

Historical Review

WILLIAM BOSWORTH CASTLE: PIONEER OF HAEMATOLOGICAL CLINICAL INVESTIGATION

William Bosworth Castle (1897–1990) spent his entire haematological career at the Harvard Medical Unit and Thorndike Memorial Laboratory at Boston City Hospital during the golden age of haematology. Castle's experiments in solving the puzzle of pernicious anaemia by identifying the intrinsic factor are models of clinical investigation and marked a new era in haematology. Castle's insatiable curiosity about the mechanisms of disease, his ability to design and conduct simple experiments to test hypotheses, and his ability to attract clinical investigators to the Thorndike Laboratory, and inspire them and make them feel like intellectual equals, fuelled the dramatic output of seminal work on nutritional anaemias, haemolysis, splenic function, haemoglobin physiology and coagulation. Indeed it was Castle's breadth of scientific achievements in haematology and his leadership of the Thorndike Memorial Laboratory that contributed to the notion that modern haematology was born in Boston but nurtured at the Thorndike Memorial Laboratory.

'Let us never forget that Nature is the most original of all experimenters and that it is the patient's physician who is privileged to learn most directly from her sometimes cruel, but never meaningless, clinical presentations.'

William Bosworth Castle

INTRODUCTION

In the early years of the twentieth century, haematology was simply a pictorial description of blood. The blood cells were regarded as elements with interesting variation in shape and size, and cumbersome methods existed to enumerate and study them. Haematological disorders produced dramatic clinical manifestations and many were deadly, and this led to a sense of urgency for empirical therapeutic interventions before underlying pathophysiology was fully understood, at least for the more common blood diseases.

Pernicious anaemia was one such disorder where millions of lives were saved by George Minot's discovery of the effectiveness of liver therapy in 1926, thereby relieving physicians of the burden of having to find a treatment for the usually fatal illness and allowing them to focus on the mechanisms of disease. In 1926, William Castle had just spent his first year as a resident physician at the Thorndike

Memorial Laboratory at Boston City Hospital under its first director, Francis Peabody. Peabody's untimely death the following year resulted in the appointment of George Minot as the second director (Paul, 1991). Thus, in 1927, Castle was working directly under George Minot who had already gained worldwide fame for the discovery of liver therapy for pernicious anaemia (Minot & Murphy, 1926) and who was to win the Nobel Prize in 1934.

The Thorndike was opened in 1923 as the first clinical research laboratory at a municipal hospital in the USA, and was run by the Harvard Medical School. The unique laboratory had office space, research laboratories and a 17-bed ward funded by the City of Boston for the study of the patient, and was situated at Boston City Hospital, one of the nation's largest municipal hospitals (Castle, 1964).

Castle was, therefore, poised to take haematology from a purely descriptive study of the blood to a distinctly physiological point of view and enter an era of the study of the mechanisms of disease. His early experiments led to the discovery of the intrinsic factor and stand as exemplary models of clinical investigation to this day. His life's work was accomplished at this institution, and by leadership and example he helped to create an atmosphere that would foster clinical research and spawn a glorious era of clinical investigation (Karnad, 1997).

THE LIFE OF WILLIAM BOSWORTH CASTLE

Castle was born on 21 October 1897, in Cambridge, Massachusetts, the first of three children to William Ernest Castle and Clara Sears Bosworth. At the time of his birth, Castle's father had a PhD in zoology and, as an instructor at Harvard's department of zoology, was developing his interests in mammalian genetics. By the time Castle would graduate from College, his father William Ernest Castle had established the finest genetics programme in the country, started the journal *Genetics* and published the textbook *Genetics and Eugenics*, and earned a name for himself as the Father of Modern Genetics (Dunn, 1965).

Graduating from Browne and Nichols School, a private school in Cambridge, Castle found that he was not interested in the attention-demanding animal experiments in genetics that his father was known for. He entered Harvard College at the outbreak of World War I and, by 1917, had decided on a medical career and enrolled at Harvard Medical School, vaguely aware that in medicine, in contrast to surgery, clinical investigation was in its infancy. As a second year medical student, he failed a haematology examination when he was unable to provide accurate red cell counts by using a counting chamber. To make up the

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examination, he faced Francis Peabody (the young Harvard Professor who would soon recruit Castle to the Thorndike) who asked him some general questions on anaemia and passed him. Graduating from medical school, Castle was not impressed by Osler's textbook with its limited specific therapeutic interventions and limited scientific explanations into the mechanisms of disease (Karnad, 1997).

In 1923, as the Thorndike Memorial Laboratory was inaugurated, Castle became a house officer at the Massachusetts General Hospital and, the following year, with no interest in private practice, became Instructor in Physiology at the Harvard School of Public Health. Here, under Dr Cecil Drinker, he had the opportunity to investigate the causes of radiation injury in employees who applied luminous radium-containing paint onto watch dials at the New Jersey Radium Corporation. Castle determined that it was the significant radium dust exposure throughout the plant and not just the procedure of applying the radium onto watch dials that had caused the injuries, and the results were published and recommendations made to eliminate these occupational hazards (Castle *et al*, 1925). Castle then took on tedious experiments to study the respiratory quotient of dog muscle, an experience that taught him that research was pure dedication and hard work (Karnad, 1997).

In the spring of 1925, Castle was invited by Peabody to join the Thorndike Memorial Laboratory as a resident physician. He accepted, and found room and board adjacent to the wards of the Laboratory. In his first 2 years there, he assisted Peabody in collecting bone marrow samples from patients with pernicious anaemia, and had one publication to his credit reporting on cholesterol and lecithin levels in patients with pernicious anaemia (Muller *et al*, 1928). It was at this juncture that George Minot was appointed as the new Director after the untimely death of Peabody from a malignant gastric tumour. Castle recalled that his apprehension at facing the famous new Director spurred on new ideas for research, and in a flash he developed an idea for experiments to study the relationship between achylia gastrica (atrophic gastritis) and pernicious anaemia (Fig 1).

These experiments were astonishingly successful and were hailed by Minot as 'epoch making' discoveries (Rackemann, 1956). Over the next 20 years, Castle would build on these experiments and establish the role of intrinsic factor in the pathogenesis of pernicious anaemia. These studies spawned an era of clinical investigation and research in nutritional anaemias. Owing to his scientific achievements in this field, which were at times overshadowed by the Nobel prize-winning liver therapy of pernicious anaemia, Professor David Weatherall called him the '*unsung hero of the pernicious anaemia saga*' (Weatherall, 1995).

Although an imposing figure, over six feet tall with a firm jaw and deep set eyes, throughout his career he was known for his modesty, his unique ability to make others feel they were intellectual equals and for his earthy, self-deprecating humour (Fig 2). In 1948, as a full professor at Harvard, Castle drove a 1932 Model A Ford, already an antique car. He was regularly seen with his sleeves rolled up fixing broken tables, radiators and centrifuges at Boston City Hospital. His hobby of fixing things came in handy in



Fig 1. Castle, c 1930, in the pernicious anaemia era. Reproduced from the author's collection with the kind permission of Mrs Castle.



Fig 2. George Richards Minot Professor of Medicine, 1957. Reproduced from the author's collection with the kind permission of Mrs Castle.



Fig 3. Castle, the sailor, c 1980. Reproduced from the author's collection with the kind permission of Mrs Castle.

the impoverished environment of Boston City Hospital, prompting him to say often that to get things done at Boston City Hospital you had to learn to do things on your own. His main hobby was sailing, and he would take his entire family, wife Louise, son William Roger and daughter Anne, sailing off the coast of Cape Cod (Fig 3). Castle enjoyed the camaraderie of the Thorndike investigators and remembered fondly the noisy banter in the hospital dining room, and the warmth of the Christmas gatherings at his home in Brookline (Karnad, 1997).

From 1926 until 1948 when Castle succeeded Minot as the third Director of the Thorndike Memorial Laboratory, an era that Maxwell Wintrobe labelled the first phase of the Golden Age of Haematology (Wintrobe, 1985), Castle made several key contributions to many areas of haematology that are outlined below. Castle had superb administrative assistance at the Thorndike: Charles Davidson directed Harvard's educational programmes and Maxwell Finland handled administrative issues related to research.

The period after World War II in the USA saw remarkable growth in research funding and this further fuelled research at the Thorndike. In 1957, Castle was appointed the first George Richards Minot Professor of Medicine; he retired from his administrative duties in 1963 and was succeeded by Maxwell Finland.

Upon his retirement as Director of the Thorndike, he became holder of another endowed Professorship when he was appointed the first Francis Weld Peabody Professor

of Medicine at Harvard. He was also appointed first Distinguished Physician of the Veterans' Administration system, and would serve as visiting professor and scientific advisor to the institutions of the Veterans' Administration throughout the country. He was honoured at Harvard by the creation of an endowed Professorship in his name, by an annual lecture in his name and the naming of a medical student society in his honour. At home, he was President of the American Society for Clinical Investigation and President of the Association of American Physicians, elected member of the National Academy of Sciences, and was awarded the Kober Medal of the Association of American Physicians. Abroad, he was made an honorary member of the Royal Society, and Royal College of Physicians of the UK, Edinburgh, Australia and Canada.

In addition to the breadth of his scientific achievements, he helped establish the international reputation of the Thorndike Memorial Laboratory and trained a generation of clinical investigators and leaders in medicine. Jan Waldenstrom wrote, '*Very few colleagues have impressed me more than Castle, both for his intense interest in problems and his marvellous capability to describe them*' (Waldenstrom, 1994).

Castle died on 9 August 1990, aged 92. Of this true giant in medicine and haematology, John Harris wrote: '*We could not get enough of him. Although his legacy lives on in many, nevertheless with his death a certain stable, optimal standard has been lost from this universe*' (Karnad, 1997).

LIFE'S WORK

Pernicious anaemia

In 1927, Castle performed his initial set of brilliantly conceived experiments that demonstrated the existence of the gastric intrinsic factor for the first time (Castle, 1929). Normal human gastric juice alone and nearly raw hamburger meat alone did not stimulate a reticulocyte response when fed to patients with pernicious anaemia. However, hamburger meat that had resided in Castle's stomach for 1 h before it was regurgitated and then fed to patients with pernicious anaemia via a nasogastric tube promptly provoked a reticulocyte response. Results of these experiments on 10 patients were published, and Castle stated: '*that in contrast to the conditions within the stomach of the pernicious anaemia patient, there is found within the normal stomach during digestion of beef muscle some substance capable of promptly and markedly relieving the anaemia of these patients*' (Castle, 1929).

In his second set of experiments, Castle fed normal gastric juice alone to patients with pernicious anaemia with no effect, feeding them normal gastric juice in the evenings after they had been fed beef in the morning also produced no reticulocyte response, but feeding them 200 g of beef incubated for 2 h with normal gastric juice in the presence of hydrochloric acid provoked a brisk reticulocyte response. Castle concluded: '*It is believed that for the first time a relationship between the stomach and the function of the bone marrow of the human being has been demonstrated*' (Castle & Townsend, 1929).

By 1930, he was able to write: '*The lack of this particular property (Intrinsic Factor) of the gastric contents in pernicious anaemia is probably the essential defect leading to the*

development of the disease, through a failure of the normal reaction, occurring in these experiments with beef muscle proteins (Extrinsic factor) and normal gastric juice' (Castle *et al.*, 1930).

These experiments also showed the importance of the reticulocyte response as an index of activity of the bone marrow and of the effectiveness of the therapeutic agents. Daily observation of the reticulocyte count played a pivotal role in analysing the basis of various nutritional anaemias such as iron deficiency anaemia and the macrocytic anaemias (Minot & Castle, 1935).

These series of simple experiments by Castle (equipment used: a meat chopper, a sieve, a few containers and a flexible rubber tube for nasogastric intubation), conducted a full 20 years before the discovery of the extrinsic factor (vitamin B₁₂), remain some of the most elegant clinical investigations ever carried out in this country. Over the next 27 years, Castle and colleagues at the Thorndike Memorial Laboratory further elucidated the role of intrinsic factor and clearly outlined the pathophysiology of pernicious anaemia.

Tropical sprue and hookworm anaemia

Joining Dr Cornelius Packard Rhoads on a Rockefeller Foundation sponsored trip to San Juan, Puerto Rico, Castle studied the local problem of hook worm infestation and eradicated it with iron therapy and appropriate public health measures (Rhoads *et al.*, 1934).

They also studied 100 patients with sprue and effectively treated most patients with parenteral liver extract. They conducted complex experiments on these patients that involved samples being sent back and forth to the Thorndike Laboratory and concluded, '*in sprue as in pernicious anaemia...difficulty with the absorption of substances from the intestinal tract...is probably involved in certain instances of both diseases*' (Castle *et al.*, 1935).

Iron and iron deficiency anaemia

In 1932, together with Clark Heath and Maurice Strauss, Castle treated seven patients with intramuscular injections of iron citrate and showed an intimate relationship between the iron injected and the haemoglobin formed (Heath *et al.*, 1932). They showed an extraordinarily close relationship between the amount of iron injected into the iron-deficient patients and the amount of haemoglobin gained in the circulation: the average utilization of parenteral iron in all patients was 96%. This showed, for the first time, that iron promotes haemoglobin formation not as a catalyst but as an essential component of the newly formed haemoglobin.

Next, a series of papers by Strauss and Castle explored anaemia in pregnancy, showing that the vast majority of pregnant women with anaemia have hypochromic anaemia due to iron deficiency, and that this anaemia resolves during and after gestation by effective doses of iron (Strauss & Castle, 1932a,b, 1933).

Haemolysis

The effective treatment of pernicious anaemia meant that by the 1930s there were no longer untreated patients with the disease for study at the Thorndike and Castle's attention

shifted to exploring the mechanisms of red cell destruction. Abnormal red cell shapes accompanied the anaemias that were associated with increased red cell destruction. Exactly how these abnormalities resulted in red cell destruction was not clear.

Working with Geneva Daland, an experienced haematology laboratory technologist, Castle studied the effect of hypotonic salt solutions on red cells and concluded that the haemolysis of the red cell in these solutions was a function of its form or shape and not due to its osmotic behaviour (Castle & Daland, 1937).

In 1940, Thomas Hale Ham and Castle solved a problem that had puzzled Castle since his experiments with Geneva Daland: why did red cells from patients with congenital haemolytic jaundice, which were uniquely susceptible to hypotonic salt solutions *in vitro*, suffer the same fate in the isotonic environment *in vivo*? They showed that red cells from patients with congenital haemolytic jaundice were fragile because of some intrinsic abnormality and not due to the presence of a 'haemolysin', postulating that these fragile cells could not withstand the vagaries of the splenic circulation (Ham & Castle, 1940a). John Dacie wrote that Ham and Castle's experiments on the phenomenon of erythrocytosis and fragility of the red cells in hypotonic solutions provided '*the first satisfactory demonstration of an abnormal tendency to lysis in vitro which might be applicable to conditions in vivo*' (Dacie, 1967a).

This led to a series of classic experiments on the mechanisms of haemolysis in spherocytosis at the Thorndike that spanned nearly 20 years. Hundreds of osmotic fragility tests were performed in patients with hereditary spherocytosis (HS) before and after a splenectomy, and in some patients osmotic fragility tests were performed days, weeks, months and years after splenectomy. In separate experiments, survival and fragility tests of normal red cells transfused into patients with HS was compared with the survival and osmotic fragility of the HS red cells transfused into normal subjects with and without a spleen. Although this work was carried out in the early 1940s, World War II delayed publication of the results of these experiments and they were first published in abstract form in 1946 and 1947. Their classic paper was published only in 1956, in which Castle and his co-investigators established that HS red cells retain their osmotic fragility after splenectomy, that HS red cells transfused into a normal individual without a spleen result in normal red cell survival, but are destroyed rapidly when transfused into a normal recipient with an intact spleen, and that the degree of osmotic fragility of HS red cells was greatest in red cells collected from the splenic red pulp (Emerson *et al.*, 1956). Castle *et al.*, therefore, proposed a hypothesis that the exquisitely fragile red cells found in the splenic pulp had been 'conditioned' in the spleen after sequestration. From these experiments, they concluded, '*...that the function of the spleen in hereditary spherocytosis may be normal and the inherited defect is limited to the red cells*' (Emerson *et al.*, 1956). Castle and his co-workers were, therefore, the first to establish that the haemolysis in HS was due to an intrinsic abnormality of the red cell, but also the first to clearly define the phagocytic role of the spleen in this disorder.

Castle was also interested in other haemolytic anaemias. Dacie (1967b) referred to the 'pioneer work' of the Thorndike investigators Emerson, Ham and Castle, who showed for the first time that certain drugs act as oxidation-reduction catalysts, causing oxidation of haemoglobin leading to cell membrane injury and haemolysis (Emerson *et al.*, 1941). Several years later, James H. Jandl at the Thorndike demonstrated the events triggered by oxidant stress that led to Heinz body formation (Jandl *et al.*, 1960; Allen & Jandl, 1961). Castle also worked with Jandl to identify the sites of sequestration of red cells in haemolytic anaemias using radiolabelled cells (Jandl *et al.*, 1956, 1957).

Haemoglobin

Ham and Castle (1940b) made an important observation on the viscosity of blood in patients with sickle cell anaemia and proposed the explanation of a 'vicious cycle of erythrostatics' set up by the sickling of red cells, a fundamental explanation of the clinical manifestations of the disease taught to this day.

These observations triggered Castle's interest in sickle cell anaemia. With Daland, Castle observed that sodium metabisulphite (an additive agent in the ascorbic acid solution Cevalin) induced sickling within 15 min (Daland & Castle, 1948). They reported this technique as a simple diagnostic test for sickle cell anaemia, to be used at the bedside.

Castle's conversations with Linus Pauling in 1945 about the sickling phenomena triggered Pauling's interest in understanding this disorder. Pauling, a protein chemist, was intrigued by Castle's observations on the unusual appearance of sickled red cells under polarized light. He inferred that the defect of the sickled red cell might lie in the haemoglobin molecule. In 1949, together with Harvey Itano, Pauling showed that the haemoglobin of patients with sickle cell anaemia had a different electrophoretic pattern compared with normal haemoglobin. This, they surmised, meant that the two molecules were different, coining the term 'molecular disease' (Pauling *et al.*, 1949).

In 1948, John Harris joined the Thorndike and, using haemoglobin in solution, showed that sickle haemoglobin became semisolid, plugging up the pipettes and the viscosimeter. The increased viscosity could easily be reversed by oxygenating the jelly-like substance. At Castle's suggestion, he showed this viscous deoxygenated sickle cell haemoglobin solution to David Waugh at the Massachusetts Institute of Technology, who readily identified microscopic haemoglobin tactoids as the actual physical basis of the sickling process (Harris, 1950). Castle played a significant role in the story of sickle cell anaemia, and his astute observations on the clinical manifestations of the disease and the 'vicious cycle' of erythrostatics that he observed planted the seeds of molecular haematology.

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