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In 1903, William Osler published his classic report, "Chronic Cyanosis, with Polycythemia and Enlarged Spleen; A New Clinical Entity", in which he described the clinical characteristics and diagnostic criteria for the disease we call polycythemia vera, a disorder in which there is overproduction of red cells, white cells and platelets and splenomegaly. Osler's diagnostic criteria were modified later by the Polycythemia Vera Study Group to include laboratory tests not available to him, and these criteria became the gold standard for the diagnosis of the disease for the rest of the twentieth century. Epidemiologic studies based on these diagnostic criteria held that polycythemia vera was most common in men, with a median age of 60 years at diagnosis. In 2005, a little over 100 years after Osler's seminal paper, an activating mutation (V617F) in an important blood cell enzyme, Janus Kinase 2 (JAK2) was discovered in the blood cells in polycythemia vera and in its companion myeloproliferative disorders, essential thrombocytosis and primary myelofibrosis. JAK2 is necessary for the growth of red

# Genes and Polycythemia Vera

cells, white cells and megakaryocytes, the progenitor cells for platelets, and its activity is normally tightly controlled. The V617F mutation allows the enzyme to be continuously active, resulting in unrestricted blood cell production. Of the three disorders, polycythemia vera is not only the most common, but also the only one in which JAK2 V617F is found in most of the patients. The reason for this is that polycythemia vera is the ultimate expression of this JAK2-activating mutation, which drives the expansion of all three of types of blood cells, but in many patients there exist other genetic or epigenetic processes that prevent this from occurring despite the presence of the V617F mutation. In others, mutations in genes downstream from JAK2 can cause a phenotypically similar myeloproliferative disorder.

We can, therefore, now say that in the 21st century, we have entered the molecular era of diagnosis and management of the chronic myeloproliferative disorders and it is now easier to distinguish polycythemia vera, essential thrombocytosis and primary myelofibrosis from the many benign and malignant disorders that mimic them. As a consequence, it has been of interest to reassess the epidemiology of polycythemia vera as well as its companion disorders with informative results. First, we now recognize that not only is essential thrombocytosis

more common in women than in men but, contrary to the initial observations, polycythemia vera is as well. Second, women also are more likely to develop the polycythemia vera earlier in



life than men and, in particular, below age 40. Third, women with polycythemia vera have different disease manifestations than men, most strikingly, a predilection for intra-abdominal venous thrombosis, often as the first manifestation of the disorder. Fourth, in contradistinction to men, and in keeping with the female predilection for essential thrombocytosis, where the number of blood cells containing the JAK2 V617F is usually low, the number of blood cells containing JAK2 V617F is lower in women with polycythemia vera than in men. Interestingly in this regard, in a pregnant myeloproliferative disorder patient, the number of blood cells expressing JAK2 V617F declines during the pregnancy, only to increase again after the pregnancy terminates. Fifth, in keeping with the higher

incidence of polycythemia vera in women, is the predilection of female essential thrombocytosis patients to evolve into polycythemia vera. It is also of interest that there is no sex predilection for primary myelofibrosis and in this regard, the transformation of polycythemia vera to primary myelofibrosis, which occurs in only a small number of patients, also shows no sex

predilection. The biologic basis for these sex-related preferences is unknown but is clearly genetically based since we have observed that men with polycythemia vera dysregulate almost two times as many genes in their stem cells as women, and different genetic pathways are activated in these stem cells in each sex. At the same time, in keeping with clinical observations, those men and women polycythemia vera patients who transform into primary myelofibrosis dysregulate a common set of genes. Furthermore, different genes are dysregulated polycythemia vera and essential thrombocytosis. Such changes in disease gene dysregulation hold promise for developing new molecular markers for a more precise distinction between the three chronic myeloproliferative disorders,

since they all share in expression of JAK2 V617F and thus, have certain clinical features in common as well, making their distinction based on clinical grounds often difficult. Equally important, based on our current knowledge of gene dysregulation in polycythemia vera, we have been able to develop a

set of molecular markers for accurately identifying which polycythemia vera patients will transform into primary myelofibrosis, and which will have a more benign course. This should enable us to avoid exposing many polycythemia vera patients to unnecessary and potentially toxic therapies,

while initiating treatment earlier in the course of the disease in those patients who are going to have a more aggressive clinical course. Finally, with knowledge of the specific molecular pathways that are dysregulated in polycythemia vera and, hopefully, in the future, in essential thrombocytosis and primary

myelofibrosis as well, we should be able to design rationally based therapy targeting those specific pathways alone, thus avoiding nonspecific drug toxicity while eradicating the disease process.