Serum Ferritin, or Being in the Right Place at the Right Time

A. Jacobs and M. Worwood
Department of Haematology
University of Wales College of Medicine
Heath Park, Cardiff CF4 4XN
Wales
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At the time this paper was published, we had already had some considerable interest in human iron metabolism, which we had explored both clinically and experimentally for some years. We were initially stimulated by the high incidence of iron deficiency and the need to understand iron balance. In the late 1960s, Mike Beamish came to work in the laboratory as a haematologist trainee and pointed out that ferritin was readily detectable in the serum of some patients with malignant lymph node disease or liver damage. In pursuing this phenomenon, we evolved a simple laboratory method for detecting this using patterns of immunoelectrophoresis, but the technique had limited sensitivity. Nick Hales had recently joined the medical school as professor of medical biochemistry and he suggested at lunch one day that we could easily increase the sensitivity of our method by joining in his excitement for immunoradiometric assays (IRMA). He and Mike Addision collaborated with us in establishing an IRMA for ferritin in serum, and it immediately became obvious that we could not only detect the protein in pathological sera but also in normal subjects. To our surprise, the mean concentration in men was about double that in women, and iron-deficient patients had levels below the normal range but still within the capacity of the technique. We thought we now had a simple laboratory method for measuring iron stores, and the paper in the British Medical Journal was the first clinical validation of this concept.

Although the original technique was simple in concept, it was not an easy technique, and one author (MMW), Pat Llewellyn, and Beamish spent many frustrating hours preparing immunoadsorbants and labelling antibodies. However, one early hope was soon realised when the use of quantitative plethysmography demonstrated the relationship between body iron stores and serum ferritin concentration in 26 normal subjects2 (MW lost 14 pints of blood before anaemia developed). This study was the responsibility of Geraint Walters, who tragically died in 1975.

In order to encourage use of the assay, we arranged a number of "workshops" and participants came from the UK and other parts of Europe. Today, when every new assay must be patented, it seems a strange course to take! However, the original IRMA was tedious and reagent quality was very critical. The assay did not really attract attention until the introduction of the "2-site IRMA." The application of ferritin was first described in a paper by L.E.M. Miles and associates.3 Miles was a colleague of Hales, who had moved to San Francisco. The original findings on serum ferritin and iron stores were rapidly confirmed by several groups, and the major problem in its diagnostic use was soon discovered—the ferritin assay is also an excellent liver function test. Since then we and others have explored the biochemistry, immunology, and physiology of serum ferritin and have sought "carcinogenic ferritins" and other means of using ferritin for the detection of malignancy (a largely unsuccessful quest).4

Apart from its widespread application to the diagnosis of iron deficiency and iron overload, the introduction of the assay has influenced other areas of science and medicine. It stimulated interest in the biochemistry of ferritin and in its immunological properties. It rekindled interest in hereditary (idiopathic) haemochromatosis. It was hoped that this would make possible early detection of the disorder, but this was not to be as it was found that ferritin concentrations were often in the normal range in the early stages of the disease. The sense of disappointment was expressed in an editorial by W.H. Crosby.5 The application of the assay to patients with renal failure undergoing dialysis revealed that many had developed iron overload because of excessive supplementation to compensate for blood losses.6 Here the assay was of benefit to many patients and monitoring with serum ferritin is now usual. Events since 1972 have thoroughly justified our speculations, and the ramifications of clinical use of this assay have been considerable both in iron-deficient and in iron-overload states. This paper represents the take-off point in the evolution of a lunchtime conversation into routine clinical practice.


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