” or appropriately respond to hypoxic stimulus “appropriate polycythemia.” Elevated hematocrit in turn leads to increased viscosity and at extreme ranges of elevation to decreases in tissue oxygen delivery (Prchal 1995). Biochemical parameters associated with this condition are:

1. Elevated (or inappropriately normal for elevated red cell mass) circulating Epo levels, and

Based on physiological requirements, secondary polycythemias can present as (Prchal and Prchal 1999):

1. Physiologically appropriate elevation of Epo in response to tissue hypoxia (polycythemias of high altitude, chronic mountain sickness, chronic pulmonary disease, cyanotic heart disease, hemoglobin variant with abnormal oxygen affinity, 2,3-diphosphoglycerate (DPG) deficiency, and methemoglobinemia).
2. Physiologically inappropriate Epo production in the absence of tissue hypoxia (paraneoplastic Epo production, renal cysts, liver tumors, pheochromocytoma, post kidney transplant polycythemias, and drug-induced polycythemia such as seen in Epo doping).

17.2.1 Genetics of Polycythemia

Most polycythemias are acquired, but both primary and secondary polycythemias may be inherited (Prchal 2003). There are dominant and recessive forms of inherited polycythemias. Polycythemia can also be associated with genetic syndromes such as von Hippel Landau syndrome, hereditary hemorrhagic telangiectasia, glycogen storage disease type VII (also known as Tarui disease), fibrocystic pulmonary dysplasia, and hypokalemic alka-