

## Historical Review

### FANCONI AND GLANZMANN: THE MEN AND THEIR WORKS

Most haematologists will recognize the name Fanconi as that given to the rare form of aplastic anaemia frequently associated with other constitutional abnormalities. When questioned, most would suggest that he was Italian born. The name Glanzmann should kindle memories of that equally rare congenital platelet function disorder and most would guess that he was of Austro-German extraction.

In fact, both of these names arose from Switzerland and were paediatricians foremost and, to a lesser extent, haematologists. They represent the early pioneers of paediatric haematology both nationally and internationally but also had a wide range of other clinical interests (Wagner, 1994).

The history of paediatrics in Europe is linked with the development of hospital establishments. Before 1850, 25 children's hospitals already existed, the oldest being the Hôpital des Enfants Malades in Paris (1802), followed by the Paediatric Pavillion of the Charite of Berlin (1830) and those of St. Petersburg (1834), Vienna and Breslau (1837). From 1850 to 1879, a further 67 paediatric hospitals opened in Europe, although many of these were paediatric departments integrated into general hospitals (Ballabriga, 1991). In Britain, Charles West created the Hospital for Sick Children in Great Ormond Street, London, in 1852, after founding the National Children's Hospital in Dublin 25 years before (Higgins, 1952).

#### EDUARD GLANZMANN (1887–1959)

Eduard Glanzmann (Fig 1) was born in Luzern on 12 April 1887. After completing his specialist training in Zurich and Bern under Professor Rudolf Demme, he spent a year (1915–1916) at Professor Adalbert Czerny's Children's Hospital in Berlin, then a pre-eminent centre for paediatrics.

#### *Glanzmann's disease*

Glanzmann then returned to Bern and in 1918, 2 years after starting his own practice, he described the condition, which now carries his name, Hereditäre Hämorrhagische Thrombasthenie (Glanzmann, 1918). He recognized that the condition was not due to a lack of platelet numbers but rather a functional disturbance characterized by slow or absent clot retraction and a prolonged bleeding time.

This was a new concept proposed by Glanzmann, whereby not only a reduction in numbers of blood cells



Fig 1. E. Glanzmann.

(-penia), but also an abnormality of cellular function (-pathia) can result in disease. Glanzmann's description pertained to non-functioning 'weak' platelets (thrombasthenia) but we now know that this principle can be applied to all cell lines.

Glanzmann noted the prevalence of the disease in families and its presence in early life, which suggested that it might have a hereditary basis. It is likely that Glanzmann's patients had several types of platelet abnormalities, but the principle of functional as well as quantitative defects was established and set the path for subsequent research (Spaet, 1980).

#### *Other contributions*

In 1920, when still in his early 30s, Glanzmann introduced the term *Anaphylaktoide Purpura*, and therefore this disease

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is sometimes called Schönlein–Henoch–Glanzmann disease (Glanzmann, 1920). He recognized the allergic components to this clinical syndrome. In 1930, he characterized the features of ‘the fever of the lymphatic glands in children’ which we know today as infectious mononucleosis (Oehme, 1985).

Twelve years later, in 1932, Glanzmann became Professor and Director of the Children’s Hospital (Das Jenner-Kinderspital) in Bern. He followed the strong tradition of paediatrics in the Swiss capital started by Demme (1836–1892) and continued by Stoos (1855–1939). He was an outstanding clinician with a versatile field of interest, including haematology, infectious diseases, psychopathology, growth and development, to list but a few. Every day, he visited the wards, making comments in a low tone because of difficulties with his voice. His book ‘Einführung in die Kinderheilkunde’ (Introduction to Paediatrics) was published in seven editions, and also translated in to Spanish and French (Glanzmann, 1949).

Dietetics was an important part of the routine in his clinic, using ‘Sauervollmilch’ (clotted whole milk) in infants and ‘Linsenbrei’ (lentils) in coeliac patients. In 1946, he published his concept of ‘dysporia’ about fibrocystic disease of the pancreas (Glanzmann, 1946).

In 1950, Glanzmann and Paul Riniker described two infants with ‘essentieller Lymphocytophthise’, the first cases of severe combined immune deficiency (Glanzmann & Riniker, 1950).

His pupil H. Berger (Innsbruck) gave his master a durable memorandum: ‘All his achievements should be recognized as originating from his care of the sick child and the right of access to the man and his personality. He does not conduct research as an end in itself, but as a means of betterment’.

Glanzmann remained Director of the Children’s Hospital in Bern until 1957 only to die 2 years after his retirement.

#### GUIDO FANCONI (1892–1979)

Guido Fanconi (Fig 2) was born on 1 January 1892 in the small town of Poschiavo in the canton of Graubünden in south-east Switzerland, close to the Italian border. He went to school in Schiers in the German speaking part of Switzerland. He studied medicine in Munich, Lausanne and Bern. After a short time in pathology, he started his paediatric training in 1920 at the Kinderspital in Zurich under Emil Feer, the first Professor of Paediatrics in Switzerland.

#### *Early work*

At a time when infectious and nutritional disorders in childhood must have resulted in an immense clinical workload – in the Kinderspital Zürich, a paediatrician always had to be available for surgical airways for children with diphtheria (the ‘Croupier’), and medical residents had to extract teeth, incise abscesses and tonsils, and resect ribs – Fanconi recognized uncommon clinical patterns as important disease entities. In addition, he complimented his clinical work with biochemistry. To learn more about

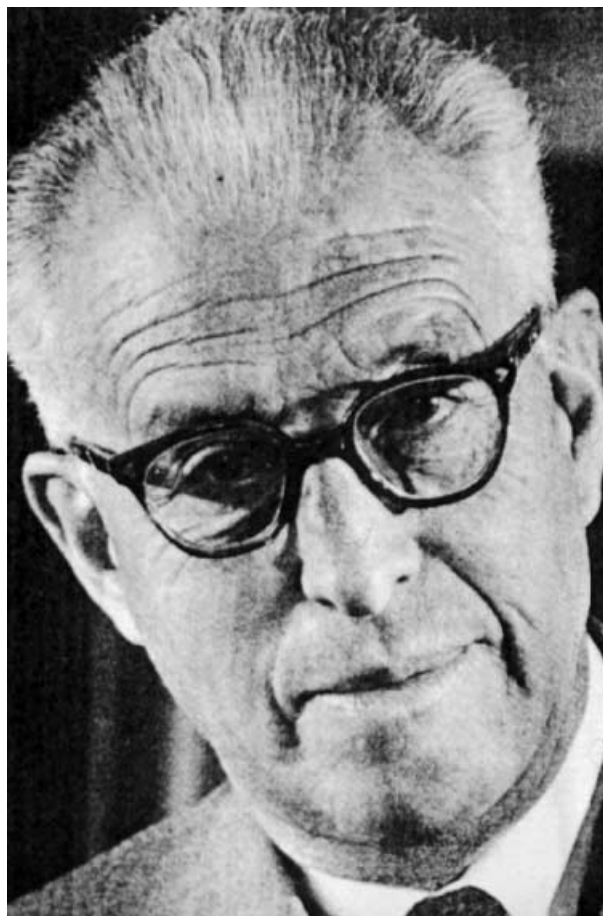


Fig 2. G. Fanconi.

biochemistry, a subject very much in its infancy at the time, he joined Emil Abderhalden in Halle in Germany. In his doctoral thesis (Fanconi, 1920), he studied congenital ileus and later, in his ‘Habilitation’ (Fanconi, 1926), he discussed clinical and serological aspects of scarlet fever.

#### *Fanconi anaemia*

Based on the observation of three brothers with a lethal hyperchromic anaemia associated with anisocytosis and poikilocytosis but no splenomegaly, Fanconi first considered the possibility of familial pernicious anaemia. However, he discarded this diagnosis because of the lack of the typical bone marrow findings at autopsy. In 1927, he published the account of his observations under the title ‘Familiäre, infantile, perniziosaartige Anämie’ (Fanconi, 1927). Soon the pathologist Erwin Uehlinger and others recognized that this type of constitutional anaemia was often associated with pancytopenia and that congenital malformations were often present (Uehlinger, 1929). In 1931, Otto Naegeli, in his time considered the ‘pope’ of Swiss haematology, introduced the name ‘Fanconi’s Anaemia’ (Naegeli, 1931). In 1927, only four other constitutional haemolytic anaemias (spherocytosis, sickle cell anaemia, ovalocytosis and Cooley’s anaemia) had been differentiated from the old

'Jaksch-Hayem anaemia pseudoleukaemia infantum'. Remarkably, the last sentence in Fanconi's original paper anticipated what was confirmed much later: 'Die Knochenmarksdysfunktion, die zum perniziösen Blutbild führt, ist wahrscheinlich auch nur ein Zeichen einer erbten Minderwertigkeit (*The bone marrow dysfunction that leads to the pernicious blood film is probably only a symptom of an inherited deficiency*)'.

#### Later work

In 1936, Fanconi described the biochemical aspects of the condition, previously attributed to de Toni and Debre, characterized by growth retardation, aminoaciduria, glycosuria and hypophosphataemic rickets, which we now call the Renal Fanconi Syndrome (Fanconi, 1936). He also published on the dietary aspects of coeliac disease and was the first to recognize the coeliac-like syndrome with congenital fibromatosis of the pancreas and bronchiectasis: cystic fibrosis. Overall, he was the first to describe 11 syndromes.

Fanconi succeeded Emil Feer as the Professor at the Kinderspital in Zurich in 1929 and remained as the 'Ordinarius' for paediatrics until 1962. He led the Kinderspital, Zurich, to a worldwide reputation. In conjunction with the Swedish paediatrician Wallgren, Fanconi published what was to become the leading textbook of paediatrics for many years and which was translated into many languages (Fanconi & Wallgren, 1972). In 1962, he was succeeded by Andrea Prader. After his retirement, Fanconi continued to be an important leader in the integration of European Paediatrics and was an honoured international figure in paediatrics worldwide.

More than 70 years after its first description, the genetic and cellular defect in Fanconi's anaemia has become clearer and is currently the subject of much research (Joenje & Patel, 2001). With its name, the Fanconi anaemia pathway maintaining DNA integrity immortalizes one of the most important paediatricians.

Fanconi died in October 1979 aged 87 years. He is buried in Poschiavo.

#### EPILOGUE

Guido Fanconi and Eduard Glanzmann come from a strong line of Swiss paediatricians with a wide range of interests, including haematology. They have been followed by names such as Heinrich Willi (1900–1971), Conrad Gasser (1912–1982), Hans Cottier, Silvio Barandun, Ettore Rossi and Eduard Gugler.

Switzerland is famed for its lakes and mountains. Visitors travelling to the Bernese Oberland are very likely to pass through the Swiss capital before reaching their final destination. A short break in Bern will result in a feeling of stately elegance, friendliness and culture epitomized by Eduard Glanzmann.

The main train routes from Switzerland through to Italy are via the Lotschberg/Simplon or St. Gotthard tunnels. A slower but much more spectacular route is via St. Moritz and the Rhaetian line. The Bernina railway travels from

St. Moritz over the Bernina Pass (the highest trans-alpine rail line without the assistance of a tunnel) to then descend nearly 6000 ft in less than 24 miles. A few miles before arriving at the terminus of Tirano (just over the Italian border), the train passes through the Poschiavo valley and the town of Poschiavo itself, the birthplace of Guido Fanconi. The magnificent scenery is a tribute to him.

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#### REFERENCES

- Ballabriga, A. (1991) One Century of Paediatrics in Europe. In: *History of Pediatrics 1850–1950* (ed. by B.L. Nichols, A. Ballabriga & M. Kretchner) *Nestle Nutrition Workshop Series*, Vol. 22. Raven Press, New York.
- Fanconi, G. (1920) Fünf Fälle von angeborenem Darmverschluss. Inaugural-Dissertation, Universität Zurich (Doctoral Thesis).
- Fanconi, G. (1926) *Klinische und Serologische Beiträge zum Scharlachproblem*. Habilitationsschrift. Universität Zurich.
- Fanconi, G. (1927) Familiäre, infantile, perniziösartige Anämie (perniziöses Blutbild und Konstitution). *Jb Kinderheilk*, **117**, 257.
- Fanconi, G. (1936) Der nephrotisch-glykosurische Zwerchwuchs mit hypophosphatämischer Rachitis. *Deutsche Med Wochenschr Pädiatric*, **62**, 1169.
- Fanconi, G. & Wallgren, A. (1972) *Lehrbuch der Pädiatrie*. 9. Aufl. Verlag Schwabe & Co, Basel.
- Glanzmann, E. (1918) Hereditäre Hämorrhagische Thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen. *Jb. Kinderheilk*, **88**, 113.
- Glanzmann, E. (1920) Die Konzeption der Anaphylaktoiden Purpura. *Jb. Kinderheilk*, **91**, 371.
- Glanzmann, E. (1946) Dysporia Entero-broncho-pancreatica Congenita Familiaris. *Cystische Pankreasfibrose*. *Annal Paediatr*, **166**, 289–313.
- Glanzmann, E. (1949) *Einführung in die Kinderheilkunde*. Springer-Verlag, Vienna.
- Glanzmann, E. & Riniker, P. (1950) Essentielle Lymphocytopenhthuse. Ein neues Krankheitsbild aus der Säuglingspathologie. *Annal Paediatr*, **175**, 1.
- Higgins, T.T. (1952) *Great Ormond Street 1852–1952*, London. Odhams Press.
- Joenje, H. & Patel, K.J. (2001 June) The emerging genetic and molecular basis of Fanconi anaemia. *National Review of Genetics*, **2**, 446–457.
- Naegeli, O. (1931) *Blutkrankheiten und Blutdiagnostik, Lehrbuch der Klinischen Hämatologie*. Springer-Verlag, Berlin.

- Oehme, J. (1985) Pioniere der Kinderheilkunde: Eduard Glanzmann (1887–1959). In *Kinderkrankenschwester* (ed. by J. Oehme) pp. 97–98.
- Spaet, T.H. (1980) Platelets, the Blood Dust. In *Blood Pure and Eloquent* (ed. by M.M. Wintrobe) p. 564. McGraw-Hill, New York.
- Uehlinger, E. (1929) Konstitutionelle infantile (perniziosaartige) Anämie. *Klinische Wochenschrift*, **2**, 1501.

Wagner, H.P. (1994) Historical Note on Paediatric Haematology and Oncology in Switzerland. *Paediatric Haematology and Oncology*, **11**, 575–586.

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