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Jacobs A, Miller F, Worwood M, Beamish M R & Wardrop C A. Ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *Brit. Med. J.* 4:206-8, 1972.
[Welsh National School of Medicine, Cardiff, Wales]

The concentration of ferritin in serum gives the quantity of storage iron in normal patients and those with iron deficiency and overload. The mean values for normal men and women and the threshold value for nondeficient erythropoiesis are given. [The *SCI*® indicates that this paper has been cited in more than 385 publications.]

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

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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 haematology 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, he evolved a simple laboratory method for detecting this using counter immunoelectrophoresis, but the technique had limited sensitivity.[1] 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 current enthusiasm for immunoradiometric assays (IRMA). He and Mike Addison 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 (MW), Pat Llewellin, and Beamish spent many frustrating hours preparing immunoadsorbants and labelling antibodies. However, one early hope was soon realised when the use of quantitative phlebotomy demonstrated the relationship between body iron stores and serum ferritin concentrations in 26 normal subjects[2] (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 "carcino-fetal 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 the assay 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]

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.

1. **Beamish M R, Llewellin P & Jacobs A.** A method for the detection of ferritin in serum. *J. Clin. Pathol.* 24:581-2, 1971. (Cited 25 times.)
2. **Walters G O, Miller F M & Worwood M.** Serum ferritin concentration and iron stores in normal subjects. *J. Clin. Pathol.* 26:770-2, 1973. (Cited 315 times.)
3. **Miles L E M, Lipschitz D A, Bieber C P & Cook J D.** Measurement of serum ferritin by a 2-site immunoradiometric assay. *Anal. Biochem.* 61:209-24, 1974. (Cited 365 times.)
4. **Worwood M.** Serum ferritin. *Clin. Sci.* 70:215-20, 1986. (Cited 10 times.)
5. **Crosby W H.** Serum ferritin fails to indicate hemochromatosis—nothing gold can stay. *N. Engl. J. Med.* 294:333-4, 1976. (Cited 20 times.)
6. **Hussein S, Prieto J, O'Shea M, Hoffbrand A V, Baillod R A & Moorhead J F.** Serum ferritin assay and iron status in chronic renal failure and haemodialysis. *Brit. Med. J.* 1:546-8, 1975. (Cited 85 times.)

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