A GLIMPSE OF OUR PAST

The Mystery of the Thymus Gland

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The thymus is the last organ in the human body to have its mechanisms fully understood, having had its function fully delineated more than 50 years ago (Miller 2004, Tissue Antigens 63:509–517). Prior to this, the thymus gland has had an interesting history with theories having included a role in fetal growth and development before becoming more sinisterly, a cause of sudden infant death in the late 19th century known as *status lymphaticus* (Paltauf 1889, Wien Klin Wochenschr 2:877–881). Until Miller (1961, Lancet 278:748–749) eventually proved its primarily immunological role, the history of this mysterious gland has closely mirrored the history of medicine itself, troubling the minds of pathologists such as Virchow (1872, Ueber die Chlorose und die damit zusammenhängenden Anomalien im Gefässapparate, insbesondere über "Endocarditis puerperalis," vorgetragen in der Sitzung der Berliner Geburtshülflichen Gesellschaft vom 12) and Grawitz (1888, Deut Med Wochenschr 22:429–431), surgeons such as Astley Cooper (1832, The Anatomy of the Thymus Gland) and Keynes (1953, Ann R Coll Surg 12:88), and eminent medical epidemiologists such as Greenwood and Woods [1927, J Hyg (Lond) 26:305–326]. This article will hopefully be of interest therefore to both clinician and historian alike. Clin. Anat. 00:000–000, 2016.

Key words: thymus gland; history of medicine; status lymphaticus; Felix Plater; Astley Cooper; John Simon; Kopp's asthma; Jacques Miller

INTRODUCTION

It has been more than 50 years now since the function of the thymus gland was fully delineated and the last organ in the human body to have its workings fully understood. This development was the result of Miller's seminal article "Immunological Function of the Thymus" in *The Lancet* (Miller, 1961) and with his presentation the following year to the *Royal Society* (Miller, 1962).

The story of the thymus prior to this event, however, is one of interest and mystery. From antiquity up until its role in myasthenia gravis, it has been thought to be the seat of the soul (Morse, 1928), play a putative role in lower limb development (Wright, 1852), and until recently, a pathological cause of sudden infant death in the disease known as *status lymphaticus* (Paltauf, 1889).

The story of the thymus gland and its functional significance has in many ways closely mirrored the progress of medicine as a science, and therefore, it is of interest and importance to the practicing clinician and historian alike.

ANATOMY OF THE THYMUS

The thymus is a soft gland which lies in the superior mediastinum and extends downward into the anterior part of the inferior mediastinum between the sternum and pericardium. It is a lobulated organ with lateral lobes which come into close contact at the midline. These two lobes, which are thickest inferiorly and

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Received 6 March 2016; Revised 28 March 2016; Accepted 30 March 2016

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ca.22724

thin out toward their superior aspect, can extend upward in the fetus and infant toward the lower border of the thyroid along the thyrothymic "ligament," which lies posterior to sternothyroid and sternohyoid.

The upper portion of these thymic poles lies anterior to the left brachiocephalic vein and superior vena cava in the superior mediastinum, with the thoracic duct as a posterior relation as it crosses over to insert into the root of the left brachiocephalic vein.

Ectopic foci of thymic origin are also not uncommon, having also been identified in the mediastinal and cervical fat, the latter being the result of their detachment during early fetal descent (Lavini et al., 2009).

Histologically, each thymic lobe is made up of a cortex and medulla, containing cells of hematopoietic origin surrounded by a distinct capsule. This capsule of loose connective tissue extends into the gland as septa, which divide it into lobules of various sizes.

The thymus is a vascular organ during early life and becomes progressively infiltrated with fatty tissue, involuting at a gradual rate from birth onward (Steinmann et al., 1985). Small branches enter the thymus from the inferior thyroid artery as well as from the internal thoracic arteries with corresponding venous drainage. Less commonly, it is also supplied by the superior thyroid artery and rarely from the aortic arch, brachiocephalic, or left common carotid artery. Notably, efferent lymphatics drain into the parasternal, tracheobronchial, and brachiocephalic nodes, with no afferent lymphatics noted.

THE GLAND IN ANTIQUITY

The origins of the name thymus have been lost in history, but the term is thought to have been derived from the plant of the similar name, which was known as far back as the ancient Egyptians. The Greek homonym of θυμός (*thymos*) also translates as "animus," "smoke," or "spirit," and it was for this reason that the thymus was considered the seat of the soul by the ancient Greeks (Jacobs et al., 1999).

The earliest known direct reference to the thymus as an organ was noted by a Greek physician Rufus of Ephesus (98–117 AD) circa 100 AD, who is believed to have resided in Alexandria. In his treatise "*De corporis humani partium appellationibus*" he wrote that:

> "Amongst these glands there is the one called thymus, situated under the head of the heart, oriented toward the seventh vertebra of the neck and toward the end of the trachea that touches the lung; it is not to be found in all animals" (Lavini et al., 2009).

Galen of Pergamon (129-c. 216 AD) was first to have described the thymus as "far from being small, instead large, most especially in young animals and gradually dwindles with growth". He believed that this organ played an important role in the purification of the nervous system, documenting this in his treatise "*De usu partium corporis humani*" (Galen, 1968). Galen's work, although useful, was restricted by the fact that his research was based on animal dissection, specifically those of the Barbary macaque and the pig. Nevertheless, his writings on anatomy were to dominate teaching on the subject from the Dark Ages through on into the Renaissance.

One of the first medical men to question Galenic doctrine on this organ was Berengario da Carpi (c. 1460–1530), an Italian physician who in 1502 was the lecturer in surgery in Bologna. He dissected the thymus in humans, writing that "The mediastinum is represented by a ligamentous—rather than nervous—tissue … its function is that of separating the lung from the chest thus confining any possible damage to one of two sides only … It is situated in the middle of the chest and connected posteriorly to the dorsal vertebrae and anteriorly to a gland called *mora*[1] placed like a blanket in front of the ascending veins and arteries." He also referenced the still popular culinary use of the thymus gland in Italy (and Wales), mentioning that, "common people refer to it as 'animella' and as food it is very tasty, most especially that from young calves and lambs" (Lavini et al., 2009).

Andrea Vesalio, better known as Vesalius (1514–1564), noted the protective function of the organ in his book "*De humani corporis fabrica libri septum*" (Vesalius et al., 2003), this time as a cushion for the vasculature of the superior mediastinum. He described how "the vena cava, ascending toward the jugulum, finds a soft, glandular organ that the Greeks called thymus and the Latins called, more simply, "animella." This same gland is also very nobly placed to protect from whatsoever damage the thick network of vessels suspended in this area" (Lavini et al., 2009). This idea of the thymus as a protective cushion remained a prevailing theory throughout the rest of the 16th century, reaffirmed by surgeons such as Ambroise Paré (1510–1590) who added also his observations on the change in size from the young to the elderly in his writings (Paré, 1840).

One notable piece of writing on the subject was contributed by the Swiss physician Felix Plater (1536–1614) in his book "*Observations*" which was published in the year of his death. Notable amongst these case histories was mention of a child who was found to have "the gland in the region of the throat as a large protruding tumor, one ounce in weight, spongy fleshing and pendent, replete with veins, adhering to the membrane to the largest vessels adjacent to the throat; these being filled with blood and flowing into the struma, dilating it to such an extent that it compressed the blood vessels in the locality; in which manner I concluded that the child was thus suffocated."

This was the first example of the thymus, or at least a mediastinal tumor, being related to significant pathology and was to become a historical landmark well into the 20th century for proponents of sudden death related to thymic hypertrophy.

[1]"[blackberry]".

THE INFLUENCE OF BRITISH EMPIRICISM

The optical microscope was developed over the course of the early 17th century pioneered by names such as Antonie van Leeuwenhoek (1632–1723) and Robert Hooke (1635–1703), although it was a while before its use became widespread. In 1774, William Hewson (1739–1774) used this invention to identify the lymphatic nature of the thymus, noting that it contained "particles" similar to those found in the peripheral circulation via the thoracic duct. He furthermore noted the unity of what we now refer to as the lymphoreticular system and also the devolution of the thymus with age and disease (Hewson, 1846).

Other than this brief contribution, little further progress was made toward an explanation of the biological function of the thymus until the 19th century, and most theories about its function remained unsubstantiated.

In the 19th century, a series of treatises focused on the thymus following in the footsteps of Hewson. This included the English surgeon and anatomist Sir Astley Cooper (1768–1841), Sir John Simon (1816–1904), and George Rainey (1801–1884). Sir Astley Cooper became a lecturer of anatomy at St. Thomas' Hospital in 1791 and then at Guy's Hospital in 1800. In 1832, his book "*The Anatomy of the Thymus Gland*" was published although it was to be superseded by Sir John Simon's essay in 1845 "Physiological Essay on the Thymus Gland," which won the Astley Cooper Prize of the Royal College of Surgeons of England.

The Cooper monograph focused on calf and lamb thymic preparations, assessing its anatomy both directly and with the use of quicksilver injections directly into what he termed the central thymic "reservoir" to identify its internal characteristics. He was also assisted by a Dr. Dowler of Richmond who had previously been noted for his analysis of "the buffy coat of ... blood and gelatinous looking masses often effused during the processes of acute inflammation" to analyze the fluid chemically, but was unable to deduce anything helpful.

Simon was later better known for his role in Public Health as the first Medical Officer of Health for the City of London, and then subsequently to the Privy Council (Silverman, 1993). However, at the time of his essay, he was still an assistant surgeon at King's College Hospital and an anatomy demonstrator at the medical school. This work (with later additions in 1846) outlined the previous 18th century theories including the role of the thymus in nourishment for the fetus, the receptacle for osseous matter, or as a secretor of "liquor pericardii" to "moisten the trachea and bronchial tubes." He then dismissed these one by one, noting that the thymus remained large in infancy and not just in fetal life. He also mentioned for the first time visualizing the blood–thymic barrier referring to it as a "limitary membrane," which blocked the cells of the thymus from directly passing into the bloodstream. His final conclusion was to be only certain of two things regarding the thymus, that its role was to secrete a "fluid form of nourishment" and then to "pass into fat," in other words involute over time.

In 1846, during this flurry of interest, Arthur Hill Hassall (1817–1894), an English physician and chemist, who was to be known for his later work into the adulteration of foodstuffs published a two-volume study in 1846 named "*The Microscopic Anatomy of the Human Body in Health and Disease*." This was the first English textbook to detail the histological distinction of the thymus from other lymphatic organs, the earlier authors having noted correctly their similarities. It was subsequently in 1849 that he was to identify the corpuscles made of epithelial reticular cells, which he found in the medulla of the thymus and which are given his name (Hassall's corpuscles).

PATHOLOGY OF THE THYMUS

During this time, influenced by the British empiricists of the 19th century, medicine was beginning to evolve into a science. However, the function of the thymus remained a mystery, and questions regarding the anatomy of the thymus began to give way to its possible role in disease.

The first treatise to remark on thymic pathology was by a German physician Kopp whose "*Denkwürdigkeiten in den ärztlichen Praxis*" (*Memoirs in Medical Practice)* was published in 1830. Translated in the *Dublin Journal of Medical Science* along with some cases from Ireland in 1836 (Kopp and Hirsch, 1836), it was noted:

> "a disease peculiar to infancy, characterized by tonic spasm of the lungs, larynx, and glottis, returning in fits extending at a later period to the cerebro-spinal nervous system under the form of epileptic convulsions, and causing death by suffocation, by apoplexy, or by asphyxia. The cause of this disease consists in a hypertrophied thymus [other]wise altered in its substance, which by its weight and volume presses on the heart, the lungs, the large arterial and venous vessels, and prevents the free exercise of their functions. The prognostic is almost always fatal; however when the subject is robust but little disposed to catarrhal affections, when the case is recent, the paroxysms weak and remote, and that it is not complicated with epileptic convulsions, some hope may be entertained" (Kopp and Hirsch, 1836).

This became known as Kopp's asthma and was grouped together with the term "laryngismus stridulus." Soon after, a number of cases reported in other journals, including *The Lancet* and *British Medical Gazette*, seemed to corroborate these findings (Anon., 1841; Montgomery, 1836) citing Dr Kopp directly as well as the 1614 case by Plater. It was at this time that the Cooper Monograph (1832) also notably included the first description of a case of death related to probable malignant thymic tumor leading to tracheal compression (Kirschner, 2000).

It was also during this "period" to prevent repetition that legislation for registration of deaths in England was being overhauled and this coincided with a

resurgence of interest in thymic pathology. The Births and Deaths Registration Act of 1836 (instituted in 1837) required records of births and deaths to be maintained as a matter of course, with the cause of death mentioned only if known. By 1874, however, it became mandatory with a penalty of up to 40 shillings to cite the cause responsible. The introduction of such a law required that medical practitioners agreed on what could be used as a valid cause of death, and the reference for this was the 1869 publication, "Nomenclature of Diseases" originally drawn up by a committee appointed by the Royal College of Physicians. This change in legislation, together with the 1836 and 1887 Coroners Act which gave the Coroners greater powers to order autopsies and to investigate suspicious deaths, began to reflect a changing mindset that medicine was able to distinguish between those who died of natural and of unnatural causes (Dally, 1997).

In 1889, Paltauf (1860–1893) published his "epoch-making" article about the predisposition of children to sudden death with the thymus as a culprit (Greenwood and Woods, 1927; Paltauf, 1889). In comparison with Kopp's earlier findings, he postulated that there was a peculiar "lymphatico-chlorotic" constitution in which there was enlargement of all lymphoid tissues and which caused a predisposition to sudden death. Unlike Kopp's Asthma, this was much more sinister as it extended the involvement of the thymus to patients who showed no evidence of stridor or respiratory distress prior to their demise.

In the early 20th century, *status lymphaticus* became increasingly identified with what we now term sudden infant death syndrome and between 1911 and 1924, at least 2,721 cases were attributed to this one condition (Greenwood and Woods, 1927). This rise in popularity could be attributed to a number of factors at that time. First, the registration of deaths soon led to a difficulty for pathologists to find an explicable cause for many so-called "unnatural deaths." A new phenomenon was how to deal with deaths attributed to medical care, especially the burgeoning number of those undergoing anesthesia by chloroform (Dally, 1997). Greenwood and Woods (1927) in a later discussion of these deaths attributed by the Registrar General of England and Wales to *status lymphaticus* noted, "If we could 'explain' by a doctrine of temperaments made verbally orthodox the sudden deaths for no sufficient reason which are within the experience of all medical men in large practice, we should flatter our professional sense of self-esteem." A constitutional type, such as *status lymphaticus*, exonerated many pathologists from looking further. In fact, other commentators later did note that many cases of so-called enlarged thymus were in fact other ailments entirely (Morse, 1928; Silverman, 1993).

Second, there was significant support for *status lymphaticus* from eminent pathologists of the "Vienna School" including Virchow, Grawitz, and others (Dodwell, 1954). This enthusiasm spread quickly to the United States, first by the pathologist Ewing (1897) who termed it "constitutio lymphatica" and then for a while cited by Osler in his textbook "*The Principles and Practice of Medicine*" from 1898 up until the 9th edition published in 1921 (Dally, 1997).

In the United Kingdom, one such early proponent of *status lymphaticus* was McCardie (1908), an anesthetist from Birmingham, who described several cases where patients had died while undergoing anesthesia. Almost as soon as it became a diagnosis, prophylactic treatment was advocated, and the recent advances in antisepsis and anesthesia made surgery for fixation (thymopexy) or otherwise surgical removal of the thymus, possible if not always successful. In fact, surgery on the thymus had begun as early as 1896 with Ludwig Rehn's transcervical exothymopexy: pulling up of the thymus up out of the superior mediastinum and attaching it to the manubrium (Kirschner, 2000). Further procedures attempted included intracapsular thymectomy and manubrial resection with variable success (Veau and Olivier, 1910).

With regards to the morbidity of these procedures, Mayo (1912), commenting to the American Surgical Association on surgery of the thymus, reported a death rate of 15 of 42 cases by Olivier in France, but stayed out of the question of *status lymphaticus*, mentioning only that "it seems probable that some of the reports attributing to 'status lymphaticus' the cause of sudden deaths, especially in children, either during or following operation, have been written with a view of distracting attention from the anesthetic as a factor."

It is uncertain exactly how many thymectomies were performed for *status lymphaticus*; however, it is probable that this was superseded by the discovery of X-rays by Röntgen (1896), and Friedlander (1907), a Cincinnati-based pediatrician, reported the first case of thymic hypertrophy treated with irradiation. Chest radiographs enabled this myth to be further propagated as now it could be attributed to any child with stridulous respiratory symptoms without resorting to autopsy. Although the relative mortality of these procedures was far less than an invasive operation, it is well documented that some of these children would go on to develop radiotherapy-induced cancers later in life (Hildreth et al., 1985; Hildreth et al., 1989; Gofman, 1996).

With the advent of death registries and the quantitative methods and statistical philosophy of Karl Pearson (1857–1936), Weldon (1860–1906), and Galton (1822–1911) (Hardy and Magnello, 2002), epidemiological studies of the thymus began to uncover the myth of *status lymphaticus*. First examined by Hammar (1906) and then by another notable English statistician, Major Greenwood in 1927 (Greenwood and Woods, 1927) who took 221 cases from the London Hospital showed that the thymus not only persisted up until the age of puberty but would involute within 7 days of illness and thus show up as large only if the patient had died suddenly. Finally, in 1931, a Joint Committee of the Medical Research Council and the Pathological Society of Great Britain and Ireland published its report where some 680 postmortem examinations were made, and the results found to be in complete agreement with the previous studies by Hammar and Greenwood (Young and Turnbull, 1931). Although *The Lancet* published an editorial regarding this "The End of Status Lymphaticus," it is worth mentioning that the controversy remained despite the

evidence long into the 1950s (Boyd, 1932; Silverman, 1993).

THE FINAL PIECE OF THE PUZZLE

In 1936, Blalock (1939) performed the first removal of a thymic tumor via median sternotomy and noted an improvement in the patient's myasthenia. This was further pioneered by surgeons such as Keynes (1953), who proved the beneficial response to removal of the thymus in thymic hyperplasia (Kirschner, 2000). It would, however, take the work of an Australian immunologist Jacques Miller (1961) to ultimately understand the role of the thymus as the "master gland" regulating the immune response.

Advances in understanding the development of the immune system had been made by Macfarlane Burnett (1899–1985) and Peter Medawar (1915–1987) who jointly received the Nobel Prize for the discovery of acquired immunological tolerance in 1960. Their experiments in mice gave Miller the opportunity to perform allogenic thymic grafts between various strains, which laid the foundations for his later demonstrations that neonatal thymectomies inhibited immune function and could be subsequently restored with thymic grafts from a separate mouse (Miller, 2004).

Controversy surrounding the role of the thymus remained up until Miller's publication, including the fact that the thymus had been extensively investigated and found to be devoid of significant lymphoid activity. Other circumstantial work confused things further, including the discovery of a similar avian organ that also atrophied soon after birth, called the bursa of Fabricius (situated posteriorly in the cloaca), which had been demonstrated to be essential to the production of antibodies (Glick et al., 1956). Despite the fact that Miller's work supported Burnett's theory for clonal selection by providing a location for self-non-self-discrimination, even Burnett (1962) himself remained cautious about this theory, noting that the role of the thymus in immunological tolerance was likely both "variable and largely indirect."

By the late 1960s, the role of the thymus became more accepted; however, the observations of a distinct immune response involving antibodies and one involving cell-mediated graft rejection were yet to be explained. Neonatally thymectomized mice showed deficiencies in both, and thus, the specific role of thymus-derived cells had yet to be explained. It was only after Miller returned to Australia in 1966 to set up his own further expanded experiments (Miller, 2004) that the interaction between these "T cells" and "B cells" (named after the aforementioned Bursa) demonstrated two distinct subsets of lymphocytes required for the effective function in mammalian acquired immunity (Miller and Mitchell, 1967).

CONCLUSION

The discovery of the role of the thymus in immunological tolerance put to rest the mystery of this special organ and explained its relative senescence after the neonatal period. The pathological entities of Kopp's asthma and *status lymphaticus* became another stumbling block on the path of modern medicine and are now consigned to the history books. The story of thymic function, however, remains a less familiar but still timely reminder of the perils of misattributing the human condition as pathology, a lesson of ever greater significance in the 21st century.

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