

## The bursa of Hieronymus Fabricius ab Aquapendente: from original iconography to most recent research

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### Abstract

Hieronymus Fabricius ab Aquapendente (1533–1619) described the homonymous bursa in the “*De Formatione Ovi et Pulli*”, published posthumously in 1621. He also included a figure in which the bursa was depicted. We here present the figure of the bursa of Fabricius, along with corrections of some mislabeling still presents in some anastatic copies. The bursa of Fabricius is universally known as the origin of B-lymphocytes; morphogenetical and physiological issues are also considered.

**Keywords:** anatomical iconography, bursa of Fabricius, Hieronymus Fabricius ab Aquapendente.

Hieronymus Fabricius ab Aquapendente was born in 1533, he graduated in medicine at the University of Padua, and he was a student of Gabriel Falloppius. In 1565, he became a professor of anatomy and surgery in Padua. In 1594, Fabricius was the proponent of the permanent theatre for public anatomical dissections, which is still visible in the Bo’ Palace of the University of Padua as the most ancient permanent anatomical theatre in the world. From a professional point of view, Fabricius was a renowned physician who treated the most important personalities, such as Galileo Galilei, the King of Poland, and the Duke of Urbino [1, 2]. In 1607, he was appointed Knight of St. Mark.

With respect to previous anatomists, Fabricius tried to address the functional implications of the various anatomical structures. In this sense, it is interesting to note that most titles of his works are focused on functions more than structures. In 1600, he published “*De Visione, Voce, Auditu*” and “*De Formato Foetu*”. In 1601, he published “*De Locutione et Eius Instrumentis*” and in 1603, “*De Brutorum Loquela*”. In “*De Venarum Ostiolis*” (1603), he detailed the venous valves, their descriptions and illustrations being following used by Harvey to demonstrate blood circulation [1, 2]. In 1619, Hieronymus F. ab Aquapendente died and his corpse was buried in the San Francesco’s church in Padua [3].

In 1621, the manuscript entitled “*De Formatione Ovi et Pulli*” was published. It contains the first description of the bursa: “*Tertium quod in podice est adnotandum, est duplex vesicula, quae in ima eius parte ad os pubis supereminet, et conspicua, exteriorque apparet, fimulatque vterus iam propofitus conspectui fefe offert*” (Figure 1A); “The third thing which should be noted in the podex is the double sac (bursa), which in its lower portion projects toward the pubic bone and appears visible to the observer as soon as the uterus already mentioned presents itself to view” [4]. On the right margin of the manuscript, “*Duplex vesicula in podice*” is written. On the left margin of the

manuscript, there is the notation “\* 3. F.”, as reference for the asterisk in the text; in fact, in the figure III of the manuscript (Figure 1, B and C), with the letter “F” is represented the “*vesicular in quam gallus emittis semen*” (the vesicle in which the rooster emits its semen). The double sac has ever since been known as the bursa of Fabricius. In 1967, Adelman [4] translated the entire manuscript “*De Formatione Ovi et Pulli*” and provided an anastatic copy of the figures with translation. However, as can be verified in Figure 2, an incorrect labeling of the drawing caused a mistake in the identification of the bursa. In fact, in the original version of the book (Figure 1), the letter “F” indicates the smallest round structure touching the structure “D”, whereas the letter “E” marks the round structure above the letter “B” (although the letters “E” and “F” are indeed quite small and not easily readable). On the contrary, in the anastatic copy of the figure (Figure 2), the letter “E” indicates the original “F” structure and the letter “F” is instead absent; as a consequence, the bursa of Fabricius is not indicated in the figure!

As it regards anatomy and morphogenesis in birds, the bursa of Fabricius is located at the level of the terminal portion of the intestine, on its posterior surface. The bursal anlage as a dorsal diverticulum of the cloaca on the 4<sup>th</sup> day of incubation. In the 5/6-day chick embryo, it is visible posterior to the cloaca, where takes the form of a median lamina of the endodermal epithelium rich in vacuoles, which then merge to create a lumen [5]. During development, the bursa grows from a rounded to a more oval shape, and, in the direction of the bursa lumen, several longitudinal plicae are visible. It originates due to hypertrophy of the mesoderm surrounding the epithelial layer of the bursa [6].

Initially, the bursa is composed of epithelial tissue only, but then the stem cells of the yolk sac, or coming from the liver, invade it, giving rise to a lymphoid structure. In the epithelial layer of the plicae, the 90% is interfollicular epithelium and the remaining 10% is follicle-associated epithelium (FAE) [7, 8].

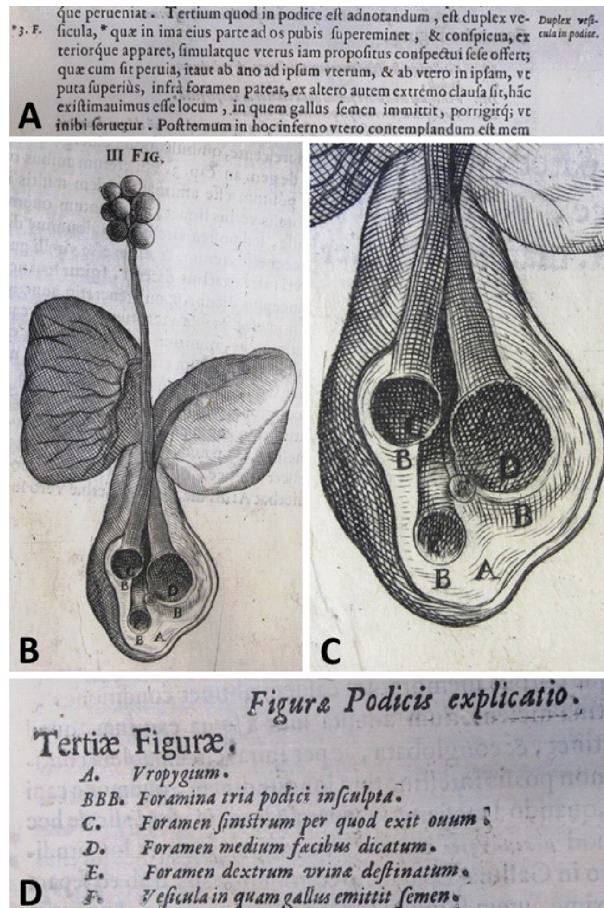


Figure 1 – (A) Original description of the bursa of Fabricius in the “De Formatione Ovi et Pulli”. (B and C) Original figure of the above-mentioned manuscript showing the bursa of Fabricius. (D) Original figure legend.

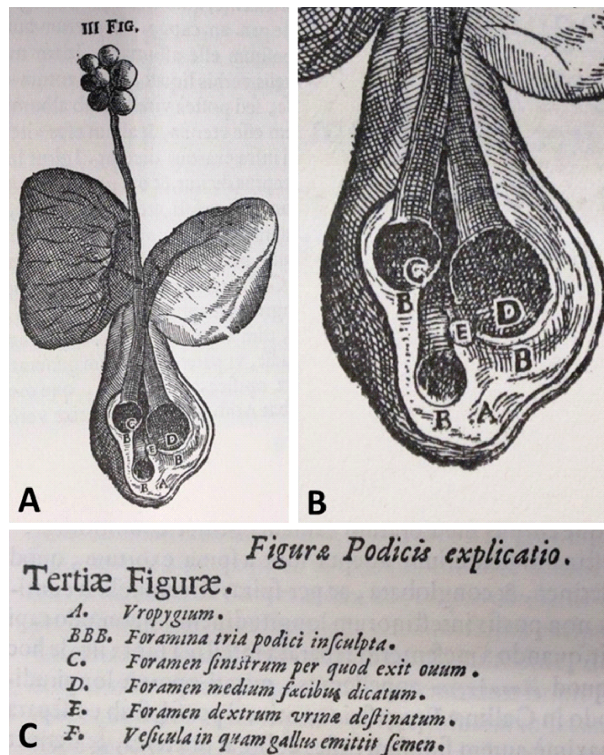


Figure 2 – (A and B) Anastatic copy of the figure of the “De Formatione Ovi et Pulli” manuscript with incorrect labeling. (C) Original figure legend.

Between the 13<sup>th</sup> and 15<sup>th</sup> days, the superficial epithelial cells of the plicae grow and then invade the layer of the tunica propria giving rise to epithelial buds separated from the epithelium. FAE connects the follicular medulla, where is active lymphopoiesis, and the lumen of the bursa [9, 10]. Follicles are visible after 16 days of embryonic development but are easily observed at hatching and during the early bursa of Fabricius development [11]. Total follicles in the bursa are about 8000–12 000, each follicle contains 1000 bursal cells, and in each cortex, medulla, cortico-medullary border, and FAE portions are distinguishable [7, 12]. At hatching, a bursa contains approximately 10 000 follicles, and each follicle contains about 100 000–150 000 lymphocytes. During the day 11–12 of embryo development, the medullary anlage arises and, as mentioned above, follows FAE formation [7], with the first cortical cells emerging around hatching [13]. The full cortex will develop in the two weeks after hatching.

The medulla portion of the bursa is instead made up of epithelial cells, dendritic cells, macrophages and lymphocytes, and few plasma cells in the bursa plicae.

The main cell type present in both cortex and medulla are B-lymphocytes (about 98%). Most B-lymphocytes are precursor cells during embryonic development, and only those in para-aortic foci and bone marrow are mature cells [14]. In the follicles, B-lymphocytes from the medulla and cortex express immunoglobulin M (IgM), while only those from the cortex also express the major histocompatibility complex (MHC) class II. IgM expression is detectable from day 12 of incubation, and from hatching, most B-lymphocytes are mature.

B-lymphocytes proliferation and differentiation are guaranteed by the unique bursa microenvironment [15]. During embryonic development between the 8<sup>th</sup> and 14<sup>th</sup> day, lymphoid precursors derived from extra-bursal tissue invaded the bursa [16]. Bursal extracts induce early B- and T-lymphocytes differentiation, with a more significant effect on B-cells, as demonstrated through *in vitro* study in chickens [17]. In bursal follicles, the precursor cells that do not express surface immunoglobulins are eliminated by apoptosis, while those that express them are selected for clone expansion, resulting in the production of distinct antibody molecules [18]. Bursin is the differentiating hormone responsible for B-cell precursors differentiation [19].

After eggs hatching, “epithelial tufts” are generated from the bursal epithelium around each follicle [9]. These crests permit the migration of bursal lumen content from here into the lymphoid compartment. In mammalian, the equivalent of these cells is the M-cells of the appendix or Peyer’s patch [7]. The identification of M-cells within the FAE explains the antigen movement from bursal lumen to bursal follicle, more precisely in the medullary compartment, where immature B-cells develop [20]. Around the hatching, the other significant event is the follicles segregation into defined cortical and medullary compartments. The bursa gets its maximum size at 8–10 weeks after hatching, and it is active until about the sixth month, then it atrophies undergoing involution [21] at the same time as the number of lymphocytes of the medulla decreases. The hematopoietic colonization of the bursal follicles occurs first with the formation of dendro-epithelial

tissue [13], which is then colonized by B-cell precursors [16].

In conclusion, the bursa of Fabricius represents a relevant structure both from historical and scientific points of view. In the present paper, the original labeling of its first representation in the “*De Formatione Ovi et Pulli*” has been recovered. Moreover, further considerations about its morphogenesis and lymphopoiesis mechanisms have given a general view of the evolution of research on the matter, from Hieronymus Fabricius ab Acquapendente to nowadays.

#### Conflict of interests

The authors declare that they have no conflict of interests.

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