Glucose 6-phosphate dehydrogenase (G6PD) has been known in biochemistry since it was discovered by Otto Warburg in 1932 in yeast and in red cells; and it has been known in haematology since it was discovered by Paul Carson in 1956 that its genetically determined deficiency was responsible for the acute haemolytic anaemia (AHA) that follows administration of primaquine (PQ) in some but not in all people. Since that time it has become clear that G6PD deficiency is one of the commonest genetic abnormalities world-wide (estimated over 500 million people affected), but it is generally benign, because for most of their lifetime people with this trait remain asymptomatic, and thus not aware of it.

G6PD deficiency accounts for three distinct clinical syndromes. (1) AHA induced by drugs, infection or ingestion of fava beans (favism). AHA may vary from mild to severe; and it may be life-threatening especially in children, when emergency blood transfusion may be life-saving. The haemolysis is both intravascular (causing haemoglobinuria) and extravascular; its basic mechanism is injury to red cells that, being G6PD deficient, have a decreased capacity to withstand oxidative damage. Favism is still today probably the most prevalent manifestation of G6PD deficiency, and thus a public health issue. (2) Neonatal jaundice (NNJ). In most G6PD deficient newborns jaundice is not severe: either it requires no treatment, or phototherapy may suffice; however, when it is severe and it is not appropriately treated – by exchange transfusion when necessary – it may produce permanent neurological damage which, in some populations, may be in fact a major cause of disability. It is not yet fully understood why NNJ associated with G6PD deficiency is more severe in some babies than in others: but one factor that has been identified is co-existence of the UDP-glucuronyltransferase (UGT1A1) mutation that is responsible for the Gilbert syndrome. (3) Chronic non-spherocytic haemolytic anaemia (CNSHA). Unlike AHA and NNJ, CNSHA is a very rare manifestation of G6PD deficiency: as the name suggests, it is a life-long condition of variable severity, that can benefit significantly from splenectomy.

The G6PD gene maps to the sub-telomeric region of the X chromosome, in a region fully subject to the X inactivation phenomenon. There is now a database of over 180 G6PD mutations: all of them are point (missense) mutations or small in-frame deletions, and in all cases there is some residual G6PD enzyme activity: supporting the notion that a null mutation would be lethal, as has been proven to be the case in the mouse. The 3D structure of human G6PD has been now solved, and by the spatial location of individual amino acid replacements we have a reasonably good idea as to why some mutations are sufficiently mild so that they have become polymorphic, whereas others are only sporadic or unique. The former group underlie AHA and NNJ, whereas the latter group underlie CNSHA.

This is all part of history. In the second part of this review I intend to concentrate on aspects of the G6PD system that are novel, not universally understood, or controversial. (1) Transcriptional regulation of G6PD expression involves chromatin conformation, alternative splicing and binding of miRNAs. (2) Since G6PD is X-linked, it is essential in population studies that data on males and
females are not pooled. In addition, although compared to hemizygous deficient males heterozygotes for G6PD deficiency are of course on average less severely affected, a proportion of their red cells (ranging from 10 to 90%) are, as a result of X-inactivation mosaicism, just as G6PD deficient as in hemizygous males. (3) Despite G6PD being a prime example in the teaching of pharmacogenetics, as recently as 2003-2008 a potent haemolytic drug, dapsone, was included in an antimalarial combined preparation and marketed in many African countries with high prevalence of G6PD deficiency. In part this was done because the type of G6PD deficiency common in Africa, G6PD A-, was regarded as being ‘mild’: it is now clear that this notion was not correct, although it is true that there is variation in the severity of AHA arising in persons with different G6PD variants. In this respect the conventional classification of G6PD variants might benefit from revision. (4) There is a resurgence in the use of PQ in countries aiming to malaria elimination: in view of what we know about primaquine-induced AHA, and in view of item (3) above, it is clear that in mass drug administration projects G6PD testing must be carried out before giving PQ. (5) Among drugs introduced in relatively recent times rasburicase (an enzyme that produces H₂O₂ from uric acid) has proven particularly risky for G6PD deficient patients, especially because it is used to prevent tumor lysis syndrome in patients who may have a large tumor mass or in newborns with presumed kidney injury. (6) In view of items 3-5 above, an animal model of G6PD deficiency for pre-clinical drug testing is direly needed: recently attempts have been made by using a mildly G6PD deficient mouse, NOD-SCID mice engrafted with human G6PD deficient red cells, and zebrafish treated with G6PD-specific morpholino compounds. (7) The evidence for malaria having been the selective force responsible for the spread of G6PD deficiency is so overwhelming as to make the malaria ‘hypothesis’ much more than a hypothesis: however, there is still controversy as to which genotypes are protected, and by what precise mechanisms. On this topic some novel data will be presented.