

Thyroidology over the ages

Asfandiyar Khan Niazi, Sanjay Kalra¹, Awais Irfan, Aliya Islam²

Shifa College of Medicine, Islamabad, ¹Bharti Hospital and BRIDE, Karnal, Haryana, India, ²International Medical College, Abbottabad, Pakistan

ABSTRACT

Thyroidology, the study of the thyroid gland, is considered to be a relatively new field of endocrinology. However, references to the thyroid gland and its diseases can be seen in the literature of ancient Greek, Indian and Egyptian medicine. Goiter has always been a disease of immense interest of the general population due to its widespread prevalence. It is one of the most common medical problems portrayed in ancient paintings. Owing to the lack of awareness and poor nutritious habits of the people in that era, diseases such as iodine deficiency goiter were common. Physicians, healers and philosophers had been attempting time and again until the 19th century to come up with explanations of the thyroid gland and provide a reasonable basis of its diseases. Although the discovery of thyroid gland, its structure, function and diseases has been accredited to modern scientists who presented their work mostly in the 19th and 20th century, it is of significance to note that much of what we discovered in the 19th and 20th century had already been known centuries ago. This review attempts to explain the knowledge of thyroid gland, its function and diseases as held by the people in the previous centuries; and how this knowledge evolved over the years to become what it is today.

Key words: Goiter, history, thyroidology

ANCIENT-EGYPTIAN, CHINESE, AYURVEDIC, GREEK

References to goiter it have been seen in texts dating back to 2700 BC.^[1] This is probably because of its extensive prevalence in the times when its exact etiology and possible preventive measures were unknown. It is said that the Chinese were aware of the enlarged thyroids from around 2700 BC. The Chinese physician Tshui Chin-thi, in 85 AD, differentiated between solid (malignant) tumors of the neck which were incurable and movable (benign) tumors which were curable.^[2] Whether or not, he was aware of the organ which was responsible for these enlargements is unknown.

In the Indian Ayurvedic medicine, which originated in the

1400 BC, goiters are called 'galaganda' and are described in detail.^[2] It classifies thyroid diseases into three types; Vataja (hyperthyroidism), Kaphaja (hypothyroidism) and Medaja (thyroidal cyst). The symptoms of these diseases are described in detail in the Ayurvedic medicine. They correlate with those described by the modern medicine.

Hypothyroidism in Ayurveda is well described by a well-known Ayurvedic physician Charaka. He said that it may be prevented by ingestion of adequate quantities of milk, rice, barley, green grams, sugarcane juice and cucumber. He discouraged people from eating sour foods as they may aggravate the thyroid diseases. Kaanchanara (*Bauhinia variegata*) and Bladderwrack (*Fucus Vesiculosus*) are prescribed for all sorts of thyroid problems. Guggulu (*Commiphora mukul*) is used to increase the basal metabolic rate in hypothyroid patients. Punarnava (*boerhaavia diffusa* Linn) is an excellent diuretic which is prescribed to reduce the swelling in thyroid diseases.

For the hyperthyroid patient, Bugleweed [*Lycopus virginicus*], gypsywort [*Lycopus europaeus*], water horehound [*Lycopus lucidus* or *Lycopus americanus*], gromwell [*Lithospermum ruderale*] and European gromwell [*Lithospermum officinale*] are

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Corresponding Author: Mr. Asfandiyar Khan Niazi, Shifa College of Medicine, H-8/4, Pitras Bukhari Road, Islamabad, Pakistan.
E-mail: asfand92@gmail.com

used. Ancient Indian physicians also recognized pitting and non-pitting edema, and facial and pedal edema. However, instead of hypothyroidism leading to goiter, they were of the view that edema caused goiter.^[3]

One of the earliest recorded accounts of the thyroid gland in Greek medicine is by Hippocrates and Plato. They described the thyroid gland with salivary and thymus glands.^[4] They were of the view that these glands are spongy in constitution and are responsible for lubricating the respiratory passageways.^[5] Galen who was a prominent physician, surgeon and philosopher of Greek ethnicity gave a different opinion. He argued that the spongy nature of this gland was better suited for the purpose of absorption rather than secretion.^[5]

Galen supported his argument by saying that secretion of the gland was prevented from entering the respiratory passageways. He labeled the thyroid gland as an organ of connection and buffer between the heart and brain. He made a significant breakthrough in the anatomy of the third ventricle during the 2nd century.^[6] He reported that the pituitary gland is located in the sella turcica and is surrounded by a vascular network. Galen suggested that the 'heat' of the body travels through these vascular networks and is converted to nerve impulses which affected the 'substance of the neck', or the thyroid gland.

Hippocrates and Gaius Plinius Secundus of Pliny regarded goiter to occur solely because of drinking of snow-water.^[2,7,8] Initially goiter was not thought to be an enlargement of the thyroid, but rather it was believed to be a herniation of larynx. Pedanius Dioscorides, a 1st century AD Greek physician, and Galen during the 2nd century AD supported this view.

Leonardo da Vinci drew the thyroid gland in 1511 during his anatomical studies. Even though he was aware of its exact anatomical structure, he could not understand its function and assumed that it was created to fill the gap between muscles of the neck and to hold the trachea away from the sternum.^[7]

Chinese physicians used burnt sponges and seaweeds for the treatment of goiter as early as the 1600 BC.^[9] However, they were unaware of the cause of this disease. The medical treatment for goiter was also described by Dioscorides in the 1st century AD.^[10] Except for shells from marine organisms, iodine-rich substances were not mentioned. Several plants and animals, even lizards and dog excrements, were used for the treatment of goiter.

The substances used by the Byzantine physicians to treat

goiter were mostly calcium, copper, sulfur and ammonium salts. Roger Frugardi, in the 12th century, wrote that goiter is treatable by drinking a tincture made with barren walnut leaves and roots, boiled in good wine with a pinch of pepper added.^[11] An alternative pharmacological treatment used in ancient Italy was a powder obtained from burnt and dried marine sponges.^[12] This powder was rich in silica, calcium phosphate, sodium chloride, sulfur chloride, iodine, bromine, magnesium carbonate and calcium carbonate. Since it was rich in iodine, goiter may well have been cured.

Although Robert Graves and Carl von Basedow are credited with modern description of thyroid related orbitopathy, history shows that older civilizations were well aware of this condition. The description by Graves and Basedow came in the 19th century while mentions of this disease are found in works of Aristotle and Xenophon from 5th century BC.^[13]

Goiter has also been portrayed in the sculptures of the ancient Gandhara civilization. This dates back to the 1st or 2nd century AD.^[14] Controversy surrounds the matter whether the appearances related to the God Bes of ancient Egypt and Cleopatra are related to thyroid diseases. There is no conclusive evidence available; however, quite possibly their depictions may have been affected by thyroid disorders.

EARLY CENTURIES-BYZANTINE, PERSIAN

The surgical treatment of goiter was mentioned in the 6th century by Aetius.^[15] Aetius was of the view that goiter was in fact a hernia of the larynx. This opinion of goiter being a laryngeal hernia persisted for a long time. Even the modern term 'goiter' carries a link to it. The term 'goiter' probably originated from the word 'guttur' which means larynx or bronchus in Latin.^[15] 'Atheromatous' goiters were referred to by Aetius in as early as the 6th century.^[16]

Aetius was conservative in the surgical treatment of goiter and described the risks of the procedure in detail. He noted very early that it was important to conserve vocal nerves during the operation; failure of which may result in the loss of voice.^[16] The surgical treatment was also mentioned by Frugardi. In his surgical textbook, he instructed to use two wires bound to red hot iron to thread at the bottom of the neck. This process was to be repeated twice a day. If unsuccessful, he advised to use a scalpel to dig out the nodules by hand.^[12]

In the 7th century, Paulus Aegineta described two forms of goiter: steatomatous goiter and hyperplastic, hyperemic goiter.^[17] One of the earliest references to the thyroid surgery may come from the 7th century when Paulus

Aegineta supposedly performed a surgery on struma.^[16] But whether or not struma carries the same meaning as goiter is uncertain.

The first reliable account of a thyroid surgery comes from the 10th century when Albucasis removed a large goiter of a man under opium sedation.^[18] In the 14th century, the French surgeon Guy de Chaliac reported that goiter is a hereditary disease and recommended surgical treatment for it.^[2]

Numerous sculptures, paintings and drawings made by the Byzantine artists depict an enlarged thyroid gland. The earliest paintings showing goiter date back to the 7th century.^[19] Among the different pathological conditions shown in the Byzantine paintings, goiter is the most common. Even the saints, angels, children, the Virgin Mary and Christ were painted with enlarged thyroid glands on several occasions. This may have been done coincidentally if the model had goiter or to depict the general living conditions or, according to some beliefs, even for erotic purposes.

Byzantine physicians in the 8th century had recognized exophthalmos and its associated symptoms.^[15] They associated it with nervousness and changes in the mood. In their legal literature, they mention that these people are unfit for work. Similarly Avicenna and Aljurjani, both Persian physicians from the 12th century, describe in their books that a swollen neck is closely interrelated with eye disease.^[20] They also described that both these diseases form a single clinical entity and it is also associated with increased appetite in which satiety is not reached even after ingestion of great quantities of food. They considered lassitude of the extraocular muscles as the cause of this protrusion of eyes.

17TH-19TH CENTURY

In 1656, Thomas Wharton, a famous anatomist, discovered the exact anatomical structure of the thyroid gland, along with the other glands of the body. He explained that secretion is a gland's primary function. He assigned specific functions to each gland. He wrote that the thyroid gland was responsible for heating the thyroid cartilage, which is normally cold due to its superficial position, lubricate the neck and to give rotundity and beauty to the neck.^[21]

It is strange that even though Galen had already explained how it is unlikely for the thyroid to be responsible for lubricating the neck, Wharton still followed the older belief. The gland was named thyroid, not because of its own shape, but because it closely approximated the shield

shape of the thyroid cartilage of the larynx.

De Bordeau felt that each organ in the body gives off certain 'emanations' which are necessary, as well as, useful for the body.^[22] He noted that goiter was common in the Western part of the Pyrenees mountains (between France and Spain). He also observed that women had larger thyroids, and suffered more frequently from goiter. De Bordeu was able to associate goitre with hoarseness of voice. In 1776, von Haller of Bern (Switzerland), grouped the thyroid with the thymus and spleen, as ductless glands which poured their special secretions into the bloodstream.^[23]

Many workers in the 18th century noted the lavish blood supply of the thyroid. While some felt that it was a vascular shunt, preventing sudden rush of blood into the brain, others though it was part of the vocal apparatus.^[24] Heister, the father of scientific surgery in Germany, called thyroid enlargement as 'bronchocele' or 'tracheocele', noted geographical variations in its occurrence, and advised ointments or surgical removal, while warning of the chances of hemorrhage. He described thyroidectomy in 1742.^[25]

Morgagni, the founder of modern pathological anatomy,^[25] described the two lobes and isthmus of the thyroid.^[26] The pyramidal lobe had been described earlier by Lalouette. Exophthalmic goiter was described, and connected with 'malady of the heart' and 'bronchocele' by Caleb Hiller Parry.^[25] Even though he was unaware of the association of these three diseases, Guiseppe Flajani successfully cured a man with exophthalmos, goiter and palpitations in 1802.^[27] He compressed the swelling in the neck of the patient with vinegar and ammonia and reported disappearance of the swelling within four months.

Goiter due to iodine deficiency was widespread in the early days. As previously mentioned, seaweed and shells of marine organisms were commonly used for the treatment of goiter. The 19th century saw the discovery of iodine by the Parisians Courtois (C), element and Desormes, in 1811.^[28] The first person to use it as a remedy for goiter was Coindet of Geneva, who prescribed hydriodate of potash or 'tincture of iodine' successfully.^[23] Toxic effects of iodine use were also described as 'constitutional iodism' by Rilliet of Geneva.^[29]

Thomas Wilkinson King, the Father of Endocrinology, wrote the paper 'Observations on the Thyroid Gland' in 1836. He described thyroid colloid, and its importance.^[30] His colleague, Sir Cooper described experimental thyroidectomies in puppies in 1824.^[23] Endemic goiter was

discussed by Malacarne, based on his work in the Aosta valley.^[23] It was not linked with cretinism, however, as the latter was thought to be due to stagnant and overheated air in confined narrow valleys.

The 1885 edition of Hirsch's classic pathology text states that even though goiter and cretinism have to be reckoned among the infective diseases, iodine treatment is still recommended for this condition.^[31] Eugen Baumann, a scientist in the 19th century, was particularly interested in the biochemistry of the thyroid gland because of the high prevalence of goiter at that time. He boiled the thyroid glands of 1000 sheep in dilute sulfuric acid and then collected the flocculent precipitate that was deposited. While examining this precipitate, he noticed a high level of iodine present in it.^[32] He named it 'iodothyryn'. It was used to treat patients with goiter and showed successful results.

Many surgeons of the 19th century also attempted (unsuccessfully) to treat thyroid disease.^[23] In spite of so much work, Mueller wrote "the function of the thyroid gland is unknown" in the 1835 edition of Handbook of Physiology. Others, however, had described the condition of myxoedema and/or cretinism, in detail, and connected it with thyroid dysfunction. These included Curling in 1850, Gull in 1873, and Ord in 1871, Fagge had described the difference between sporadic and endemic cretinism.^[23] Sir Horsley, working on monkeys between 1884 and 1886, found that thyroidectomy led to myxoedema and cretinism.

Public health and thyroidology also blended together in the 19th century. In 1833, Boussingault suggested salt iodization to prevent goiter. Chatin (1803-1901) proved in 1850 that fresh water aquatic plant derived iodine could prevent endemic goiter and cretinism. He correlated these conditions with iodine deficiency, and recommended iodine supplementation in drinking water, using mineral water springs.^[23] He demonstrated in 1835 that salt sent from goiter-free regions to regions with endemic goiter reduced the incidence of goiter.^[26]

However, it was nearly 100 years later that his vision was realized and iodine-rich salt was made commercially available. Although this idea was scientifically correct, it was rejected by French authorities. The first public health experiment in thyroidology was also carried out in this century, using potassium iodine in salt, as solution, or as tablets. However, because of side effects due to the high doses used, iodine prophylaxis was abandoned.

Much work was done on excessive function of the thyroid gland as well. The Irishman Robert James Graves (1796-

1853), described many patients with exophthalmos and goiter. von Basedow of Merseburg (1799-1854) described the Merseburg Triad of exophthalmos, goiter and palpitations in 1840.^[23] Many eponyms, descriptions and etiological theories were published related to this disease, and the lists make interesting reading.^[23] Plummer (1874-1937) was able to differentiate between toxic adenoma of the thyroid and graves disease.^[23]

20TH CENTURY

David Marine (1880-1976), also known as the Nestor of Thyroidology,^[23] proved that iodine is necessary for thyroid function in 1907. Four years later, he treated Graves disease with iodine. In 1917, he introduced goiter prevention with iodine, using a low dose of 1:100000 parts of iodine. In 1932, he described cyanide goitre due to thiocyanates found in plants of the genus Brassicaceae (cabbage, cauliflower, turnip).^[23]

Organotherapy

In 1889, Brown-Sequard suggested the use of testicular extract for the rejuvenation of elderly men.^[33] Although the use of testicular 'organotherapy' declined, the concept of using thyroid extracts caught hold rapidly. The first persons to use thyroid extract were Horsley and Murray. Many skeptics voiced concern at the use of sheep's thyroid. A senior member of the Royal Society of Medicine said it would be just as sensible to treat a case of locomotor ataxia with an emulsion of spinal cord.^[23]

Thyroid preparations were administered orally and as injectables by various workers. Thyroid extract soon became an accepted part of current medical practice. Adolf Oswald was able to identify thyroid colloid protein as thyroglob.^[23] Kendall was able to isolate thyroxine crystals in 1914. It took 3 tons of porcine thyroids to obtain 33 g of pure thyroxine.^[34] Improved methods of extraction were devised, which reduced the cost of manufacture. Synthetic thyroxine was made by Harigton and Barger in 1927.^[35]

Triiodothyroxine was discovered much later in 1952 by Gross and Pitt-Rivers. A major advance in thyroidology occurred in 1956, when Roitt, Doniach, Campbell and Hudson demonstrated autoantibodies in Hashimoto's disease.^[36] This occurred 44 years after Hoku Hashimoto (1881-1934) had described the disease as lymphoid infiltration of the thyroid.^[37]

Along with developments in diagnosis, clinical thyroidology also grew in the 20th century, Charles Mayo first used the term hyperthyroidism in 1907, and in the same year, Brissaud described thyroid infantilism. In 1910, Kocher

coined the term 'Jod-Basedow', and in 1931, Naffziger pioneered orbital decompression as a treatment for exophthalmos.

Iodine therapy was used in 1911 by Marine for Graves disease, and in preoperative management of exophthalmic goiter in 1924 by Plummer and Boothby. Radioactive iodine was used in Graves disease, independently, in 1943, by Hertz and Roberts, as well as Leblond. Medical management did not lag behind. In 1943, Astwood used thiourea and thiouracil in Graves disease. In 1949, the synthesis of methimazole by Jones, Kornfeld, Mc Laughlin and Anderson was witnessed, while 1951 was the year when Lawson, Rimington and Searle synthesized carbimazole, Commercial synthesis of levothyroxine was successful on 1949.

Edward Kendall started working on isolating the pure form of thyroxine in 1910. By paying careful attention to the hydrolysis of the gland, he was able to isolate thyroxine in a pure form in 1914.^[38] By 1917, he had isolated enough crystals of thyroxine to begin clinical trials on them. Believing it was an oxindole, he coined the term 'thyroxin', which was later changed to thyroxine. Charles Harrington prepared synthetically a compound by condensation of two molecules of diiodotyrosine in 1927.^[39] This compound was shown to have similar properties as thyroxine. This led to the discovery of the exact structure of thyroxine.

In 1909, the Nobel Prize in Medicine or Physiology was awarded to the 68-year-old Swiss surgeon Emil Theodor Kocher, for his work in thyroidology. He had innovated many techniques in hernia, osteomyelitis, dislocations, use of silk sutures, asepsis and thyroid surgery. He observed 'icachexia strumipriva' or postoperative hypothyroidism in his thyroidectomy patients. Till date, he remains the only winner of the Noble Prize for work done in thyroidology (G). In 1952, Jack Gross and Rosalind Pittrivers detected the presence of a more potent thyroid hormone while carrying out researches on mice fed with radioactive iodine.^[30] This compound differed from thyroxine in having three iodine atoms instead of four. It was named 'liothyronine', which was later changed to triiodothyronine.

CONCLUSIONS

Even though the scientists credited with the discovery of the thyroid gland and its diseases are mostly from the 19th or 20th century, the contributions of the earlier scientists should not be disregarded. The interests of people in the thyroid gland have always been immense because of the widespread prevalence of its diseases. Therefore the earliest references to the gland date back to 1st century AD. The

Chinese, Egyptian, Indian, Greek and Byzantine medicines are especially rich in their knowledge on the subject.

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