

Božo Trbojević

## NOTES FROM THE HISTORY OF AUTOIMMUNE ORBITOPATHY

**Summary:** The development of knowledge about the appearance, nature, origins and outcomes of the orbit and eye disorders in thyroid gland diseases has been very slow with a number of dilemmas, controversies and side tracks. It is interesting that the first reliable descriptions of this unity come from a lawyer and not from a doctor. Later contributions of Arab doctors and philosophers greatly improved medical theory and practice. Western medicine adopted discoveries of eastern nations adding European rationality to them; the result was a better understanding of the nature of the process and better knowledge of the causes of the disorder and its development, but treatment options were still falling behind theory. Not until the last few decades of the twentieth century was there a noticeable progress in the definite identification of the nature of the changes in orbitopathy, which made it clear that it was an autoimmune process and which led to a better and more successful treatment. Despite all this, autoimmune orbitopathy is still one of the conditions in endocrinology which is most difficult to control and cure.

Struma (from a Latin expression for swelling in neck glands) or goiter (guttur: Latin word for the throat) has been known since ancient times. References about the disease can be found in Chinese and Greek texts but the combination of bulging eyes, goiter and symptoms of Hyperthyroidism seems to be of more recent origin – it first appeared in legal Roman texts from 2<sup>nd</sup> and 3<sup>rd</sup> centuries and in a Byzantine text from 6<sup>th</sup> century A.D. At the turn of the 3<sup>rd</sup> century, the Roman jurist and legal adviser to Emperor Septimius Severus, Domitius Ulpianus, introduced a legal regulation according to which a slave with goiter had a reduced working ability (*Si quis natura gutturosus sit aut oculos eminentes habeat, sanus videtur*). Ulpianus concluded that a salesman was not responsible for the reduced working ability of a person with these symptoms.

Just like in Ulpianus' documents, probably related to his legal heritage, a Byzantine legal text from 6<sup>th</sup> century whose Latin name is *Digesta Corpus Juris Civilis Justiniani*, and on which the later Greek text *Vasilica* is based, states: 'quis natura

gutturusus sit aut oculos eminentes habeat'. Since they are mainly legal and not medical documents, it is not clear whether the jurist recognized the connection between these two medical symptoms. It is well-known that the physiognomy of Roman population at the time was characterized by prominent eyeballs and that is why it is believed that Ulianus did not notice the connection between goiter and prominent eyes, although other theories are also possible.

The first medical manuscript in which changes in the eyes and struma are connected is attributed to monk Meletius, alias iatrosophist, who lived in 8<sup>th</sup> century A.D. We now know that these descriptions refer to exophthalmos and the disease which is today known as a thyroid gland disorder, and not some other, on the basis of the description of exceptional irritation of these people and a remarkable change in behavior. Meletius says: "... eyes have a tendency to swell and protrude ... because of which a person is very upset and frightened". This description undoubtedly proves that Byzantine doctors knew about the thyroid gland disorder and that they deserve a place in the history of thyroidology.

The text of an Arab author Zayn al-Din Sayyed Isma'il ibn Husayn Gorgani, also known as Sayyid Ismail Al- Jurjani, "The treasure of Khwarazm Shah" (Zakhireye Khwarazmshahi ) was published around 1110. Al-Jurjani was a doctor and a philosopher and in his encyclopedic book he stated, as it was believed, the first description that connected a swollen thickened neck with changes in the eyes, and he thought that they were a unique unity of closely connected disorders. However, al-Jurjani was a devoted follower of Avicenna, who lived almost a century earlier, and he was greatly influenced by his famous manuscript, Al-Qanoon or The canon of medicine, particularly by the third book. This history is important because it underlines the dominant role of Islamic medicine in the Middle Ages transferring the knowledge from the earlier Hellenistic, Roman and Far East medicine and adding its own discoveries to them. When analyzing earlier Persian medical manuscripts, written more than a century before Al-Jurjani made his description, it is surprising to see that Avicenna had already analysed the connection between orbitopathy and a swollen neck. Although Al-Jurjani's medical encyclopedia really offers a wide range of knowledge and incorporates ideas that have not been found before, not even in Avicenna's Canon, it still has to be said that it is greatly based on Avicenna's discoveries.

Ibn Sina or Abu Ali al-Husayn ibn Abd Allah ibn Sina, known as Avicenna in the West, is probably the most famous doctor of Islamic civilization. He was also a very fruitful author, he wrote almost 270 different tractats of which the largest number was in the area of medicine. In his masterpiece Al-Qanoon, which contains more than a million words, Avicenna describes complete studies in physiology, pathology, hygiene into which he incorporates the most important sources of Hellenic and Chinese medicine. His books are real role models of his time. Among other things, , Al-Qanoon or The Canon describes the swelling in the front part of the neck (goiter) in people

who have had a better appetite and who have not been able to feel full despite the large quantities of food they have eaten (Al-Qanoon, Book III, chapter 6). In the two chapters of his Canon, he describes the connection between the swollen neck and prominent eyes (Canon, Book III, part three, article two, chapter 15 and Book III, part three, chapter 4). In the chapter on exophthalmos, he describes the differential diagnosis of proptosis. He notices that exophthalmos may appear due to the pressure from the back of the orbit, he notifies the swelling of the cornea, chemosis, increased mass of orbital fat and weakness, fatigue of eye muscles in the clinical presentation of exophthalmos. He describes ocular characteristics when the cause of exophthalmos is fatigue of extraocular muscles (The Canon, book III, part three, article 2, chapter 15). His works were translated in the second half of 12<sup>th</sup> century in Toledo by Gerard of Cremona. Later in 16<sup>th</sup> century, Andrea Alpago in Venice translated his works into Latin again. Since then, through many centuries, Avicenna's books have represented some of the most significant medical books in Western Europe. In fact, until 17<sup>th</sup> century, medical curriculum of European universities was based on Avicenna's manuscripts. It is highly likely that the most famous Mediterranean universities such as Cordoba and Salerno used Avicenna's texts even before they were translated into Latin since in these schools Hellenic, Roman, Arabic and Hebrew experiences were integrated parts of the curriculum. With his broad interests and knowledge of different areas of science and arts, Avicenna is actually a prototype of a Renaissance man almost three centuries before the appearance of the Medici and their circle.

After this, there is a very long pause in the descriptions and analyses of eye diseases and the appearance of goiter, the swelling in the neck.

Caleb Hillier Parry (1755–1822) spent most of his life working as a general practitioner in Bath, England. In the documents found after his death, in a chapter related to heart diseases, he described five patients with goiter and undoubtedly a case of hyperthyroidism under the title: "Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the Heart." One of them was Mrs. Grace B, age 37, who Parry saw for the first time in August, 1786. She suffered from palpitations and irregular heartbeat which went up to 156. Her thyroid gland was enormous, reaching the edge of the lower jaw... "her eyes were prominent, leaving the orbits and had the appearance of constant fear, she could not stand anxiety and strain, particularly the one of the muscles, which I had rarely seen before." The patient was treated by drawing blood and with silver concoctions, but she developed a massive swelling with the night orthopnea. Parry was not involved in the disease any longer, but it is assumed that the patient very soon "paid her debt to nature." This short description was usually considered to be the first description of ophthalmopathy in thyroid gland disorders, which, as we have already seen, was not correct.

Chronologically speaking, the next description of exophthalmos together with the thyroid gland disorder was an anonymous one from 1816 in *Medico-Chirurgical Journal and Review*. According to Legg “A young woman, aged 22, had palpitations, swellings on both sides of the neck as big as a goose egg. The eyes were so prominent that they looked as if they were going to fall out of the orbits. She was very nervous, thin and extremely plethoric. She was treated on the basis of a strict antiphlogistic system; her blood was drawn, she drank only water, she was not allowed to eat animal meat, she did not receive calomel and digitalis. About seven months later, I met her in the street, she was very well.” Legg described several more cases of thyroid ophthalmopathy, which he published between 1820 and 1828.

Robert Graves (1796–1853) gave several lectures at the University Hospital in Dublin in the period of 1834–1835. In one of them, he described three people with goiter and palpitations. The fourth patient was “a lady around 20 years of age, with symptoms that resembled hysteria.” She had tachycardia, a swollen thyroid gland and suffered from anxiety; “orbits were noticeably prominent so that the eyelids could not cover them while she was sleeping or trying to close her eyes. When her eyes were open, the whites could be seen in the width of several lines round the cornea.”

Since 1822, Carl Adolph von Basedow (1799–1854) was a doctor in the small town of Merzeburg between Leipzig and Halle in Germany. He saw three patients with goiter within several years. The first two (Madame G and Madame F) had the symptoms of florid hyperthyroidism and exophthalmos. During the illness, they were both considered to be insane and Madame F was sent to an asylum. One of the women had changes which are today known to be pretibial myxedema or dermopathy.

The third patient, Herr M, aged 50, started to complain about weakness and diarrhea in 1832. He complained about “blood heat”, extreme perspiration and precordial oppression. His face was pale, and the eyes bulged out from the orbits; the thyroid gland was enlarged; the patient was losing weight despite his good appetite and was still having frequent liquid bowel movements. The course of the disease was very difficult. After the appearance of keratitis, purulent infection of both eyes appeared too. Basedow recommended him to make a wide incision in both eyeballs in order to eliminate the pus, but the patient rejected it. He lost sight in both eyes and Basedow wrote down that “the unfortunate patient had unbearable pain”. Severe heart disorder symptoms appeared with tachycardia and respiratory difficulties due to serious goiter. The patient died suddenly in 1843.

In 1877, Yeo was the first to describe two people with one-sided exophthalmos. The reason for this phenomenon is still an enigma just like it was 130 years ago. In reference to this description, it has to be mentioned that two Italians, Flaiani and Testa published similar observations in 1802 and 1810. Their studies, unfortunately, are not available today.

### *Pathological anatomy*

Basedow did the first autopsy of a patient with thyroid ophtamopathy. In fact, he did the autopsy of his patient, Herr M. The findings were not particularly typical since both eyeballs were fibrous and reduced to half their normal size. He found large quantities of yellow fat tissue in the orbits. Jean-Martin Charcot (1825–1893) gathered his findings of postmortal studies of the orbits of patients with exophtalmos and confirmed that the eyeball looked normal but that an extremely large mass of fat was collected in the orbits. Armand Trousseau (1801–1867) quoted a Danish article in which orbital tissue in thyroid ophtalmopathy was described. When looked for, a large quantity of fat could be found in the orbits. Trousseau was able to confirm these findings in his patients.

In 1920, R Foster Moore published a postmortal dissection of orbits of patients who died and had thyroid gland and eye disorders. He summarized the main hypothesis of the causes of exophtalmos of that time “: (1) irritation of sympaticus nervous system which causes spasms of smooth muscles in the orbit; (2) congestion of the orbit with blood; and (3) increased mass of orbital fat.” Moore pointed out that since exophtalmos did not disappear after death, then it probably was not the consequence of the hyperactivity of sympaticus or blood congestion. “in that case, orbits are definitely full due to the hypercirculation inside of them and there is nothing else that is abnormal and that can be found there; proptosis is undoubtedly the result of excessive fat ... As far as I am concerned, it is unacceptable to consider the increase in orbital fat as the main cause of exophtalmos in Graves disease and that today there is no other satisfactory proof for it. ”

During 1933, Howard Christian Naffziger (1884–1961) published an overview of a large number of studies of orbital structures in exophtalmos – some tried to explain the changes by means of broadened varicose veins or dilated arteries or myositis of extraocular muscles. Naffziger pointed out that thickening of extraocular muscles dominated his material. Rundle and Pochin did a study on the properties of different tissues in the orbit in exophtalmos. They concluded that the increased quantity of fat was mainly responsible for the increase in the mass content of the orbits.

### *The cause*

In the following century, after both Graves and Basedow, a great many studies were published about the connections between goiter, heart symptoms and proptosis. The authors tried to explain this unusual combination of symptoms. In one of his earlier overviews of the connections between goiter and ophtalmopathy, Cooper pointed out that in two out of five patients the diagnosis was wrongly set to be hydrophthalmia (the probable meaning of this is glaucoma) and the largest number of problems derived from

mercury treatment that was used on them. Cooper did not try to establish the course of the disease, but he insisted on presenting the treatment: “if there are signs of anemia, there is a sound in the vessels of the neck, if there are palpitations, in addition to the enlargement of the thyroid gland, there is enough reason to think that the changes in the eye are of secondary nature: this is even more true when the patient complains about pains and uneasiness in the eyes or about the disorder of the eyesight. The most successful medication is iron, aloe, myrta with sedatives, immersing the body into cold salty water after which frictions are used, and, if there are signs of hysteria, a friction was used along the spine with stimulative liniments”

Although it is easy to mock theories and ideas that were accepted 100 years ago under the circumstances that were completely different from the present ones, even then some of the opinions seemed too revolutionary and almost unreasonable. So, in 1860 Jones wrote:” The basis of the disease is weakness, especially of the nervous system which, by affecting various vasomotor nerves, causes different symptoms. Thus, the effusion of eyeballs causes proptosis; hyperemia and increased activity of cellular elements of the thyroid gland cause goiter; vagus paresis causes palpitations and vomiting. The favourable effect of tonicum greatly supports this opinion.” Many authors pointed at the heart and neurological disorders as the probable causes (not consequences) of the disease. “Exophthalmos goiter” as a neurological disease was mentioned for the first time in 1861. Famous French doctors such as Trousseau and Charcot supported this attitude. So, Pierre Marie (1853– 1940) wrote an article about tremor characteristics, which, in his opinion, many earlier researchers had overlooked.

In 1890, Mackenzie published two clinical articles about Graves - Basedow disease and concluded: “That is, gentlemen, what I want to suggest to you as the origins and development of this unusual disease. It is possible that the disorder in the functioning of the thyroid body, whose importance in terms of nutrition and transmission of nervous powers has been proved, is highly relevant in the appearance of many secondary symptoms that I have paid attention to, but the real disease is a widespread disorder in the nervous system. ” In his short but influential article, Paul Julius Moebius (1853–1907) rejected the opinion that Basedow disease was a blood disorder, heart disease or a neurological disease. He admitted that while he was thinking about the nature of Basedow disease, he thought it to be some kind of hysteria. He noticed that myxadema symptoms were in a way completely different from hyperthyroidism symptoms and he suggested that Basedow disease was a thyroid gland disorder. He rejected the arguments that were popular at the time about the thyroid being a rudimentary organ or that its role was to regulate blood circulation in the brain. He did not deal with the explanations of exophthalmos.

In 1893, George Redmayne Murray (1865–1939)— who, in April 1891, was the first to give a thyroid extract to the patient with hyperthyroidism - published a study

in which he stated that “some of the symptoms of exophthalmos goiter are the result of hyperactivity of the thyroid gland”. He claimed that “the reduction in secretory activities improved the patient’s condition.” He quoted the report which said that the surgical removal of the gland led to the complete recovery. He particularly pointed out that the cause of exophthalmos did not necessarily have to be the hypersecretion of the thyroid gland. In some patients treated for hyperthyroidism, after the operation, exophthalmos remained unchanged or even deteriorates. In addition to this, giving thyroid extracts to patients does not cause exophthalmos.

Hirsch published a journal on exophthalmos where he expressed an opinion that was completely rejected a generation later. He made a distinction between “malignant exophthalmos” and “exophthalmos with a diffused toxic goiter”: “Malignant exophthalmos is a clinical unit different from exophthalmos observed in thyrotoxicosis. These conditions may be similar in etymology; a different clinical picture and differences in the procedure point at the fact that it is necessary for the diagnostician to be familiar with diagnosing criteria for the disease and for the surgeon to be familiar with the basic process on which the treatment is based.”

Although many patients with proptosis have hyperthyroidism, a small number is euthyroid or even hypothyroid. The reasons for clinical variations in effusion are not known yet. Mechanical or external factors could be relevant – for example, smoking or radioiodine treatment. In 1946, Iason mentioned more than 25 suggested causes of exophthalmos. Some were somewhat strange (rupture of jugular vessels due to sucking snow or drinking icy water or adrenalin insufficiency).

Studies from the period round World War II showed that the thyroid gland of larvae and amphibiae secretes a thyrotropic substance, which was later confirmed in mammals, too. It was speculated that this hormone might play a role in the appearance of exophthalmos goiter. However, in 1953, Werner concluded in an elaborate study, that thyrotrophine was not included in the pathogenesis of Graves disease. Regardless of this, hypophysectomy continued to be used in the treatment of exophthalmos for another decade.

### ***Operations on the sympaticus system***

In 1899, Abadie did the section of the cervical trunk of sympaticus in patients with severe bilateral exophthalmos. He claimed that the operation was extremely successful. He never doubted that the procedure was a valuable method in exophthalmos treatment. In the following years, several other, mainly French authors (Jaboulay, Jonnesco, Poncet, Reclus, Faure) took over the procedure which was still very popular in the 1920s since it was still believed that exophthalmos goiter was a neurological disease. Cannon and his associates insisted that it was possible to cause hyperthyroidism in a cat by stimulating sympaticus nerves. Experiments to prove this hypothesis were

done in 1939 but unsuccessfully, and Brian's work finally put an end to speculations about exophthalmos being a neurological disease.

### *Orbital surgery*

Exophthalmos can be an agonal disease not only because of the extreme deformation of the patient but also because of the pain and the risk for the patient's sight, which was Basedow the first to describe. It was no surprise then that medical communities insisted on identifying the disease in an early phase and searching for treatment procedures. As early as 1867, v Graefe recommended local surgery for putting the eyeballs back and symptomatic improvement. In October 1910, in Budapest, Julius Dollinger did the first huge surgery with the explicit aim to alleviate exophthalmos in Graves–Basedow disease. The patient did not have a clinically noticeable thyroid hyperfunction, but he had a severe proptosis of the right eye with keratitis. Despite large doses of morphine, she went through great pain. The external wall of the orbit was removed and there was a remarkable but brief recovery. This approach was based on the technique developed by Rudolf Ulrich Kroenlein (1847–1910)—one of the leading surgeons in the second half of 19<sup>th</sup> century.

It might have been expected that 100 years after Dollinger's operation there would be a concensus in terms of orbital surgery. Oskar Hirsch (1877–1965), after a pioneer work on pituitary surgery, described the removal of the orbital floor in 1920–30. Dollinger's article seemed to be unknown or forgotten in the United States until several studies between 1936 and 1940 described the removal of the lateral wall of the orbit as a new procedure.

Many other surgical procedures on the bony edges of the orbit were described and developed, some described the resection of three out of four sides; in fact, there was hardly a bone in the orbit that was spared.

The decompression of soft tissues seemed to be a logical alternative in the light of the early knowledge about fat accumulation being a significant phenomenon in thyroid orbitopathy. In effect, early publications reported of a satisfactory outcome after the removal of pieces of orbital fat by extracting them with forceps as much as possible. Hirsch applied the same principle in combination with the removal of the lower level of the orbit. This principle is still applied according to Adenis and his associates. Different techniques for adjusting the affected external muscles of the eyes and eyelids have also been developed.

Recently, in 2009, Leong and associates noticed that “there was a myriad of techniques in the procedures for the decompression of orbits but none of them achieved a long-term outcome with few complications.” In the literature in English, they found 56 articles on this problem, published between 1990 and 2006. It was possible to identify 15 different surgical techniques in them.



## ***Radiotherapy***

In patients with Graves Basedow disease, modalities of radiation therapy were used. First, American surgeons recommended external radiation of the neck. Since 1904, several reports were published in Europe, too. In some countries, radiation became the most frequently used method in the treatment of goiter and hyperthyroidism. At the beginning of World War II, in the United States of America, there were studies of the treatment of Graves Basedow disease and other hyperthyroid conditions by radioactive iodine (Hamilton and Lawrence; Hertz and Roberts). The results of the first studies were published in 1946; a mixture of isotopes I130 and I131 in the 90:10 ratio. The results of the larger series were published later. In most patients, the radioiodine therapy cured hyperthyroidism a few months after its application. In most of them, hypothyroidism was developed afterwards, whereas a small number of them were resistant to radioiodine. Additionally, radioiodine causes the growth of thyroceptor antibodies in the serum, which could be followed by the development of the disease of the orbit. The treatment of hyperthyroidism with radioiodine is still connected to dilemmas and the procedure is used much more in the United States than in Europe.

Another type of treatment was described in 1929 (Mandeville): radiotherapy of the orbits. The results are described only in a small number of patients and they were contradictory. The first more elaborate report of the long-term monitoring of orbital radiotherapy was made public almost 30 years later, and it was later followed by a blind study on the comparison between corticosteroid therapy and radiotherapy.

## ***Conservative therapy***

A major step forward was made in 1943 when Astwood reported that he had tried 106 chemical substances and found out that thiourea derivatives inhibit the thyroid function. Very soon, thiourea became widely used in the treatment of hyperthyroidism.

It seems that there is a certain relationship between hyperthyroidism treatment and the development of exophthalmos. Very often but still not necessarily, changes in the eyes are alleviated simultaneously with the remission of autoimmune hyperthyroidism. It has become clear that specific therapeutic steps are necessary in some cases of exophthalmos. With the evidence that exophthalmos goiter is an autoimmune disease, it has been concluded that using corticosteroids might be useful. The first two assessments of steroid treatment were based on the incorrect assumption that TSH or some other factor which caused exophthalmos also took part in the pathogenesis and that steroids worked in such a way as to inhibit the secretion of these factors from the thyroid gland. In 1955, The Medical Research Council Committee did a research on cortison or corticotropine (ACTH). The results were disappointing – first of all

because very small doses of cortisone were used. Systematic application of corticosteroids proved to be efficient, but large doses of corticosteroids were needed, which is something that is still a huge problem. Some time later, studies that proved that intravenous application of steroids was followed by a better ratio between favourable and unfavourable effects also appeared.

Garber reported about the influence of methylprednisolon in moderate doses injected in subconjunctival space. He concluded that the procedure was harmless and efficient. Later analyses of this procedure proved that it was not so efficient, but it is still being used. Wiersinga and associates were the first to publish the results of the controlled study of the effects of steroids on cyclosporine in the treatment of Graves Basedow disease. Other modalities of the treatment were also reported: application of somatostatine, non-steroid immunosuppressives, cytostatics, monoclonal antibodies ...

### *Amsterdam declaration*

“The pathogenesis of Graves’ orbitopathy is still poorly understood. Through research into the normal and abnormal situations, approached by different disciplines, might elucidate the problems and enable better management to prevent this disfiguring disease.”

This opinion seems to be correct just like it was several hundred years ago. Some patients recover remarkably well whereas others suffer from a long-lasting and serious disease. Patients with good outcomes do not receive a completely new and different treatment. The differences in the successfulness of treatment and the development of the disease are more visible in the evaluation discrepancies and possibilities for medical and surgical treatment, which have changed very little in the last few decades. Similar ideas induced clinicians, patients and politicians to design St. Vincent declaration for people with diabetes. St. Vincent Declaration turned out to be overambitious in the given time limits, but it was undoubtedly successful. It brought diabetes to the top of agendas of health centres, health economists and clinicians. It set the criteria for the improvement of treatment of patients with diabetes not by means of new and exotic procedures but by building infrastructure necessary for health care to reach everybody who needs it.

The similarity between the treatment of patients with diabetes and people with Graves orbitopathy inspired the appearance of Amsterdam Declaration. This document points out that patients with Graves orbitopathy can and should receive a better treatment and better care. It pays special attention to the improvement of quality of life of the patients, prevention, faster treatment and care, mainly in the centres with the highest standards in orbitopathy treatment.

In October 2009, at the Tenth international symposium on Graves orbitopathy, Amsterdam Declaration was signed.

General objectives of the Declaration are:

– reduced morbidity related to Graves orbitopathy and improvement of patients' feelings and quality of life;

– prevention of Graves orbitopathy in high-risk patients;

Five-year long objectives are:

– increasing precautions against this disease in health professionals and managers;

– establishing ways of directing and giving help;

– supporting the existing centres in procedures applied in this condition;

– creating new specialized centres in the areas where they do not exist;

– establishing control and mechanisms for monitoring insurance quality and offering help to people with Graves orbitopathy;

Implementation measures for the reduction of incidence and morbidity in this disease:

– Making the interval between the appearance and diagnosis half as long;

– Making the interval between the diagnosis and sending a patient to a specialized centre half as long;

– An adequate procedure with thyroid dysfunction including radioiodine;

– Energetic measures against smoking in patients with the risk of developing Graves orbitopathy;

– improving the existing research networks and developing joint international research.

### ***Thyroid eponyms***

It is not uncommon for a disease that has been known for centuries and whose ethyology and optimum treatment we do not know that there is not even an agreement on its name. It seems that there are no reasons for disagreement with the fact that Parry was the first who, although briefly, described the basic symptoms of exophthalmoses goiter. Thus it seemed justified when Sir William Osler said that “if the disease should be given the name of a doctor, then it should be the name of the outstanding doctor from Bath”. Basedow was one of the doctors who were the first to give a complete description of clinical symptoms of exophthalmos in exophthalmos goiter. It first seemed that the disease would be named after Basedow, and Charcot agreed with it. Since 1862, the problem was discussed at the meetings of the French Medical Academy on several occasions. It was decided that the most frequently used term “exophthalmos goiter” was incorrect since neither exophthalmos nor goiter was always observed in patients. Trousseau, the doyen of French medicine, supported the eponym of Graves and naming this disease Graves disease (“il nous faudrait substituer au nom de Basedow celui de Graves... serait dit maladie de Graves”) and

thus he enabled this name to be accepted by the majority in the medical community. In the German speaking areas and in one part of the European continent, the name Basedow disease is still formally used. Today, the attempt to name the disease after Parry would be unsuccessful, but it seems that the name of Graves Basedow disease would be a very good alternative.

As time went by, different names for exophthalmos component of the disease were used and some of them still are. The newest term “orbithopathy” might sound better as Graves Basedow orbithopathy instead of thyroid or “thyroid associated” since some patients with orbital changes do not have or only have mild thyroid disorders. Graves Basedow orbithopathy, not opthalmopathy, would be a good name since the changes occur in the whole orbit and not just in the eyeballs.