The methods described in this publication enabled the direct measurement of human intrinsic factor in normal individuals and in patients with disorders of the stomach. Furthermore, it was established that circulating intrinsic factor antibodies were found exclusively in patients with Addisonian pernicious anaemia. [The SC® indicates that this paper has been cited in over 270 publications since 1963.]

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As a fledgeling haematologist in the early 1960s, I was honored to be invited by I. Chanarin to join the staff of the Medical Research Council's Experimental Haematology Research Unit, whose director was P.L. Molison. My task was to devise a method for the measurement of human intrinsic factor (IF), the stomach secretion needed for the absorption of dietary vitamin B₁₂, which is vital for normal haemopoiesis.

It had been known for many years that gastric juice (GJ) "bound" B₁₂, and although IF was thought to be the major component, it was known that there were other "nonspecific" factors (R-binders) present, such as those in bile and saliva. Therefore measurement of the B₁₂-binding capacity of GJ alone was not an assessment of its IF content. It was necessary to sort out the wheat (IF) from the chaff (IF + R-binder).

The way ahead was signposted by the crucial observations of K.B. Taylor, who demonstrated that a proportion of patients with Addisonian pernicious anaemia (PA) had a circulating antibody to IF. The technique used was cumbersome, involving B₁₂ absorption tests in patients with PA. The patient drank PA serum together with hog IF and radioactive B₁₂. If the PA serum contained antibody, there was impaired B₁₂ absorption. We devised an in-vitro test for detecting IF antibodies that involved pre-incubating known normal GJ with PA serum, adding radiolabelled B₁₂ in excess, removing unbound B₁₂ with activated charcoal, and calculating the amount of radioactive B₁₂ in the supernatant following centrifugation. If antibody was present, it would react with IF and prevent it binding labelled B₁₂. A control using normal serum was also set up, and an antibody was deemed to be present in the PA serum if there was a reduction of B₁₂ binding capacity relative to the control.

Using IF-antibody-containing sera of sufficiently high titre to neutralise all the IF present in normal GJ, it was now possible to evaluate the IF-content of any GJ sample. Thus the difference between total B₁₂-binding capacity (IF + R-binder) using control serum in the assay system and R-binding (using IF-antibody serum) was a measure of IF content. We defined the unit of IF as the amount that bound one ng of labelled B₁₂. A method using a B₁₂ analog (cobinamide) to block R-binder has recently been described, which enables IF to be measured directly and obviates the need for IF antibody in the assay system.

I think our publication has been highly cited because it was the first account of a simple, rapid, and reproducible in-vitro quantitative assay of a vital body secretion that had been discovered more than 30 years previously. Furthermore, our work facilitated the accurate study of the physiological and pharmacological properties of IF and was also of value in the differential diagnosis of patients with megaloblastic anaemia. The detection of circulating IF antibody was of particular importance in this context, since this is virtually only found in patients with PA.

2. Taylor K B. Eduction of intrinsic factor by pernicious anaemia sera Lancet 1 106-8, 1959 (Cited 150 times)

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