

The pioneering role of the Rennes School in haemochromatosis

Pierre Brissot, Rennes

Notes are linked to the references page.

INTRODUCTION

Whenever the idea of pioneer comes up in the context of metal, one immediately thinks about the Gold Rush in California in the mid-19th century—an unbridled quest for such a prized metal that seduced crowds of adventurers from all over the world. However, this was just a fad that lasted barely ten years. Compared with gold, iron may not be able to compete in terms of mercenary value, but when it comes to attracting scientists and doctors, its importance to life and human health proves a big draw. Remember that iron meteorites—found on both Earth and Mars—are projections come from the farthest parts of the Universe to start up life characterised by cellular respiration. Without iron, humans would not be able to respire and any deficiency in iron is known to cause serious damage to health, notably related to the important role of iron in the functioning of red blood cells. Although iron is essential for life, too much of it in the body can also be harmful because of its potent potential for the generation of oxygen free radicals so damaging to cells and organs. In fact, the human body is doubly vulnerable to iron on the one hand, it is susceptible to lack of the metal because, as it is incapable of producing it itself, it is entirely dependent on dietary intake; and on the other hand, if too much is introduced via the diet or otherwise, the body is susceptible to iron overload because it is not equipped to eliminate the excess. This dichotomy defines the two broad categories of different iron-related diseases, lack on one side and excess on the other. However, public perceptions of these two categories are quite different: although most people are aware of the damaging consequences of insufficient iron (iron remaining associated with strength and power in the public consciousness), the same is not the case for iron overload, which is still seriously underestimated, and this despite so much having been found out about the toxicity of iron in humans over the decades. The history of investigations into iron overload goes back to the time of the Gold Rush, i.e. the mid-19th century, and French science—notably at the Rennes School—can be proud of having pioneered this long, distinguished history.

Before Rennes, the Paris Medical School helped identify iron overload disease with the pioneering observations of Trousseau (1865),² Troisier (1871)³ and Hanot and Chauffard (1882)⁴ leading to recognition of a disease that combined melanoderma, diabetes and cirrhosis. Then in 1889, a German pathologist, von Recklinghausen, made the link with iron overload and coined the term ‘haemochromatosis’ (meaning colour of blood, probably alluding to the red colour of organs loaded with iron derived from the blood).

PIONEERING ROLE OF THE RENNES SCHOOL

Two greats

It was Professor Michel Bourel who inspired and launched this whole story (*Figure 1*). After studies in Paris, this brilliant internist specialising in rheumatology after training with the most distinguished experts in Paris, brought internal medicine to Rennes before turning towards the study of liver disease and iron overload. In 1955, he co-authored his first article on iron⁵ but it was not until ten years later that he took under his wing Marcel Simon, who would dedicate himself to the study of haemochromatosis. One of Michel Bourel's strokes of genius was definitely giving this young Breton internist (who was so talented as well as proud of his roots) the thesis topic 'Problems of heredity in idiopathic haemochromatosis'. This thesis defended half a century ago in 1966 presaged the discovery ten years later—by Marcel Simon himself—of the condition's genetic aetiology.

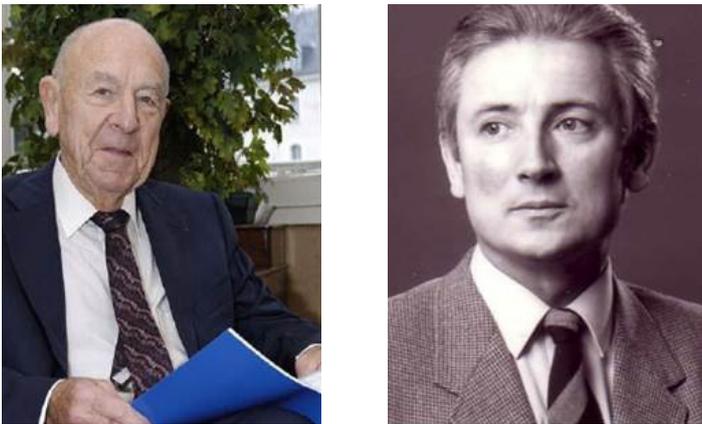


Figure 1. Professors Michel BOUREL (left) and Marcel SIMON, 2 pionneers of the *Ecole rennaisse de l'hémochromatose*

Rennes School contributions to the study of haemochromatosis

The school's work covered many different domains of research which can be split between six main themes.

Semiology

This work addressed various aspects of the disorder that remained poorly understood at that time.

Dermatology

In addition to melanoderma, the frequency of ichthyosis and nail abnormalities (such as platonychia and, paradoxically, koilonychia) was reported.^{6,7}

Liver problems

Frequency of hepatomegaly, especially in the left lobe, but with globally satisfactory liver function despite cirrhosis; clinically neither liver failure nor portal hypertension and test results showing only moderate cytolysis (no more than two or three times the normal level). Yves Deugnier, Bernard Ferrand and Bruno Turlin established new histological classification systems to quantify iron overload.^{8,9} The frequency of hepatocellular carcinoma¹⁰ that can develop even if all iron is eliminated by bloodletting if the liver was already cirrhotic before treatment. The usefulness of histological identification of iron-free nodules as a predictor of the likelihood of liver cancer.¹¹ The demonstration by Yves Gandon of a new magnetic resonance imaging (MRI) approach to iron overload in the liver,¹² a key advance towards non-invasive diagnosis, i.e. one not requiring a liver aspiration biopsy.¹³

Endocrinology

Characterisation of haemochromatosis-related diabetes,^{14, 15} without any family history of type 1 diabetes and with the same severity of symptoms.¹⁶ Characterisation of haemochromatosis-related hypogonadism linked not only to pituitary malfunction but also a specific gonadic aetiology.¹⁷

Rheumatology

Yves Pawlotsky and Gérard Chalès refined the description of joint symptoms and proposed the ‘painful hand wrist’ sign as well as studying haemochromatosis-related osteoporosis.^{18, 19}

Heart

Jacques Gouffault and his group described haemochromatosis-related cardiomyopathy and the highly beneficial effect of bloodletting.²⁰

Ways of investigating iron overload

In addition to the histological and MRI advances mentioned above, tests were developed for desferrioxamine,²¹ blood ferritin^{22, 23} and the concentration of iron in the liver²⁴ as respective measurements in urine, blood and liver tissue to estimate the body’s iron load. Many of these techniques proved essential to research into haemochromatosis.

Confirmation of the hereditary nature of the disease

Since the 1930s, the aetiology of haemochromatosis was hotly debated with some like Sheldon (1935)²⁵ advocating a genetic cause, and others like Macdonald (1965)²⁶ pointing to it being acquired (notably due to alcohol). It was up to the Rennes School, and in particular Marcel Simon, to settle the issue. Using a clinical approach in collaboration with Renée Fauchet and Bernard Genetet, he demonstrated the high prevalence of HLA-A3 (associated with B14 or B7) among patients with haemochromatosis. This not only provided a powerful diagnostic aid but also definitively proved that haemochromatosis is a genetic disorder because the human leukocyte antigen (HLA) system is located on chromosome 6.^{27, 28} This major discovery was the basis for subsequent remarkable family studies that also proved that transmission is recessive,²⁹ provided a valuable model for the conduct of family surveys, and differentiated haemochromatosis from the type of iron overload that is seen in alcoholic liver disease.³⁰ In addition, given the geographical distribution of HLA-A3 across the world, it was proposed that the original mutation occurred in the Celtic population.^{31, 32} This hypothesis was supported by results from work on gene dating in which the Rennes group took part in 2004,³³ and has been further bolstered by the recent discovery by Irish scientists of the haemochromatosis mutation in an Irish skeleton from the Bronze Age.³⁴ The hunt for the gene took some 20 years. Although the group of Jean-Yves Le Gall, Véronique David and Anne-Marie Jouanolle^{35, 36} got close, the *HFE* gene (and the *C282Y* mutation) were eventually isolated by a Californian biotechnology company who were not specifically targeting haemochromatosis in their molecular genetics work.³⁷ This identification of a haemochromatosis-related mutation in the *HFE* gene opened the way to the discovery of haemochromatosis-causing mutations in other genes.³⁸ Of course, it can only be regretted that Marcel Simon, who died in 1988, far too young at the age of 53, was not able to take part in this expansion of our understanding of haemochromatosis that he paved the way for.

Pathogenesis

Following the discovery of new forms of iron in the blood in iron overload of haematological aetiology, namely non-transferrin bound iron (NTBI) and labile plasma iron (LPI), the Rennes group produced two important types of physiopathological data. First, unlike transferrin-bound iron, which preferentially targets bone marrow (where it is used in erythropoiesis), NTBI is avidly sequestered by liver cells.³⁹ This explains why, in haemochromatosis (in which the first laboratory observation is high transferrin saturation and the appearance of NTBI), iron overload in the liver starts and predominates in the parenchyma (hepatocytes) in contrast to post-transfusional overload, which is concentrated in macrophages. LPI, which is potentially the most toxic form of iron in the circulation by virtue of its capacity to generate free radicals, is found in haemo-

chromatosis and its concentration correlates with liver toxicity.⁴⁰ LPI is currently considered to be the main agent of cellular and therefore tissular toxicity in haemochromatosis.

Elucidation of the hepcidin pathway

In 2001, work towards a thesis being co-supervised by Olivier Loréal revealed a link for the first time between this antimicrobial peptide and iron metabolism.⁴¹ The methodology involved suppression subtractive hybridisation between mice suffering from iron overload and normal mice. Heparin synthesis in the liver was potently induced by iron overload. Shortly afterwards, Gaël Nicolas and Sophie Vaulont in Paris discovered that this peptide acted as the main hormone controlling systemic iron regulation,^{42, 43} paving the way towards a better understanding of how haemochromatosis leads to iron overload. In practice, overload is due to the inhibitory effect of the homozygous *C282Y* mutation on hepcidin production by hepatocytes. Recently, work in Rennes on iron metabolism after liver transplantation demonstrated that hepcidin supplementation could be an effective therapeutic strategy in haemochromatosis.⁴⁴

Giving patients their voice

One of the novel features of the Rennes approach to haemochromatosis has been to focus not exclusively on the disease itself but to take patients into account by encouraging their expression through the establishment of support structures. Patient support groups have been set up regionally (hemochromatose-ouest.fr), nationally (hemochromatose.org) (hemochromatose.fr), at the European level (efaph.eu) and globally (haemochromatosis-international.org). These groups have proved to be a powerful aid when it comes to raising consciousness about the disease among the general public, media, doctors and healthcare agencies. These have become incomparable partners in training and research initiatives related to haemochromatosis.

Such are the achievements of the Rennes School in the field of haemochromatosis. This review is dedicated to the memory of Michel Bourel and Marcel Simon, a dynamic duo who, through their creative enthusiasm, aroused the interest of a host of students in their subject. This medical field has been a model for bidirectional translational research with clinical observations guiding research and, in turn, research quickly leading to improvements in diagnosis and treatment. The creation in 2007 of the National Reference Centre in Rennes for rare genetic iron overload conditions bears witness to the recognition of this action and it constitutes a precious resource for continuation of more than 60 years of effort. As Antoine de Saint-Exupéry said, the main thing is not so much to predict the future but rather to make it possible.

REFERENCES (*Underline references are linked to pub Med abstracts*)

1. [Brissot P, Loreal O. Iron metabolism and related genetic diseases: A cleared land, keeping mysteries. J Hepatol 2016;64\(2\):505-15.](#)
2. [Trousseau A. Glycosurie, diabète sucré. Clinique Médicale de l'Hôtel-Dieu \(Paris\) 1865;2:663-98.](#)
3. [Troisier M. Diabète sucré. Bull Soc Anat \(Paris\) 1871;44:231-35.](#)
4. [Hanot VC, Chauffard, A.M.E. Cirrhose pigmentaire avec diabète sucré. Revue de Médecine Paris 1882;2:385-403.](#)
5. [Lamache A, Bourel M, Chevrel ML, et al. \[Studies on hemochromatosis in the light of 350 biopsy examinations on 228 patients: anemic forms of the disease\]. Bull Acad Natl Med 1955;139\(23-24\):405-7.](#)
6. [Chevrant-Breton J, Simon M, Bourel M, Ferrand B. Cutaneous manifestations of idiopathic hemochromatosis. Study of 100 cases. Arch Dermatol 1977;113\(2\):161-5.](#)
7. [Bourel M, Simon M, Pawlotsky Y, Murie M, Le Carreres D. \[Nail changes in idiopathic hemochromatosis\]. Sem Hop 1970;46\(10\):677-80.](#)
8. [Deugnier YM, Loreal O, Turlin B, et al. Liver pathology in genetic hemochromatosis: a review of 135 homozygous cases and their bioclinical correlations. Gastroenterology 1992;102\(6\):2050-9.](#)
9. [Ferrand B, Brissot P, Deugnier Y, Herry D, Bourel M. \[Histologic classification of hepatic siderosis \(author's transl\)\]. Arch Anat Cytol Pathol 1981;29\(5\):315-6.](#)
10. [Chayvialle JA, Brissot P, Pelletier MJ, et al. alpha-Fetoprotein screening in patients with idiopathic hemochromatosis and liver cirrhosis. Digestion 1977;16\(1-2\):118-27.](#)
11. [Deugnier YM, Charalambous P, Le Quilleuc D, et al. Preneoplastic significance of hepatic iron-free foci in genetic hemochromatosis: a study of 185 patients. Hepatology 1993;18\(6\):1363-9.](#)
12. [Gandon Y, Guyader D, Heautot JF, et al. Hemochromatosis: diagnosis and quantification of liver iron with gradient-echo MR imaging. Radiology 1994;193\(2\):533-8.](#)
13. [Gandon Y, Olivie D, Guyader D, et al. Non-invasive assessment of hepatic iron stores by MRI. Lancet 2004;363\(9406\):357-62.](#)
14. [Simon M, Vongsavanhong S, Hespel JP, Lecornu M, Bourel M. \[Diabetes and hemochromatosis. I. Diabetes in idiopathic hemochromatosis. Apropos of 130 personal cases of hemochromatosis\]. Sem Hop 1973;49\(29\):2125-32.](#)
15. [Simon M, Vongsavanhong S, Jehan JP, Roussey M, Bourel M. \[Diabetes and hemochromatosis. II. Diabetes of idiopathic hemochromatosis and common diabetes. Apropos of 130 personal cases of hemochromatosis\]. Sem Hop 1973;49\(29\):2133-41.](#)
16. [Simon M, Alexandre JL, Scordia C, Hespel JP, Bourel M. \[Diabetes of idiopathic haemochromatosis and common diabetes mellitus. Results of a prospective study of 97 families with idiopathic haemochromatosis \(author's transl\)\]. Diabete Metab 1976;2\(3\):113-8.](#)
17. [Simon M, Franchimont P, Murie N, et al. Study of somatotropic and gonadotropic pituitary function in idiopathic haemochromatosis \(31 cases\). Eur J Clin Invest 1972;2\(6\):384-9.](#)
18. [Pawlotsky Y, Lancien Y, Roudier G, et al. \[Bone histomorphometry and osteo-articular manifestations of idiopathic hemochromatosis\]. Rev Rhum Mal Osteoartic 1979;46\(2\):91-9.](#)
19. [Pawlotsky Y, Roussey M, Hany Y, Simon M, Bourel M. \[Increased blood parathormone levels in idiopathic hemochromatosis\]. Nouv Presse Med 1974;3\(28\):1757-8.](#)
20. [Mattheyses M, Hespel JP, Brissot P, et al. \[The cardiomyopathy of idiopathic hemochromatosis\]. Arch Mal Coeur Vaiss 1978;71\(4\):371-9.](#)
21. [Lenoir P, Allannic H, Chauvel A, Danon G, Bourel M. \[The desferrioxamine B induced hypersideruria test in hemochromatosis\]. Sem Hop 1965;41\(47\):2715-9.](#)
22. [Beaumont C, Simon M, Fauchet R, et al. Serum ferritin as a possible marker of the hemochromatosis allele. N Engl J Med 1979;301\(4\):169-74.](#)
23. [Beaumont C, Simon M, Smith PM, Worwood M. Hepatic and serum ferritin concentrations in patients with idiopathic hemochromatosis. Gastroenterology 1980;79\(5 Pt 1\):877-83.](#)
24. [Brissot P, Bourel M, Herry D, et al. Assessment of liver iron content in 271 patients: a reevaluation of direct and indirect methods. Gastroenterology 1981;80\(3\):557-65.](#)
25. [Sheldon J. Haemochromatosis. Oxford University Press 1935.](#)
26. [Macdonald RA. Idiopathic hemochromatosis. A variant of portal cirrhosis and idiopathic hemosiderosis. Arch Intern Med 1961;107:606-16.](#)
27. [Simon M, Bourel M, Alexandre JL, et al. \[Letter: Heridity of hemochromatosis: its relation with HL-A system\]. Nouv Presse Med 1976;5\(28\):1762.](#)
28. [Simon M, Bourel M, Fauchet R, Genetet B. Association of HLA-A3 and HLA-B14 antigens with idiopathic haemochromatosis. Gut 1976;17\(5\):332-4.](#)
29. [Simon M, Bourel M, Genetet B, Fauchet R. Idiopathic hemochromatosis. Demonstration of recessive transmission and early detection by family HLA typing. N Engl J Med 1977;297\(19\):1017-21.](#)
30. [Simon M, Bourel M, Genetet B, et al. Idiopathic hemochromatosis and iron overload in alcoholic liver disease: differentiation by HLA phenotype. Gastroenterology 1977;73\(4 Pt 1\):655-8.](#)
31. [Simon M, Le Mignon L, Fauchet R, et al. A study of 609 HLA haplotypes marking for the hemochromatosis gene: \(1\) mapping of the gene near the HLA-A locus and characters required to define a heterozygous population and \(2\) hypothesis concerning the underlying cause of hemochromatosis-HLA association. Am J Hum Genet 1987;41\(2\):89-105.](#)

32. Simon M, Brissot P. The genetics of haemochromatosis. *J Hepatol* 1988;6(1):116-24.
 33. Distant S, Robson KJ, Graham-Campbell J, et al. The origin and spread of the HFE-C282Y haemochromatosis mutation. *Human genetics* 2004;115(4):269-79.
 34. Cassidy LM, Martiniano R, Murphy EM, et al. Neolithic and Bronze Age migration to Ireland and establishment of the insular Atlantic genome. *Proc Natl Acad Sci U S A* 2016;113(2):368-73.
 35. el Kahloun A, Chauvel B, Mauvieux V, et al. Localization of seven new genes around the HLA-A locus. *Hum Mol Genet* 1993;2(1):55-60.
 36. Gandon G, Jouanolle AM, Chauvel B, et al. Linkage disequilibrium and extended haplotypes in the HLA-A to D6S105 region: implications for mapping the hemochromatosis gene (HFE). *Hum Genet* 1996;97(1):103-13.
 37. Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature genetics* 1996;13(4):399-408.
 38. Brissot P, Bardou-Jacquet E, Jouanolle AM, Loreal O. Iron disorders of genetic origin: a changing world. *Trends Mol Med* 2011;17(12):707-13.
 39. Brissot P, Wright TL, Ma WL, Weisiger RA. Efficient clearance of non-transferrin-bound iron by rat liver. Implications for hepatic iron loading in iron overload states. *J Clin Invest* 1985;76(4):1463-70.
 40. Le Lan C, Loreal O, Cohen T, et al. Redox active plasma iron in C282Y/C282Y hemochromatosis. *Blood* 2005;105(11):4527-31.
 41. Pigeon C, Ilyin G, Courselaud B, et al. A new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. *J Biol Chem* 2001;276(11):7811-9.
 42. Nicolas G, Bennoun M, Devaux I, et al. Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. *Proceedings of the National Academy of Sciences of the United States of America* 2001;98(15):8780-5.
 43. Nicolas G, Viatte L, Lou DQ, et al. Constitutive hepcidin expression prevents iron overload in a mouse model of hemochromatosis. *Nat Genet* 2003;34(1):97-101.
 44. Bardou-Jacquet E, Philip J, Lorho R, et al. Liver transplantation normalizes serum hepcidin level and cures iron metabolism alterations in HFE hemochromatosis. *Hepatology* 2014;59(3):839-47.
-