Howell-Jolly Bodies: A Brief Historical Review

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Abstract: Understanding the process by which red cell precursors lose their nuclei developed in the late 19th and early 20th centuries led to the identification of nuclear remnants in circulating red cells in certain pathological states, particularly absence or decreased function of the spleen. William Howell, an American, and Justin Jolly, a Frenchman, were among a number of early contributors to this field. Early on, their names were applied, singly or in tandem, to these red cell inclusions, and the eponym, Howell-Jolly bodies, has stuck. It was, however, not until after the mid-20th century that Howell-Jolly bodies were clearly differentiated from basophilic stippling and that the mechanisms of their formation and removal from red cells were understood.

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By the middle of the 19th century, it was generally agreed that circulating red blood cells arise not from white blood cells but from their own line of nucleated precursor cells (normoblasts) in the bone marrow and other blood-forming organs. Initially, it was believed that the normoblast nucleus was lost by a process of absorption, possibly preceded by fragmentation; however, in 1880, Rindfleisch[1] suggested rather that the nucleus was extruded with a small rim of surrounding protoplasm. In 1890, Howell[2] published a lengthy description of his studies of cat embryos and bled kittens and cats. He believed that these studies supported the loss of the normoblast nucleus by extrusion but, in his view, without the rim of surrounding protoplasm. In considering the fate of the extruded nucleus, Howell rejected a previous suggestion that it formed platelets. He concluded that it was dissolved in the plasma and even suggested that it might provide a source of the increased fibrinogen he had observed in the plasma of bled animals.

Howell, as had others, observed smaller granules (presumably what we now call basophilic stippling) staining like nuclei, in cells both before and after the loss of their nuclei. He thought they were bits of nuclear chromatin left behind when the nucleus was extruded, not, as others had suggested, the remaining fragments of an absorbed nucleus. He did not know the fate of these granules. Howell went on to describe the large, usually single, nuclear remnants, which now bear his name. He asserted that these nuclear fragments remained with the cell throughout its survival in the circulation and even suggested that they might therefore provide a means of measuring red cell lifespan.

Obviously, Howell erred in some of these conclusions about the loss of normoblast nuclei. He failed to identify the small rim of cytoplasm accompanying the extruded nucleus. He did not clearly distinguish between the origin of the small granules (basophilic stippling) and the large nuclear remnants. His suggestions about the fates of both the extruded nuclei and the retained large nuclear fragments were mistaken. Nevertheless, his detailed studies dispelled previous fanciful theories about the development of red blood cells and accurately described the large retained nuclear fragments, thus justifying the inclusion of his name in their eponym.

Jolly[3] published his extensive observations on the fate of the normoblast nucleus in the early years of the 20th century, more than 10 years after Howell's article. His studies, set forth in previous publications, are reviewed in his lengthy article published in 1907. Jolly used a variety of stains in histological studies of both embryonic and mature mammals of several species and, like Howell, concluded that disappearance of the normoblast nucleus was due to a process of expulsion. He postulated that the expulsion was induced by increased pressure within the cell, perhaps due to increased intracellular fluid and cell shrinkage. He also noted the elasticity of the red cell membrane. He further supported his conclusions about nuclear expulsion by studies of phagocytes which contained nuclei, but not cytoplasm, of red cells. Jolly discounted the suggestion of Howell that the extruded nuclei might form plasma fibrinogen and the suggestions of others that they might form new erythrocytes or even other cells. Jolly described fragmentation of nuclei during expulsion which left behind "pieces" of nuclei, and he additionally noted smaller basophilic granules. Presumably, these were Howell-Jolly bodies and basophilic stippling, respectively. Jolly's long and detailed descriptions of experiments on the fate of mammalian red cell nuclei and his refinement of some of Howell's conclusions justify the inclusion of his name alongside Howell's in the eponym.

In 1907, Morris, then a junior faculty physician at Johns Hopkins, when Howell was Chairman of Physiology and Dean of the Medical School, summarized the primary contributions of Howell, Jolly and several other authors to the description of the nuclear fragments seen in red cells under abnormal conditions, such as after severe hemorrhage.[4] Morris, like Howell and Jolly, described the smaller multiple inclusions (basophilic stippling) in addition to the large, usually single, nuclear fragments and considered them also of nuclear origin. All these early observations were in animal, not human, red cells. Morris subsequently became the first to identify what he named "Howell's nuclear particles" in a human, a patient with pernicious anemia, and he went on to describe them in red cells of several other human subjects.[4,5] Morris described nuclear fragments in cells still containing a nucleus and also the rare coexistence of the multiple small particles (basophilic stippling) and a nuclear remnant in the same cell. He still considered the small particles to be nuclear in origin despite noting differences in their staining properties from the large nuclear fragments.[5]

The suspicion of a relationship between splenectomy and splenic hypofunction and the presence of Howell-Jolly bodies began with a report by Schur[6] who described nuclear remnants in the red cells of a patient who had suffered from hyperthyroidism and later pernicious anemia and whose spleen at autopsy was found to be largely replaced by fibrous tissue. Roth[7] reported the presence of Howell-Jolly bodies in the red cells of a patient previously splenectomized for hemolytic disease. Morris[8] further solidified the association between

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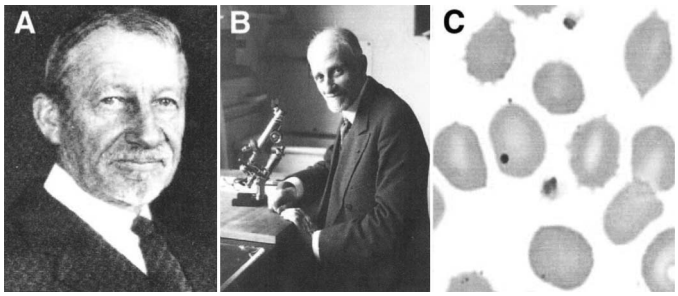

FIGURE 1. (A) Photograph of William Henry Howell reproduced from Ref. 16 with permission of the publisher. (B) Photograph of Justin Jolly reproduced with permission from a photograph in the archives of the French Academy of Sciences. (C) A photomicrograph of a Wright-stained peripheral blood smear from a splenectomized patient showing a Howell-Jolly body in 1 red cell.

splenectomy and the presence of Howell-Jolly bodies with studies on 3 splenectomized patients.

The names of Howell and Jolly began to be attached to the nuclear fragments in the early years of the 20th century. Morris referred to "Howell's particles" in 1907[4] and Roth to "Jollykörper" in 1912.[7] With the passage of time, the hyphenated "Howell-Jolly" eponym has been most commonly used, but occasionally the nuclear fragments are still referred to simply as "Jolly bodies."[9]

Some of the errors and uncertainties in the original conclusions of Howell, Jolly and others were clarified only after several decades, particularly after the advent of electron microscopy. The nuclear fragments may arise as a result of chromosomes separated from the mitotic spindle during abnormal mitoses or as a result of karyorrhexis at terminal stages of maturation.[9] On the other hand, basophilic stippling is recognized to arise from abnormal ribosomes only during the preparation of blood smears and not to involve nuclei, mitochondria or iron in the undried, unstained cell.[10] The mechanism by which nuclei and nuclear fragments are removed from red cells was also further elucidated. Crosby[11] coined the picturesque term "pitting function of the spleen" to describe the splenic removal of inclusions from red cells without destruction of the cells containing them. Weed and Weiss[12] pointed out how this may occur by a process of red cell fragmentation. Tavassoli and Crosby[13] subsequently showed how normal enucleation of the normoblast takes place by a similar process as cells exit the hematopoietic areas to the sinuses of the bone marrow through endothelial pores. Elucidation of these processes makes it understandable why Howell-Jolly bodies are seen in the blood most commonly in circumstances of increased red cell production, particularly when nuclear maturation is abnormal, as in megaloblastic states, and in the absence or diminished function of the spleen.

William Henry Howell was born in Baltimore in 1860, the 4th of 5 children in a family that had lived in Maryland for more than 2 centuries.[14] His father was described as an unsuccessful businessman, and William was apparently the first in his family to attend college.[15] He received an AB degree from Johns Hopkins University in 1881 and considered the study of medicine. For various reasons, which included lack of money and a delay in the opening of the Johns Hopkins Medical School, he pursued graduate study in physiology instead and received a PhD from Johns Hopkins in 1884. His thesis on the origin of fibrin in blood coagulation initiated the major area of his research during his subsequent academic career. After receiving his PhD, Howell joined the faculty of the Department of Biology at Hopkins. In 1889, he became Professor of Physiology at the University of Michigan. His 3 years at Michigan and a year at Harvard Medical School were his only separation from Johns Hopkins to which he returned in 1892 to become Chairman of Physiology in the new medical school, joining the famous faculty that included Welch, Osler and Halstead. He continued as Physiology Chairman for 24 years until 1916, serving also as Dean of the Medical School from 1899 to 1911. In 1916, with Welch, he organized the Johns Hopkins School of Hygiene and Public Health and succeeded Welch as Director of that school in 1925. He retired in 1931 at the age of 71 years but continued with research. He died in 1945, just 2 weeks before his 85th birthday. Although Howell was heavily involved in medical education and administration, his bibliography includes more than 30 research contributions on coagulation, including, with his student McLean, the isolation of heparin, and 16 articles on cardiovascular subjects, including important observations on the effect of ions on the heart. He was single author of a textbook of physiology for medical students and physicians through 14 editions from 1905 to 1940. Howell's only major article on nuclear inclusions in red cells[2] was written while he was at the University of Michigan. Howell married Anne Tucker of Baltimore in 1887. They had 3 children, 2 of whom became college deans. Wintrobe[16] remembers Howell as "a pleasant, quiet, unassuming little man, ready to listen, but firm in his own opinions" who in his laboratory "preferred to do the work himself because it was more fun" (Figure 1).

Justin Marie Jolly was born in 1870 in Melun, now a Paris suburb, into a family of magistrates and physicians. He obtained his doctorate in 1898 at the Universite de Paris and interned with surgeon Paul Georges Dieulafoy. He was, however, eager to pursue a career in the laboratory and studied at the College de France under pathologists-histologists Louis Antoine Ranvier and Louis-Charles Malassez who had themselves been students of Claude Bernard. Jolly served as chief of the laboratory at the medical clinic of the Hotel-Dieu de Paris and directed the histology laboratory at the Ecole des Hautes Etudes. In 1923, he published his "Traite technique d'hematologie" (Technical Treatise of Haematology), a volume of more than 1000 pages and 700 figures, which became a classic used by many students. He was a pioneer in the histological study of living tissues and made microscopic moving pictures of mitosis in living cells. From 1925 until his retirement in 1940, Jolly was a professor at the College de France. He became a member of the Academie de Medecine in 1928 and its president in 1947. Jolly was one of the founders of the journal, Revue d'hematologie, and a member of the French Academy of Sciences. He died in 1953 at the age of 82 years.[17,18]

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