Diabetes ?Type

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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this installment of *Tattersall's Tales*, Robert Tattersall explores the history behind the inherited disorder haemochromatosis, looking back at key developments with regard to presentation, diagnosis, treatment and prognosis.

In 1969 the eminent geneticist Victor McKusick illustrated an article on the nosology of genetic disease with a cartoon entitled "Lumpers and splitters" (McKusick, 1969). Both those portrayed are woodcutters but the lumper is a stout self-satisfied man whereas the splitter (a spitting image of Abraham Lincoln) is lean and hard at work. The point McKusick was making was that splitting, even if it did involve more work, was the way to uncover genetic heterogeneity.

A decade later, when lecturing on the genetics of diabetes, I used this as a slide to suggest that diabetes was a syndrome with many different (genetic) causes. I think the concept of "lumpers and splitters" can be applied to the classification of patients with newly diagnosed diabetes. It is easy for the lazy doctor to label everyone under 30 years of age as "type 1" and the others as "type 2" but if someone is wrongly labelled (for example, as having type 1 diabetes instead of MODY) it may take years for the error to be corrected, if it ever is.

Let me confess an example of misdiagnosis from my own practice. A middle-aged scrap dealer with at least one gold ring on each finger had been attending my clinic for 10 years with type 2 diabetes. Things went reasonably well for the first 5 years but then whenever he came to the clinic he was full of complaints including tiredness, stiffness and aching in his hands, and vague abdominal pain. These symptoms did not seem to amount to much and were relegated to the background when he developed a foot ulcer. About 10 years after he developed diabetes he was an inpatient with another foot ulcer, and the liver function tests (LFTs), which the houseman had ordered, were abnormal. I was just about to say how common abnormal LFTs were in type 2 diabetes (Samela et al, 1984) – which was why I advised against doing the test routinely – when my registrar said, "do you think he might have haemochromatosis?" He did and I cursed myself for not having thought of it.

The history of haemochromatosis is extraordinary in that over the past 50 years it has changed from being a rarity to the commonest inherited disorder in people of North European ancestry, with a frequency of as high as 1 in 200–300 people.

Haemochromatosis was first described in 1865 when, in an autopsy on a person with diabetes with bronzing of the face and nearly black discoloration of the penis, Armand Trousseau found a greatly enlarged cirrhotic liver. However, it was Victor Hanot and Anatole Chauffard in 1882 who described the characteristic triad of symptoms – pigmentation of the skin, cirrhosis of the liver and diabetes. When Hanot gave a lecture at the British Medical Association annual meeting in 1895, he described it as a new disease (Hanot, 1896). In 1889 Friedrich von Recklinghausen identified an iron-containing pigment and coined the name haemochromatosis. At the beginning of the 20th century the source of the iron was thought to be breakdown of haemoglobin, although, since sufferers were not anaemic, it was postulated that this proceeded very slowly. We now know that it is due to increased absorption. By 1914, when Archibald Garrod and colleagues reported a single case of haemochromatosis, there were at least 60 others in the literature (Gaskell et al, 1914). Garrod described the pigmentation as being different from any other type but found it "difficult to express in words wherein the peculiarity consists." He compared its quality to that of a metallic surface.

In 1934, Joseph Sheldon of Wolverhampton reviewed 304 cases from the literature and seven of his own. He noted the very striking sex incidence and wrote that, "Typically the patient – almost certainly a middle aged man – will present four features, one or more of which may however be absent. These are an enlargement of the liver, caused by a hypertrophic cirrhosis; a bronze pigmentation of the skin, which usually has in addition a peculiar slaty blue or metallic nuance; a diabetes of severe type; and a form of sexual hypoplasia" (Sheldon, 1934).

Sheldon could only find five definite reported instances in which brothers had been affected. One of the most dramatic was reported by Frisch in 1922 in which seven siblings were known locally as the "black family". Nevertheless, these cases supported Sheldon's view that it was an inborn error of metabolism. He wrote that,"The syndrome which is commonly spoken of as bronzed diabetes, and which is characterised by the association together of cirrhosis of the liver, the peculiar pigmentation of the skin and viscera known as haemochromatosis, fibrosis of the pancreas, and, as a rule, persistent glycosuria, has been observed so often that one can hardly doubt that in it we are confronted with a pathological entity, and with no mere accidental grouping of morbid events."

In 1936 RD Lawrence wrote a review on the prognosis in haemochromatosis. Before insulin, according to his reading of the literature, 50% of sufferers had died of diabetic coma, and, even in 1935, Sheldon gave the average duration of life after diagnosis as 18½ months. Lawrence described 12 of his own patients, of whom six had survived more than five years. "I see no reason," wrote Lawrence, "to tell these patients they have a fatal disease and think it best, if necessary to say that their diabetes is complicated by a large liver" (Lawrence, 1936). This paternalistic approach was used to prevent them looking up haemochromatosis in an out-of-date encyclopaedia.

A new era in treatment was inaugurated by the introduction of regular venesection in the 1950s (McAllen et al, 1957). At this time many patients were diagnosed late and the benefits

of venesection were correspondingly limited. Regular venesection produced a modest increase in life expectancy but complications such as impotence and arthropathy did not resolve and less than one third of those with diabetes had a reduction in insulin dose. Hepatomas still developed (Bomford and Williams, 1976). Today, provided the diagnosis is made before diabetes and liver or heart disease have developed, the life expectancy with regular treatment is normal.

Confirmation that haemochromatosis was inherited came from the 1976 discovery by Marcel Simon and colleagues that it was associated with HLA-A3 and B14 (Simon et al, 1976). The gene was mapped to chromosome 6 and identified in 1996 (Feder et al, 1996). Nearly 90% of patients with haemochromatosis are homozygous for a single missense mutation called *C282Y.* This did not die out because it has no adverse clinical effects in the reproductive years. What advantage it conferred on heterozygotes is uncertain but it may have protected against iron deficiency anaemia due to pregnancy or blood loss from battle wounds. Where it originated is uncertain but a convincing argument has been made that it was spread by the Vikings since the gene frequencies today are highest in areas that the Vikings colonised such as Iceland and the Faroe Islands, and in coastal areas they conquered such as Brittany (Distante et al, 2004).

There may well be undiagnosed cases of haemochromatosis in your clinic whose "three As" (Asthenia, Arthropathy and raised Alanine aminotransferase) have been misdiagnosed. Don't rely on pigmentation (which is certainly not bronze, and more like a slate colour). My misdiagnosed patient did have pigmentation, which I had attributed to being unwashed. In conclusion, even if the diagnosis does not help your patient, it may benefit the family.

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