

Historical Review

DI GUGLIELMO AND HIS SYNDROMES

SUMMARY

The name of Giovanni Di Guglielmo is inscribed in the history of haematology as a result of his recognition that cells of the erythroid and megakaryocytic lineages could be involved in a process that was analogous to the involvement of the granulocytic lineage in leukaemia. Furthermore, he recognized bilineage and trilineage involvement in these processes, foreshadowing the later descriptions of various myeloproliferative disorders. Di Guglielmo gave his name to Di Guglielmo's disease (acute erythraemia, acute erythraemic myelosis or pure erythroid leukaemia) and Di Guglielmo's syndrome (encompassing pure erythroid neoplasms and their transition to a mixed erythroid–granulocytic lineage proliferation and pure myeloblastic proliferation). Although these terms are now little used, the concepts first formulated by Di Guglielmo in 1917 were prescient and now, more than 80 years later, their validity is undoubted.

HISTORY

Giovanni Antonio Di Guglielmo (1886–1961) (Fig 1) was a Brazilian-born Italian haematologist who, during the course of his career, made a number of significant original observations. Those for which he is best remembered are his descriptions, in 1917, 1923 and 1942, respectively, of erythroleukaemia and acute and chronic erythraemic myelosis.

Giovanni Di Guglielmo was born in 1886 in São Paulo, Brazil. His parents, of southern Italian origin, had recently migrated to the New World in search of a better life (Di Guglielmo, 1998). When he was 6, the family returned to Italy but, two years later, his parents re-emigrated to Brazil, leaving the young child in the care of his aunt and uncle in Andretta. He continued his schooling there and subsequently completed it in Avellino, later enrolling in the School of Medicine at the University of Naples. After graduation, in 1911, he returned to Brazil to practise medicine. However, finding himself insufficiently prepared for this career, he remained there less than a year before returning to Italy again. On his return, he chanced to meet, and became the first pupil and later the principal collaborator of, 'the father of Italian haematology', Adolfo Ferrata (1880–1946). Di Guglielmo worked as Ferrata's unpaid

assistant in the University of Naples from 1912 to 1916. His research was interrupted by the First World War. In 1916, he was drafted as a *tenente medico*, 'medical lieutenant', at first to a field hospital and then with the troops to the front line, at Monte Piana in the southern Tyrol (Alto Adige). During this period of military service, he published his first significant original observations, on a case of erythroleukaemia (Di Guglielmo, 1917). Later, when criticized for the lack of a citation in this paper, he defended himself, pointing out that, as he was in the front line with the infantry, he did not have the opportunity to consult bibliographic material (Di Guglielmo, 1925). With the end of the war, he returned to his research under the direction of his teacher and mentor, Adolfo Ferrata, initially in Naples (between 1919 and 1921) and subsequently (between 1921 and 1922) in Messina, where Ferrata had been appointed director of the Institute of Medical Pathology. In the early post-war years, Di Guglielmo contributed to a textbook on acute leukaemia and, under the guidance of Ferrata, published several papers relating to megakaryocytes and platelets (Di Guglielmo, 1920, 1923a). In 1920, he published more details of the patient first described in 1917, including a description of circulating, platelet-producing megakaryocytes (Di Guglielmo, 1920). In that same year, he returned briefly to Brazil where he presented a paper '*Função piastrinoblastica dos megacaryocytos no circolo sanguineo*' to the *Sociedade de Medicina e Cirurgia de São Paulo*. In 1922, Di Guglielmo accompanied Ferrata to Siena; their collaboration continued there until 1924. In 1923, at a conference in Rome, he reported the first case thought to represent *eritremia acuta* or acute erythraemia (Di Guglielmo, 1923b). In 1924, he followed Ferrata again, this time to Pavia where Ferrata had been appointed director of the *Clinica Medica della Regia Università di Pavia*. There he remained until 1927, publishing further significant papers on *eritremia acuta*. By 1926, Di Guglielmo had become *Professore Incaricato di Semeiotica e Diagnostica Medica* within Professor Ferrata's department. In 1927, he moved to the University of Modena where he became director of the Institute of Medical Pathology. In 1928, he won a *concorso*, the traditional Italian method of gaining an academic position, and was called to the Chair of Medical Pathology in Pavia. Here he remained until 1931, subsequently also becoming the director of the University's Institute of Clinical Paediatrics. He published the first Italian case of Gaucher's disease to be diagnosed by biopsy, rather than after splenectomy or at autopsy, and reported the presence of circulating Gaucher cells (Di Guglielmo, 1931). That same year, he left northern Italy for Sicily where he held chairs in pathology and medicine at the University of Catania. During these years, his research interests included

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Fig 1. Giovanni Di Guglielmo. Kindly provided by Professor Lucio Di Guglielmo from his personal collection.

brucellosis, then endemic in many parts of Italy; he carried out extensive research on the treatment of brucellosis by intravenous vaccination. In 1938, Di Guglielmo moved again, to Naples, where he remained until 1952, occupying chairs in pathology and medicine. In 1941, he published a description of the erythroid island, previously described by Heilmeyer & Schöner, recognizing it as an anatomical and functional unit. Finally, at the age of 65 years, he became Professor of Clinical Medicine at *La Sapienza*, the University of Rome, a post he was to occupy for another 5 years (until 1956). In his retirement, he continued with scholarly activities, until a few days before his death, driven by 'an insatiable desire to learn new things but at the rapid pace of one who has little time left to live' (Di Guglielmo, 1962). After his death, his last manuscript was gathered together for publication by his sons, Renato and Lucio. This book, *Le Malattie Eritremiche ed Eritroleucemiche*, which runs to some 300 pages of text and 100 pages of illustrations and cites 747 references in 10 European languages (Di Guglielmo, 1962), is a summary of his life's work.

The name of Di Guglielmo is linked to a range of haematological neoplasms with prominent erythroid involvement, specifically erythroleukaemia and acute and chronic erythraemia or erythraemic myelosis. In 1917, he described, under the designation 'eritroleucemia', a patient with proliferation of abnormal erythroid cells, myeloblasts and megakaryocytes (Di Guglielmo, 1917, 1920, 1923b, 1962). He conceived the idea that the erythroblastic proliferation was analogous to leukaemia rather than being a secondary phenomenon. This patient had immature cells of erythroid, granulocytic and megakaryocytic lineages in the peripheral blood, and the circulating megakaryocytes were producing platelets. Di Guglielmo used the term 'eritroleucopiasinaemia' to indicate this trilineage involvement. Although Demel (1924) questioned whether Di Guglielmo had been the first to make the observation of

circulating platelet-producing megakaryocytes, Di Guglielmo fiercely defended his priority, pointing out that Demel, in 1915, in a case of chronic myeloid leukaemia, had described giant platelets rather than intact platelet-producing megakaryocytes (Di Guglielmo, 1925). The ideas formulated by Di Guglielmo at this time were so prescient that they deserve to be quoted. They can be translated as follows: 'There can be haemopathies in which the alterations in all the morphological elements in the peripheral blood are so profound as to suggest a process involving the whole haemopoietic tissue rather than merely a process of one system with reactive changes in other systems.... The examination of the blood of our patient permitted a diagnosis of erythroleukaemia, since it showed the simultaneous presence of quantitative and qualitative changes both in the red cell and the white cells; furthermore it can be deduced that this process is the expression of a primitive lesion of the haemopoietic tissue striking its diverse activities – the red cell series, the white cell series and the platelets'. The trilineage involvement was indicated by the name suggested, 'eritroleucopiasinaemia', which could be translated as 'erythroleucothrombocythaemia'. In this early publication, Di Guglielmo also drew attention to the dynamic nature of this disease, referring to a phase of erythraemia followed by a phase of leukaemia. It can be seen that, even as early as 1917, Di Guglielmo had formed the concepts of a panmyelosis or a global myeloproliferative disorder, which were expounded further by William Dameshek (1900–69) more than 30 years later (Dameshek, 1958).

In 1923, Di Guglielmo presented, at an international medical congress in Rome, the first case that he considered to have *eritremia acuta* (acute erythraemia), a pure erythroid proliferation analogous to acute leukaemia (Di Guglielmo, 1923b). He had already postulated the existence of such an entity in 1919. In 1926, he reported three cases, including the patient of 1923 (Di Guglielmo,

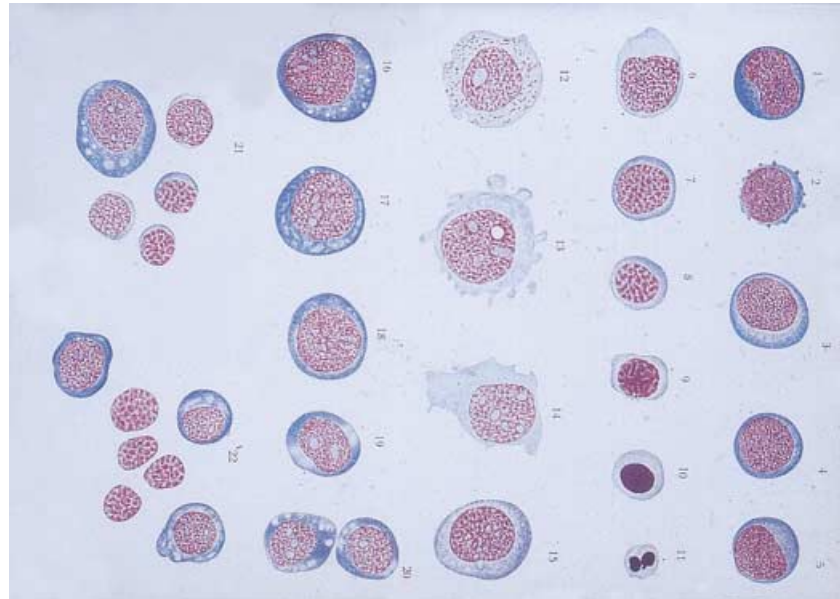


Fig 2. An illustration from Di Guglielmo (1928) showing an artist's impression of circulating erythroblasts (1–11) and characteristic bone marrow cells (12–22) in a patient with acute erythraemia (Di Guglielmo's disease). The peripheral blood shows erythroid cells of all stages of maturation, but the author noted that acidophilic erythroblasts soon disappeared from the peripheral blood film. The lack of mature erythroblasts in the bone marrow is apparent.

1926a). More details of one of these cases were given in a further paper published in the same year, although the title of the article does not reveal the nature of the condition being discussed (Di Guglielmo, 1926b). All three were reviewed in a further publication two years later (Di Guglielmo, 1928). In 1936, Ferdinando Michele (1872–1937; probably the first person to practise splenectomy for hereditary spherocytosis) suggested, at the second Congress of the Italian Society for Haematology in Turin, that acute erythraemic myelosis should be designated *il morbo Di Guglielmo*, i.e. Di Guglielmo's disease (Storti, 1998). This terminology was used in the same year by Nolli & Benario in an article in which they sought to distinguish the *morbo di Vaquez* (polycythaemia vera) from Cooley's anaemia (beta thalassaemia major) and from *eritremia ad andamento acuto* (acute erythraemia, acute erythraemic myelosis or Di Guglielmo's disease) (Nolli & Benario, 1936; Di Guglielmo, 1937). Two years later, Angelo Baserga (1908–95) used the same terminology in the title of a small book on the subject published in Pavia (Baserga, 1938). Much later, William Dameshek used the term 'Di Guglielmo's syndrome' to refer to polyphasic erythroleukaemia (see below). There must be some doubt as to whether all three of Di Guglielmo's cases of *eritremia acuta* actually had a neoplastic disorder. Schwartz & Critchlow (1952) accepted only the third case. The first patient, a young girl first reported in 1923, was described by Di Guglielmo as having *eritremia acuta a tipo pernicioso* or *eritremia acuta megaloblastica e megalocitica*, i.e. 'acute erythraemia of pernicious type' or 'acute megaloblastic and macrocytic erythraemia'. It is possible that she actually suffered from a megaloblastic anaemia. The second case was a deeply jaundiced neonate, and it seems likely that he suffered from haemolytic disease of the newborn with erythroblastosis fetalis. In both these patients, Di Guglielmo was able to examine only the

peripheral blood. The third case was a 50-year-old man, called Giovanni Albini, who presented with hepatomegaly, splenomegaly, fever, pancytopenia and circulating primitive erythroblasts; bone marrow examination showed primitive erythroblasts with very few cells of granulocyte lineage. Figure 2 shows characteristic cells, as illustrated in Di Guglielmo (1928). The clinical course was acute. The features of this case appear to be consistent with acute erythraemic myelosis and, if this diagnosis is accepted, Di Guglielmo was the first to recognize this condition. Di Guglielmo himself claimed priority for the first description of acute erythraemia on the basis of this third patient, amply studied and documented and first published in 1926, rather than on the basis of either of the other two patients (Di Guglielmo, 1962). At a conference in Rome in 1948, Di Guglielmo recorded that adequate documentation of this third patient was possible only because of the persuasiveness of his assistant, Dr A. Esposito. The patient's relatives had been so anxious about his condition that they had taken him home. They were persuaded to bring him back to the hospital where he died a few days later. A post-mortem examination was thus possible.

Cases of chronic erythraemic myelosis were published by Duesberg in 1940 and Heilmeyer & Schöner in 1941 (Michiels, 1992). Further cases were published by Di Guglielmo & Quattrin (1942), under the name *myelosi eritremica cronica*. However, priority in describing this condition may belong to another Italian, Copelli who, in 1912, reported a patient who presented with anaemia and splenomegaly but without circulating erythroid cells and was found to have foci of large primitive erythroid cells in liver, spleen, lymph nodes and bone marrow (Copelli, 1912).

Di Guglielmo's ideas became better known internationally after his presentation on this subject at the Sixth Congress of

the International Society of Haematology in Boston in 1956. The term 'Di Guglielmo's syndrome' was popularized in the anglophone haematological community by Dameshek, although Maxwell Wintrobe (1901–86) commented that, when Dameshek spoke on Di Guglielmo's syndrome at the plenary session of the congress of the International Society of Haematology in Rome in 1958, 'his picture of Di Guglielmo's syndrome was so different from that of the man after whom it had been named that Professor Di Guglielmo was puzzled and surprised' (Wintrobe, 1985). Somewhat closer to the event, Di Guglielmo himself had said that, 'the introduction of the new term "Di Guglielmo's syndrome" created a certain perplexity' (Di Guglielmo, 1962). Dameshek emphasized the natural progression from erythraemic myelosis (with a dominant erythroid proliferation) through erythroleukaemia (a mixture of myeloblasts and abnormal erythroid cells) to myeloblastic leukaemia (dominant myeloblasts) (Dameshek, 1958; Dameshek & Baldini, 1958). Di Guglielmo was afraid that, with the emphasis on the transition from one disorder to another, the existence of pure acute erythraemia might be doubted (Di Guglielmo, 1962). After Di Guglielmo's death, Dameshek again proposed that the term 'Di Guglielmo's syndrome' should be used to cover this whole disease spectrum, commenting that the term 'being sufficiently vague... can cover a large area, and being eponymic, it can be discarded when sufficient aetiological or pathogenetic information becomes available' (Dameshek, 1969).

In the last 30 years, a diagnosis of 'chronic erythraemic myelosis' has become increasingly infrequent. Cases that would once have been so designated are now most likely to be categorized as a myelodysplastic syndrome, usually being assigned to the French–American–British (FAB) categories (Bennett *et al.*, 1976) of refractory anaemia or refractory anaemia with ring sideroblasts. Erythroleukaemia, as described by Di Guglielmo (1917), would now usually be classified as acute myeloid leukaemia of FAB M6 type or, according to the World Health Organization (WHO) classification (Brunner *et al.*, 2001), as erythroleukaemia (erythroid/myeloid). Acute erythraemic myelosis, as described by Di Guglielmo in 1926, is a neglected disease, which does not fit FAB criteria for either a myelodysplastic syndrome or acute myeloid leukaemia. Although rare, its existence should be acknowledged. It is probably most appropriately regarded as a variant of acute myeloid leukaemia. If using the FAB classification, the designation M6 variant would seem appropriate (Garand *et al.*, 1995; Hasserjian *et al.*, 2001). Kowal-Vern *et al.* (1992) suggested assigning this category to cases that did not meet the FAB criteria for M6 AML but that had at least 50% erythroid cells with at least 30% of erythroid cells being proerythroblasts. The WHO classification recognizes this entity, designating it 'pure erythroid leukaemia'. It is defined as 'a neoplastic proliferation of immature cells committed exclusively to the erythroid lineage (> 80%) with no evidence of a significant myeloblastic component'. This is *eritremia acuta* rebaptised. Fashions in nomenclature change, but Di Guglielmo's concepts, unlike those of many of his contemporaries, have

endured. He maintained a life-long interest in 'his' disease, his major monograph, which he saw as his scientific and spiritual testament being published posthumously (Di Guglielmo, 1962). His careful observations of individual patients over a period of more than 40 years contributed greatly to advancing knowledge of this group of diseases. His concept that erythroid cells might undergo proliferation analogous to the proliferation of granulocytic cells in leukaemias was greatly in advance of his time, and the clarity of his vision should be acknowledged.

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