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**Publication/Creation**

Dublin : John Falconer, 1883.

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THE THEORY

OF A

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CENTRAL LESION

IN

EXOPHTHALMIC GOÏTRE.

*E. Nettleship Esq*  
*With Hunter's compliments*

BY

WILLIAM A. FITZGERALD, M.D., UNIV. DUBL.

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Reprinted from the Dublin Journal of Medical Science—March and April, 1883.

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DUBLIN:

PRINTED FOR THE AUTHOR

BY JOHN FALCONER, 53, UPPER SACKVILLE-STREET.

1883.

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THE THEORY  
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WITHIN the last few years considerable additions have been made by Continental writers to the already very bulky literature which treats of the pathology of Graves' or Basedow's disease. The fact that these additions have as yet, so far as I am aware, attracted but little attention in this country must be my excuse for endeavouring to re-open a subject on which so much has already been written.

"A theory of the disease," says Eulenburg,<sup>a</sup> "to deserve the name, ought to be able to derive all the symptoms, or at least the three cardinal ones, from a common source." And inasmuch as he seems indisposed, as do also the majority of writers, to consider it as an affection of the central nervous system, it is not at all surprising to find him expressing a fear that "we shall be obliged at the best to content ourselves with a somewhat unsatisfactory result." For it will be very generally admitted that there are great difficulties in explaining the complex collection of symptoms which go to form Graves' disease by what I may term the sympathetic theory, and that such is the case is shown by the vast amount of discussion which the subject has occasioned, and by the fact that many writers have at various times been led to suggest, some vaguely and others more precisely, a central origin of the affection. Still it is only quite recently that a precise and definite central theory, capable of satisfactorily explaining the principal symptoms, has been put forward by Professor Sattler<sup>b</sup> (whose admirable article contains probably almost everything that is known

<sup>a</sup> Ziemssen's Cyclopædia. Eng. edition. Vol. 14.

<sup>b</sup> Graefe-Saemisch Handbuch. Bd. VI., s. 949. Die Basedow'sche Krankheit. 1830.

of the subject), and by Professor W. Filehne,<sup>a</sup> who has brought the experimental method to bear on the investigation.

It may perhaps lead to a clearer understanding of this somewhat complicated subject if, before considering the conclusions arrived at by these last-named authors, I should briefly allude to the principal and most constant symptoms of the affection, and endeavour to point out the difficulties involved by the theories of earlier writers.

That the enlargement of the thyroid gland is due to dilatation of its vessels is probably universally admitted, although of course in a late stage the long-continued hyperæmia may have given rise to hypertrophy of the gland tissue. In a few cases there have been great increase of connective tissue, and even cystic degeneration, but such alterations are clearly effects of the disease and not any integral portion of it. There are many proofs that the exophthalmos is also primarily due to hyperæmia—for instance, the vascular bruit often present; the occasional disappearance of the protrusion after death, and the possibility of lessening it during life by pressure on the globes; the extremely rapid onset of the symptom which has been occasionally noticed (as in a case recorded by Trousseau,<sup>b</sup> in which marked protrusion occurred in the course of a single night); and, lastly, the fact that Boddaert<sup>c</sup> has produced in guinea-pigs and rabbits a considerable amount of exophthalmos, lasting several days, by tying the external and internal jugulars on both sides, and simultaneously dividing both cervical sympathetics to facilitate dilatation of the vessels. In most cases which have been examined *post mortem* there has been found hypertrophy of the orbital fat, but this must be considered, like the structural alterations of the thyroid, as a result of the long-continued hyperæmia.

The goître and the exophthalmos, then, as well as the enlargement and pulsation of the carotids, and of the central arteries of the retina, have been almost universally attributed to paralysis of the vasomotor nerves which run in the cervical sympathetic. The increased cardiac action has been generally explained by the assumption of a permanent irritation of the excito-motor nerves of

<sup>a</sup> Zur Pathogenese der Basedow'schen Krankheit. Sitzungsber. der physic. Med. Societät zu Erlangen. 14 Juli, 1879. S. 177.

<sup>b</sup> Clinique Médicale. Tome II., p. 587.

<sup>c</sup> Mémoire lu au congrès de Bruxelles. Gazette Hebdom., 1875. No. 41, p. 645. By tying the thyroïdal veins in addition he produced a distinct enlargement of the thyroid gland.

the heart, which also run in the cervical sympathetic, and here at once the difficulty arises that whereas some of the symptoms—namely, the goitre and the exophthalmos—are referred to paralysis, the third cardinal symptom is accounted for by the exactly opposite condition.

Various attempts have been made to explain away this obvious contradiction. Thus Eulenburg and Guttmann,<sup>a</sup> in their work on the pathology of the sympathetic, say—“If we now suppose that Graves’ disease arises from an affection of the nerve centres, we may well conceive the centre for the oculo-pupillary fibres as in a condition of irritation, while, on the contrary, the centre for the vasomotor fibres is in a state of paralysis. Even though we regarded the cause of exophthalmic goitre as not central but peripheral, and situated in the cervical sympathetic, there is nothing forced in the above supposition that the oculo-pupillary fibres are in a condition of irritation, and the vasomotor fibres in a state of paralysis.” They instance in support of this assertion the well-known facts that in neuritis there may be spasm and anæsthesia, or paralysis and hyperæsthesia, and, in the same fibres even, anæsthesia dolorosa, or paralysis with slight spasmodic movements.

They here allude to the theory of the disease put forward by Geigel,<sup>b</sup> who, taking advantage of Claude Bernard’s discovery that the oculo-pupillary and the vasomotor fibres of the cervical sympathetic are each connected with separate centres in the cervical region of the spinal cord, situated at different levels, assumed lesions of these centres, and considered the vasomotor as being in a state of paralysis, and the oculo-pupillary in a state of irritation. Geigel’s theory was based on a *post mortem* in which there was found obliteration of the central canal of the spinal cord, with sclerosis of the nerve substance in its immediate neighbourhood, especially posteriorly.

Benedict<sup>c</sup> again has endeavoured to account for the dilatation of the vessels, not by paralysis but by a condition of permanent irritation. He suggested a spasm of the muscular fibres which run longitudinally in and between the coats of the arteries, which would cause a shortening of the vessels and simultaneously an increase in their calibre. Founding his theory also on the result

<sup>a</sup> The Sympathetic System of Nerves. Eng. translation.

<sup>b</sup> Würzburg. med. Wochenschrift. VII., s. 70. 1866. Referred to by Sattler.

<sup>c</sup> Wiener med. Presse. 1869. No. 52, s. 1225.

of Geigel's *post mortem*, he says:— "This disease is thus probably a central vasomotor irritation-neurosis, which is caused by swelling of the gray substance in the neighbourhood of the central canal at the cervical enlargement." The extreme tortuosity of the thyroïdal arteries, so constantly noticed, seems sufficient to dispose of this idea.

Friedreich,<sup>a</sup> on the other hand, has suggested that the increased cardiac action is due to paralysis of the vasomotor fibres going to the heart, which causes dilatation of the coronary arteries, and an increased flow of blood to the muscular tissue of that organ, thus inducing an excitement of the ganglia which preside over its rhythmical contractions.

It is certainly remarkable that, in endeavouring to account for the cardiac symptoms, so little attention should have been paid to the possibility of impairment of the inhibitory function of the pneumogastric nerves. This explanation has, however, not been altogether wanting, for Handfield Jones,<sup>b</sup> in a paper read before the Medical and Chirurgical Society, attributed the palpitation to paresis of the vagi, as did also Habershon<sup>c</sup> at a later period.

The adherents of the irritation theory have put forward another explanation of the exophthalmos—namely, that it is due to a spasm of the musculus orbitalis of Müller, first described in 1858. It consists of unstriped fibres embedded in the periosteal tissue in the neighbourhood of the speno-maxillary fissure, and is innervated by the sympathetic. In most mammals it has a definite anatomical importance, as it helps to shut off the orbital cavity from the temporal fossa; but in man and monkeys, whose orbits possess a bony wall in this situation, it loses its significance, and is reduced to an exceedingly rudimentary condition.<sup>d</sup> It is this muscle which causes the protrusion of the eyeball in Claude Bernard's well-known experiment of galvanising the previously divided sympathetic in the neck; but in man, owing to its extremely insignificant size, it seems quite incapable of affecting the position of the globe,<sup>e</sup>

<sup>a</sup> Krankheiten des Herzens. Erlangen. 2 Aufl., s. 307. 1867. Referred to by Sattler.

<sup>b</sup> Lancet. 1860. Vol. II., p. 562.

<sup>c</sup> Lumleian Lectures. Brit. Med. Journ. 1876. Vol. I., p. 497.

<sup>d</sup> See Graefe-Saemisch Handbuch. Bd. I., s. 13, and Bd. II., s. 165.

<sup>e</sup> It is right to mention that Eulenburg (l. c.) has suggested that the production of exophthalmos may be facilitated by the straight muscles being in a condition of fatty degeneration. It is no doubt true that such a condition has been found *post mortem* in one or two instances, but in accounting for the protrusion in ordinary cases, in which it is frequently most rapid in its occurrence, and accompanied by no signs of weakness of the ocular muscles, such an explanation seems totally inadmissible.

and the experiments of Wagner and Müller<sup>a</sup> have shown that in recently decapitated criminals stimulation of the sympathetic is powerless to cause any exophthalmos.

Omitting the consideration of various conditions which, although frequently and some even usually present, cannot be ranked among the cardinal symptoms of the disease—such as anæmia, chlorosis, menstrual derangements, vomiting, diarrhœa, mental disorders, &c.—there still remain two phenomena which are among the most constant symptoms, and which are therefore of extreme value from a diagnostic point of view. I allude to the symptoms with which the names of von Graefe<sup>b</sup> and Stellwag<sup>c</sup> are associated, and which, although capable of a ready explanation by the assumption of a central lesion, have been almost invariably attributed to spasm of the sympathetic. Indeed it is probable that they have done more than almost anything else to perpetuate the sympathetic theory. Thus Eulenburg and Guttmann (l. c.), while they admit that spasm of the sympathetic cannot cause the exophthalmos, consider that Graefe's sign "unquestionably indicates the participation of the sympathetic in the production of the disease."

Graefe's sign consists of *an impairment of the consensual movement of the upper eyelid in association with the eyeball*. Thus normally when the globe is rotated downwards, as in looking down, the upper lid follows it, preserving its relative situation to the cornea. The exact explanation of this phenomenon has possibly still to be brought forward; but one thing is certain—namely, that in order to permit of the descent of the lid, as also in the action of involuntary winking, an inhibition of the levator palpebræ is necessary.<sup>d</sup> In Graves' disease, however, this descent of the upper lid on looking down is, in the great majority of cases, either in part or entirely wanting, so that a zone of sclerotic becomes visible above the cornea when the eyeball is rotated downwards. That this is not due to the protrusion of the globe is shown by the facts that it is one of the earliest symptoms of the affection, appearing often when the exophthalmos is still absent, or only present in a slight degree; that it may disappear while the protrusion still continues, and that in proptosis from other causes, such as tumour or inflam-

<sup>a</sup> Referred to by Sattler, l. c., s. 987.

<sup>b</sup> Deutsche Klinik. 1864. No. 16, s. 158.

<sup>c</sup> Wiener med. Jahrbücher. XVII, s. 25. 1869.

<sup>d</sup> Different opinions as to the mechanism by which this inhibition is effected will be found expressed by W. R. Gowers in Trans. Med. and Chirurg. Soc., 1879; and by Lang and Fitzgerald in Trans. Ophthalm. Soc., Vol. II, p. 217.



matory exudation in the orbit, the symptom is entirely wanting. And a case has been recorded by Mooren<sup>a</sup> in which, although the exophthalmos was unilateral, Graefe's sign was present on both sides.

What is known as Stellwag's sign consists of *an abnormal widening of the palpebral aperture, due to retraction of the upper lid, and of incompleteness and diminished frequency of the act of involuntary winking.*

It is to this gaping of the palpebral aperture that the remarkable and truly characteristic aspect of the patient is due rather than to the exophthalmos, and so striking is the symptom that it did not fail to attract the notice of earlier writers, but it is to Stellwag that we are indebted for having first pointed out its constancy and its consequent value in diagnosis. These eyelid phenomena have usually been attributed to spasm of the unstriated muscular fibres which were first described by Müller as occurring in the upper and lower lids—in other words, to permanent irritation of the sympathetic, but Stellwag did not accept this explanation.

In endeavouring to account for these various symptoms there is one fact which it seems impossible to reconcile with the theory of a lesion of the cervical sympathetic, whether irritative or paralytic in character—namely, the extreme rarity of any affection of the pupils. I am aware that some writers have described mydriasis as a frequent symptom in Graves' disease, while a few cases of myosis have been recorded, but such is not the generally expressed opinion, especially among ophthalmologists. Thus Sattler says that "in the preponderating majority of cases no particular alteration of the pupils is to be noticed;" and Graefe, in about two hundred cases, never observed mydriasis. And Eulenburg (a physician, be it remembered, and not an ophthalmic specialist) has endeavoured to account for the absence of this symptom by pointing out that in those autopsies which have shown lesions of the sympathetic it has usually been the inferior cervical ganglion that has been affected. This explanation seems rather an unfortunate

<sup>a</sup> Ophthalm. Mittheilungen aus dem Jahre, 1873, s. 15. On the other hand C. E. Fitzgerald has published four cases in which with unilateral exophthalmos Graefe's sign was also unilateral (Trans. Ophthalm. Soc., Vol. II., p. 233); and in I. B. Yeo's case with unilateral exophthalmos Stellwag's sign was limited to that side (Brit. Med. Journ., 1877, Vol. I., p. 320); and in a case described by Lauder Brunton, Graefe's sign was limited to the right side—that on which the protrusion was most marked (St. Barth Hosp. Rep., Vol. X., p. 253).

one, for in cases of pressure on the sympathetic, at or below the level of the ganglion in question, pupillary symptoms are commonly noticed—as, for instance, in intrathoracic aneurism.

With regard to the assumption of a state of permanent and continuous irritation of the sympathetic, it would appear decidedly questionable whether such a condition is even possible, not to say probable. Eulenburg and Guttmann indeed admit that such a condition of permanent irritation cannot be assumed as would be necessary in order to account for the cardiac symptoms, and on this point I shall quote the words of Sattler<sup>a</sup>—“If now the explanation of Basedow’s disease as an affection of the sympathetic be still maintained, it is impossible, as we have seen, to avoid the assumption of a permanent condition of irritation of certain groups of sympathetic nerve-fibres continuing for months or even years. But this would be to maintain the existence of a condition for which we possess no clearly-proved physiological analogy. Conditions of nervous irritation give way sooner or later, intermittently or permanently, to a state of rest, or even to the opposite condition, that of relaxation or exhaustion. Now, even if it be the rule in Basedow’s disease to find considerable variations in the intensity of the symptoms, yet they never pass over into the opposite state, and especially is this the case with those which, according to the views of authors, must be regarded as irritation symptoms; the pulse in typical cases never falls below 90 or 100; the abnormal position of the lids never gives place to ptosis, nor even attains the normal until the symptom disappears altogether.”

The assumption of paralysis of the sympathetic still remains to be considered, and here we are at once confronted by a decided difficulty—namely, that the two cardinal symptoms, the goitre and the exophthalmos, which it is endeavoured to refer to that condition, have never been produced, so far as I am aware, by experimental section of the sympathetic cord, although there is abundant proof that enlargement of the thyroid gland is possible in animals;<sup>b</sup> and in clinical cases of paralysis of the cervical

<sup>a</sup> L. c. S. 992.

<sup>b</sup> Baillarger (*Union Médicale*, 1862, p. 116) has shown that in districts in which goitre is endemic domestic animals are not exempt from it. This applies particularly to dogs and horses, but in the most special and remarkable manner to mules. Thus, in one stable examined, 19 out of 20 and in another 23 out of 30 mules presented distinct enlargement of the thyroid gland. With respect to rabbits the reader is referred to Boddaert’s experiment before alluded to.

sympathetic, although the pupillary symptoms are well marked, as are also, especially at first, the vasomotor phenomena, both goitre and exophthalmos are conspicuous by their absence.

The theory of the disease advanced by Sattler disposes of these various difficulties, and will probably sooner or later, meet with very general acceptance. He assumes a lesion of those circumscribed portions of the vasomotor centre<sup>a</sup> (or possibly of a still more central region of the brain) which preside over the vasomotor nerves of the thyroid gland, and of the intra-orbital tissues, and he infers from the very great constancy with which the two symptoms of goitre and exophthalmos are found combined, that the portions in question must be situated exceedingly close together. The cardiac symptoms he ascribes to lesion of the cardio-inhibitory centre<sup>b</sup> for the vagus, and in explaining Graefe's sign as a central phenomenon he uses the following words (p. 996):—"There is no doubt whatever that the movements of the lids in association with the raising and lowering of the level of fixation—that is to say, the consensual action of the levator and orbicularis on the one hand, and of the ocular muscles which rotate the eyeball about a horizontal axis on the other—are presided over by a definite coordination-centre, just as much as are the associated movements of both eyes."<sup>c</sup> The remaining lid-symptoms were ascribed by Stellwag to a lesion of those reflex centres which are set in action by stimuli from the retina, and from the sensitive nerves of the cornea and conjunctiva, and in this opinion Sattler coincides. He says (p. 996):—"In an analogous manner are to be explained the

<sup>a</sup> "The position of the vasomotor centre appears, from the researches of Ludwig and Owsjannikow, to be situated in the gray matter on each side of the median line of the floor of the fourth ventricle, extending from about 4 mm. in advance of the beak of the calamus scriptorius to within 1 mm. posterior to the corpora quadrigemina. Section above this latter point does not cause dilatation of the blood-vessels, while section posterior to the lower margin of the centre causes their complete and permanent paralysis."—Ferrier, *Functions of the Brain*, 1876, p. 30.

<sup>b</sup> Michael Foster says (*Textbook of Phys.*, p. 126):—"Hence the cardio-inhibitory centre might itself be inhibited by impulses reaching it from various quarters—in other words, the beat of heart might be quickened by the lessening of the normal action of its inhibitory centre in the medulla. It is, in fact, probable that many cases of quickening of the heart's beat are produced in this way, but the matter requires further investigation."

<sup>c</sup> That the orbicularis takes any part in the movements of the eyelids in association with the eyes is exceedingly doubtful. All that seems necessary for the descent of the upper lid is an inhibition of the levator palpebræ, and this is probably brought about by the action of an associated centre for looking down, which simultaneously causes contraction of the muscles which rotate the eyeball downwards. See note to page 7.

two other lid-symptoms, the increased gaping of the palpebral aperture, as well as the diminished frequency and incomplete character of the act of involuntary winking. It is well known that the width of the palpebral aperture, and also the completeness and number of the involuntary descents of the upper lid occurring in a given time, stand in a reflex relation on the one hand to the amount of light which stimulates the retina, and on the other to the amount of stimulation applied to the sensitive nerves of the anterior surface of the globe, which latter is of course under normal conditions very slight. And this is illustrated in the most striking manner by the narrowing of the aperture which invariably occurs on exposure to dazzling light, by the characteristic and involuntary position of the lids which is often noticed with corneal nebulae, by the marked sinking of the upper lid which accompanies even the slightest irritation of the conjunctiva or cornea, and so on, and again by the abnormal width of the aperture which impresses such a peculiar character on the gaze of amaurotic patients. There clearly exists here a similar reflex relation to that between the size of the pupil and the amount of light stimulating the retina."

He sums up as follows (p. 999):—"We have now seen that the essential, and to a certain extent constant, symptoms which make up the comprehensive picture of Basedow's disease, and which show themselves in such various and widely distributed organs, can be explained in an uniform manner *by the assumption of a lesion of certain centres*, which leads to the impairment or abolition of the functions presided over by these centres, and in fact, more precisely expressed, *of a lesion implicating the tone in the vagus centre which regulates the cardiac movements, or the peripheral but still unmixed nerve-paths proceeding from it; further, the vasomotor centres for definite regions of the body, especially of the head and neck, and finally the centres for certain coordinated movements and reflex actions.*"

The central theory of exophthalmic goitre has been considerably strengthened by the experimental investigations of Filehne (*l. c.*). Dissatisfied with the contradictions implied by an explanation which referred some of the symptoms to paralysis and others to irritation of the sympathetic, and, moreover, disbelieving in the possibility of such a permanent and continuous condition of nervous irritation, he endeavoured to explain the matter by assuming a lessening or abolition of tone in the vagus centre, associated with a

condition of vaso-motor paralysis. That the cardiac symptoms are not due merely to diminution of arterial tension he inferred from the fact that, although sudden lowering of tension causes great quickening of the heart's action, yet one often sees a chronic condition of low tension without a quick pulse, the vagus centre thus seeming to accommodate itself to gradual alterations of pressure.

He thus thought of the vaso-motor centre and of the centre for the vagus, and this at once led him to the medulla oblongata, inasmuch as the course of the cardiac fibres of the vagus inside the central nervous system is short and confined to the medulla. The following is Filehne's description of the experiments which he was led by this train of reasoning to perform:—"If, in not quite fully grown rabbits, after putting away the muscles at the back of the neck between the occiput and atlas, one removes the membrana obturatoria and the dura mater from the entire opening bounded by these bones, one sees, towards the head, the lower and posterior part of the vermiform process; to the right and left the corpora restiformia, ascending obliquely from below and behind, outwards and towards the brain, and enclosing between them the calamus scriptorius. Supposing *the portion of the restiform bodies exposed by this preparation* to be divided into four equal parts, it is in the upper fourth (that next the head) that one must operate." . . . "I cannot as yet say with anatomical precision how deep it is necessary to make the wound, but it would seem that the incision must extend into the grey substance of the corpora restiformia." He usually made on both sides a transverse incision with a fine cataract knife, but on a few occasions he used the galvano-cautery. He was careful not to carry his incision as far as the under-surface of the medulla, and thus wound the roots of the vagus. Of the results obtained the most frequent was implication of the vagus, "so that neither reflex irritation (by tobacco smoke) from the nasal mucous membrane, nor suffocation produces the cessation of cardiac action, or even slowing of the pulse which is so characteristic in rabbits, and so that subsequent division of both vagi in the neck does not cause any acceleration of it."<sup>a</sup> Next in frequency was

<sup>a</sup> Kratschmer (Abstract in Jour. of Anat. and Phys., Vol. V., part 2, 1871) found that in rabbits irritation of the nasal mucous membrane by ammonia, or even tobacco smoke, or by mechanical or electrical stimulation, caused marked slowing, and even cessation of the heart's action. Division of both fifth nerves within the cranium, or of both vagi, prevented this occurring. He, as well as Brown-Séquard (referred to by

exophthalmos, usually more pronounced on one side than on the other. It occurred even if the sympathetic had been previously divided in the neck, thus excluding the possibility of its being due to spasm of the musculus orbitalis. Although swelling of the thyroid was but seldom produced, there was well marked vaso-motor paralysis of the ears, of the thyroid, and of the anterior part of the neck.

Stellwag's signs were also occasionally noticed, while the pupils were in no case affected. In only one case, and in that he had operated with the galvano-cautery, did he succeed in producing all three cardinal symptoms in the same animal.

Filehne formulates the following conclusions:—

“1. Basedow's disease may be produced by paralysis of certain nerve regions which are controlled by the medulla oblongata. The points traversed in common by the nerve-paths concerned are the restiform bodies.

“2. Under such circumstances the exophthalmos and the goitre depend on dilatation of the blood vessels.

“3. The increased rapidity of the heart's action is brought about by diminution or abolition of tone in the vagus.

“4. That Basedow's disease in human beings depends on the same physiological relations is highly probable, but must first be established by proofs afforded by pathological anatomy. In this investigation attention should be directed not only to the medulla oblongata but also to the condition of the trunk of the cardiac portion of the vagus.”

And finally he takes care to point out that, even if *post-mortem* examinations should give negative results, this would not be necessarily fatal to his theory, as the occurrence of functional affections

Rutherford), attributed this to inhibition exerted by the vagus, and excited by a reflex influence from the nasal mucous membrane. Rutherford (*Journal of Anat. and Phys.*, 1873, p. 283) confirmed these results, but explained them by the fact that the rabbit holds its breath when ammonia is held to its nose, and he considers that what stimulates the cardio-inhibitory centre is the presence of carbonic acid gas in, or the absence of oxygen from, the blood. He also found that division of the vagi prevented the slowing of the pulse. Lauder Brunton finds that the same effects are produced by nitrite of amyl (*Journ. of Anat. and Phys.*, Vol. V., p. 92), so that in investigating the action of that drug he had to keep up artificial respiration to eliminate this source of error. He says:—“One of the chief of these (errors) is that any strongly-smelling vapour, and nitrite of amyl among others, acting on the nose of rabbits, causes suspension of the respiration for a short time, and the alteration in the condition of the blood thus produced causes irritation of the vagus, and slowing of the heart's action.” Thus all parties are agreed in ascribing the result to inhibition exerted by the vagus.

of the central nervous system (*i.e.*, those in which it is *as yet* impossible to find an organic lesion) is admitted.<sup>a</sup>

Filehne, however, was not the first physiologist who produced exophthalmos by wounding the restiform bodies, Brown-Séguard having done so several years before. I regret that I have been unable to find the description of his method of procedure, but the following extract from a lecture by him is sufficiently conclusive:—“Exophthalmia in animals born of parents in which an injury to the restiform body had produced that protrusion of the eyeball. This interesting fact I have noticed a good many times, and I have seen the transmission of the morbid state of the eye continue through four generations. In these animals, modified by heredity, the two eyes generally protruded, although in the parents usually only one showed exophthalmos, the lesion having been made in most cases only on one of the corpora restiformia.”<sup>b</sup> Brown-Séguard had previously produced othæmatoma or sanguineous tumour of the ear (also in guinea-pigs) by wounding the restiform body near the nib of the calamus scriptorius.<sup>c</sup>

As Graves' disease is of tolerably frequent occurrence among lunatics, to which class of persons this affection of the ear is almost entirely confined, it seems not unlikely that the two affections should be observed in the same individual. Such a combination has been recorded by Robertson<sup>d</sup> in a patient suffering from acute mania and Graves' disease. Both ears were affected. Lennox Brown<sup>e</sup> has expressed a doubt as to whether Robertson's case was

<sup>a</sup> A case of injury to the restiform body in the human subject has been recorded by Waters. The patient survived for 24 hours, and among other symptoms (paralysis of facial, glosso-pharyngeal nerves, &c.) “the right side of the face and the right arm and leg were of higher temperature than the corresponding parts of the opposite side.” It was found *post mortem* that the right restiform body, and the right posterior column of the cord had been divided transversely (*Med. Times and Gaz.*, 1863, Vol. I., p. 517). In a case of Graves' disease, in which exophthalmos was present on the right side only, there was also right-sided flushing of the face, and distinct elevation of temperature on that side, the pupil being unaffected. Samelsohn's case, referred to by Sattler, p. 964.

<sup>b</sup> On the Hereditary Transmission of Effects of certain Injuries to the Nervous System. *Lancet*. 1875. Vol. I., p. 7. In this connexion it may be noticed that heredity seems, in some instances, to have a share in the causation of Graves' disease. Thus Sattler (p. 977) enumerates eight writers who have recorded such cases, and Withusen (translation by Dr. W. D. Moore in *Dublin Med. Press*, Vol. 42) believes that in two of his patients an hereditary disposition to the disease existed.

<sup>c</sup> *Lancet*. 1869. Vol. I., p. 515.

<sup>d</sup> *Glasgow Med. Journal*. July, 1875.

<sup>e</sup> *West Riding Asylum Reports*. Vol. V., p. 154.

really one of othæmatoma, but I hope I shall be excused if on such a point I prefer to rely on the opinion of a physician who has made insanity his study, and who was himself in charge of the case in question, rather than on that of a throat and ear specialist, however eminent, who had never had an opportunity of seeing the patient.

A possibly somewhat similar instance has been recorded by Stiff,<sup>a</sup> who thus describes the case, that of a male patient aged thirty-four:—"General health bad; exhaustion; conduct violent; notions incoherent; countenance painfully distorted; the left eye wild and prominent; the right eyelid paralysed, with dilatation of the pupil. Not epileptic." Othæmatoma occurred on one side; it is not stated which. I am inclined to think that if attention were directed to this possible connexion, cases of the kind would perhaps be more frequently observed.<sup>b</sup>

The occasional occurrence of what are undoubtedly central lesions in patients suffering from Graves' disease cannot fail to strengthen the central theory.

Symmetrical paralysis of the external recti, of which three cases are on record, is in all probability a central lesion, but there can be no question whatever about the central nature of paralysis of the associated movements of the eyes. Stellwag (*l. c.*) has seen a case of paralysis of the associated lateral movements, while of implication of the associated upward movements three instances have been published,<sup>c</sup> and within the last few months Warner has read a paper<sup>d</sup> before the Medical and Chirurgical Society in which he described a case of Graves' disease complicated by ophthalmoplegia externa, as well as bilateral paresis of seventh and fifth nerves and tremor of the legs. Féréol<sup>e</sup> has observed the following symptoms (certainly pointing to a coarse brain lesion) come on six months after the onset of Basedow's disease in a man forty-one years of age:—Pain in head, vomiting, giddiness, tremors, reeling gait, with a tendency to fall to the right; subsequently diplopia, due to paresis of right fourth nerve, and in addition on

<sup>a</sup> Brit. and For. Med. Chir. Rev. Vol. XXI., p. 222. 1858.

<sup>b</sup> I have to express my obligations to my friends, Dr. Ringrose Atkins, Medical Superintendent of the Waterford Asylum, and Dr. E. G. Levinge, of Lucan, for kindly affording me valuable information on this part of the subject.

<sup>c</sup> Fischer. Arch. Génér. de Méd. Vol. II., pp. 521, 652. 1859. Chvostek. Wiener med. Presse. 1872. (11 Beobacht.). Roth. Ibid. 1875. No. 30, s. 680.

<sup>d</sup> Lancet. 28th October, 1882.

<sup>e</sup> L'Union Méd. No. 153, 1874, and Gaz. des Hôp. No. 137, 1874.



the right side diminished motor power, with hyperalgesia, and on the left analgesia.

The occurrence of glycosuria, of which several cases are on record,<sup>a</sup> seems to point in the same direction, although Lauder Brunton (*l. c.*) suggests that this phenomenon helps to localise the lesion in the third cervical ganglion. On this point I shall merely quote the following passage from Michael Foster<sup>b</sup> descriptive of what is known as the "diabetic puncture:"—"If the medulla oblongata of a well-fed rabbit be punctured in the region which we have previously described (p. 134) as that of the vasomotor centre (the area marked out by Eckhard as the diabetic area, agreeing very closely with that defined by Owsjannikow as the vasomotor area), the urine of the animal, which need not necessarily be in any other way obviously affected by the operation, will be found in a few hours to contain a considerable quantity of sugar, and to be increased in amount." It will be remembered that it is in a portion of this same area that the localisation of the lesion of Graves' disease has been suggested.<sup>c</sup>

The fact that a few *post mortems* have shown alterations of the cervical sympathetic will, no doubt, be quoted in support of the opposite theory; but, in reply, it may be urged that, in a still larger number of cases, careful microscopical examination by the most competent pathologists has failed to detect the slightest abnormality in the sympathetic cord or its ganglia. Further (as Sattler points out), the alterations that have been found are of an exceedingly inconstant nature, and are sometimes more marked on one side than on the other, or even confined altogether to one side, although the disease may have been almost symmetrical. Then, the cases in question have usually been old and severe cases of the disease, and have sometimes shown other degenerative changes, such as fibroid and cystic degeneration of the thyroid, and thickening of the bones of the skull,<sup>d</sup> while, on the other hand, instances of central lesions have not been wanting in several cases.

<sup>a</sup> Five referred to by Sattler (p. 970), and one by Habershon (*Brit. Med. Journ.*, 1876, Vol. I., p. 497), and another by Fischer in *Aertztliches Intelligenzblatt*, 1880, No. 27.

<sup>b</sup> *Textbook of Physiology*. P. 293.

<sup>c</sup> Luys (*L'Encephale*, May, 1882) reports four cases of diabetes in which he has found alterations in the floor of the fourth ventricle near the diabetic puncture (*Brit. Med. Journ.*, Dec. 30, 1882, p. 1311).

<sup>d</sup> It seems probable that the alterations which have been noticed in the sympathetic cord and its ganglia may be analogous to the descending tracts of degeneration in the spinal cord, and may thus be due to an extension from a focal lesion.

amongst others in that by Geigel already referred to, and notably in a case recorded by Morell Mackenzie.<sup>a</sup> Lockhart Clark, who examined the brain in this case, says:—"The substance of the cerebral tissues was not unnaturally soft; nor was there any clot or embolism anywhere, but the corpora quadrigemina, and the medulla oblongata—particularly in its posterior part—were very soft, and on minute examination displayed the usual appearance of common softening." And, more recently, Cheadle<sup>b</sup> has published a case in which, although the brain and spinal cord seemed perfectly normal to the naked eye, microscopical examination showed very great dilatation of the vessels of the medulla oblongata and cervical region of the cord. The cervical sympathetic showed no abnormality whatever, even to the most careful microscopical examination. This affection of the vessels Cheadle considers as probably a result of the disease, and he says that the condition of the nervous system is probably "more one of disorder than of organic morbid change;" but still the results of this *post mortem* seem apparently to have induced him to suggest the localisation of the lesion in the vasomotor and cardio-inhibitory centres; at any rate he had before expressed himself much more guardedly on the subject. This opinion, arrived at by such a competent pathologist, independently of, and I believe prior to, the publication of Filehne's and Sattler's articles, must certainly be regarded as a most valuable one.

There is one thing which can hardly fail to strike anyone who has carefully studied the recorded cases of this disease—namely, the marked preference shown by the symptoms for the right side of the body. Although bilateral symmetry is not infrequent, it is certainly not the general rule, especially at the commencement of the affection; and whenever any want of symmetry is present, there is almost always a preponderance of symptoms on the right side. Thus, speaking of the goitre, Trousseau says:<sup>c</sup>—"Both lobes may be equally increased in size, but more often, according to Graves, Stokes, other authors, and my own personal experience, the hypertrophy especially affects the right lobe." Sir T. Watson<sup>d</sup>

<sup>a</sup> Trans. Clin. Soc. Vol. I., p. 9.

<sup>b</sup> St. George's Hosp. Reps. Vol. IX., p. 797. 1879.

<sup>c</sup> L. c. P. 554.

<sup>d</sup> Practice of Physic. Vol. I., p. 841. I am aware that the right lobe is said to be normally very slightly larger than the left. In Quain's Anatomy it is said to be "a few lines longer and wider," but this seems quite insufficient to account for the marked difference so often observed in Graves' disease. That the right lobe is more often affected than the left in cases of endemic goitre, at least in certain districts, has been shown by G. H. Savage. Lancet. 1872. Vol. II.

says the same; and Wecker<sup>a</sup> says:—"The exophthalmos generally attacks both eyes, commencing in the right." In every case which I have found recorded, in which but one lobe of the thyroid was affected, it was the right one which was enlarged;<sup>b</sup> and of the cases in which the exophthalmos was unilateral, either through the entire course of the disease, or at all events for a very considerable period, in fifteen it was the right eye, and in five the left, which was affected, while in two cases I have been unable to ascertain which eye was involved. Sichel's two cases of unilateral proptosis I have omitted, as it appears exceedingly doubtful that they had any connexion with Graves' disease.<sup>c</sup> In short, I believe there is a very general consensus of opinion that the symptoms are, generally speaking, much more marked on the right side. I am not aware that any explanation of this fact has ever been suggested,<sup>d</sup> but it has occurred to me that the extreme constancy with which the cardiac symptoms are present may afford a clue to the problem. It is exceedingly uncommon to find them absent; and Trousseau, and most writers, except von Graefe, believe that they precede the other symptoms. On this point Sattler says (p. 972):—"It belongs to the rarest exceptions for the cardiac palpitation not to form the first symptom." Now, if it could be shown that the cardiac affection, so rarely absent, and so generally present at the very first, was itself a right-sided symptom, it would go far towards explaining the matter. And, in fact, this would seem to be the case, for it appears more than probable that it is the right vagus which is chiefly concerned in the inhibition of the heart, and that the left exerts but little power in that way. Arloing and Tripier<sup>e</sup> found that in horses the heart was much more affected when galvanism was applied to the right vagus than to the left; and they then made a careful series of dissections (also in horses), and

<sup>a</sup> Ocular Therapeutics. Eng. Trans. P. 506. Schnitzler (Wiener med. Halle, 1864, Nos. 24 and 27) says that the exophthalmos is usually more marked on the right side.

<sup>b</sup> Six referred to by Sattler (p. 952), and, in addition, one by Patchett, in which there was also ulceration of the right cornea. Lancet. 1872. Vol. I., p. 827.

<sup>c</sup> Bull. gén de Thérap. 1846. P. 346.

<sup>d</sup> Unless the theory suggested by Praël, Heusinger, and Bühring, and referred to by Panas (Archives d'Ophtalmologie, Vol. I., p. 103) be considered an explanation—namely, that the heart acts with greater force on the blood-column on the right side than on the left. The value of this suggestion may be inferred from the fact that it had previously been made use of by Sichel (*l. c.*) to account for the presence of *left* exophthalmos in a case which he had seen. He thought there was greater pressure on the left side.

<sup>e</sup> Archives de Physiologie. Tome V., p. 166. 1873.

found "that the left pneumogastric only enters into the composition of the cardiac nerves by means of one very slender filament, which it furnishes in front of the first rib, while the right vagus gives off to the cardiac nerves a much greater number of fibres." And among their conclusions they state:—"There exists a notable difference between the two vagi, principally from a functional point of view; the right acts more energetically upon the heart than the left." Masoin,<sup>a</sup> working independently of Arloing and Tripier, and without their knowing of his investigations, had previously arrived at the same conclusions. His experiments were made on seven rabbits, a dog, and a pigeon, and he concludes thus:—"The two vagi, or rather the accessory nerves of Willis, do not behave in an identical manner as regards the heart. In slowing or suspending the action of that organ the right possesses a power much superior to that of the left." Meyer<sup>b</sup> also has observed that the left vagus of a tortoise (*Emys lutaria*), obtained from certain districts in Germany, had no inhibitory action on the heart whatever, while the right vagus had a powerful one. In specimens of the species obtained from Italy the left vagus had a slight inhibitory action. That a similar arrangement exists in human beings seems highly probable, and it is significant that at least three cases are on record in which irritation of the *right* pneumogastric in man caused marked cardiac inhibition. One is the well-known instance of Professor Czermak, who could inhibit his heart by pressing on a small indurated lymphatic gland situated over his *right* vagus,<sup>c</sup> another a case in which syringing out an abscess-cavity at the *right* side of the neck caused marked slowing of the pulse,<sup>d</sup> and the third is Gerhardt's case.<sup>e</sup>

Physiologists have not, at least to my knowledge, explained why the cardiac nerves should be supplied by the right vagus rather than by the left, but it appears to me that the mode of development of the heart affords the required explanation. The organ in question first makes its appearance as an elongated vertical sac or tube, lying on the ventral surface of the embryo, in front of the throat. It is at first symmetrically situated, but soon becomes

<sup>a</sup> Bull. de l'Acad. Roy. de Méd. de Belgique. Tome VI. 3<sup>me</sup> Série, p. 4. (Abstract in Arch. de Phys. Tome IV., p. 519. 1872.)

<sup>b</sup> Das Hemmungsnervensystem des Herzens. S. 61. 1869. (Abstract in Journ. of Anat. and Phys. Vol. VII., p. 180.)

<sup>c</sup> Jenasche Zeitschrift. Band II. 1865. S. 384.

<sup>d</sup> Malerba; Archives de Physiologie. 2<sup>me</sup> Série. Tome II., p. 765.

<sup>e</sup> Eulenburg and Guttman. Trans. by Napier. P. 26.

bent on itself, like a horse-shoe, and *projects towards the right side*. That the pneumogastric nerves are developed at an early period is shown by the recurrent direction of the inferior laryngeal branches, which proves that they must have been formed before the descent of the heart from the neck into the thorax; and as at that early period the heart is situated to the right of the middle line, it is certainly not surprising that it should be chiefly supplied by the right vagus. It will be remembered that the stomach is at first placed vertically in the embryo, and that it subsequently turns over on its right side, so that the membranous fold which connects it with the vertebral column (the mesogastrium) is turned to the left, and that the result of this arrangement is that the right pneumogastric supplies its posterior, and the left its anterior surface.

If there be anything in this suggestion, one should expect to find that in a considerable proportion of those very rare cases in which cardiac symptoms are absent, the other symptoms should preponderate on the left side, and investigation shows that it is so. Thus in Mooren's case (*l. c.*) there was *left* exophthalmos, no goitre, and no cardiac symptoms, but Graefe's sign was present on both sides; and in C. E. Fitzgerald's third case (*l. c.*) exophthalmos and Graefe's sign were present on the *left* side, but there was neither goitre nor palpitation. Reith<sup>a</sup> has recorded a case in which *left* exophthalmos had been noticed for many years, but the right eye only protruded one day before the patient's death, which occurred with cerebral symptoms. *Post-mortem* examination showed slight enlargement of the thyroid (not noticed during life) and changes in the cervical sympathetic, especially on the left side. There was no history whatever of palpitation. And in Yeo's first case (*l. c.*) *left* exophthalmos had been present for about twenty-one months and palpitation for about three months before the case came under observation, and there was enlargement of the *right* lobe of the thyroid, which had not been noticed by the patient until her attention was drawn to it. It must at this time, therefore, have been slight, although it subsequently became most marked. It thus appears that *left* exophthalmos had existed about eighteen months before palpitation and right-sided goitre came on together. In a case of Hutchinson's<sup>b</sup> there was *left* exophthalmos, and five or six months later the right eye became prominent, but

<sup>a</sup> Med. Times and Gaz. 1865. Vol. II., p. 521.

<sup>b</sup> Med. Times and Gaz. 1874. Vol. II., p. 212.

not so much so as the left, and there was no goître. "Patient (male, aged twenty-nine) says he has suffered from palpitation as long as he can remember, the slightest occurrence causing his heart to 'go all of a flutter.' This feeling has not increased lately." It seems probable that the cardiac symptoms here were independent of Graves' disease, which had come on subsequently. Becker<sup>a</sup> has published the case of a lady, aged twenty-eight, whose friends had noticed, for about a year, occasional *left* exophthalmos. When seen by Becker it was but slight, and there was arterial pulsation in the left retina, but not in the right. On inquiry he found "that occasionally marked palpitation had been present, and that, on account of slight swelling of the thyroid, preparations of iodine had been several times administered." He did not see the patient again, but he ascertained that under anti-hysterical treatment and galvanism to the neck recovery took place.

It seems exceedingly questionable whether in this case the palpitation was not due to the iodine which had been taken. Virchow<sup>b</sup> calls attention to the fact that, together with the disappearance of a bronchocele in consequence of small doses of iodine, marked acceleration of the pulse and palpitation of the heart may be observed. This had also been pointed out by Rilliet,<sup>c</sup> and Soelberg Wells<sup>d</sup> has even suggested that, as the same thing has been noticed when a goître diminishes without the administration of iodine, it may be due to the admixture of soluble goître-material in the blood. Mauthner<sup>e</sup> has published a case in which there were one-sided proptosis and Stellwag's sign, but neither goître nor cardiac symptoms. Unfortunately he has omitted to mention which eye was prominent, so that the case is useless for testing this theory.

I have found no other cases recorded of left exophthalmos, and the only other cases that I have met with in which cardiac symptoms were absent are three in number—they tell against the theory. The first is C. E. Fitzgerald's fourth case, in which there were *right* proptosis and Graefe's sign, without either goître or palpitation. The second is a case by Abadie,<sup>f</sup> with *right* exophthalmos and Stellwag's sign, very slight goître, and no cardiac symptoms, and

<sup>a</sup> Zehender's Monatsblätter. Band XVIII., S. 2. 1880.

<sup>b</sup> Pathologie des Tumeurs. Traduit par Aronssohn. Vol. III., p. 270.

<sup>c</sup> Mémoire sur l'Iodism constitutionnel. Paris. 1860. P. 83.

<sup>d</sup> Diseases of the Eye. Third Edition. P. 713.

<sup>e</sup> Wiener med. Presse. 1878. No. 7, s. 190.

<sup>f</sup> L'Union Méd. 1880. No. 157.

the third is Morell Mackenzie's fourth case (*l. c.*). Both lobes of the thyroid were enlarged and both eyes protruded, and there was no palpitation or quick pulse; but the patient was seen only once, and the case is very briefly reported.

Another case has been published by A. E. Sansom,<sup>a</sup> entitled a "Case of Exophthalmos with none of the cardiac and thyroid phenomena of Graves' disease." Both eyes were prominent, and arterial tension was rather above the normal; but as no mention is made of the presence or absence of the eyelid phenomena of Graves' disease, it is impossible to form any opinion as to whether the case is one of that affection.

There is of course nothing very extraordinary (although it would seem to be unusual) in the lesion of the cardio-inhibitory centre, for example, being more marked on one side, and that of the vasomotor centre preponderating on the other; and a particularly good example of this crossed arrangement of the symptoms is afforded by Yeo's case, before alluded to. There was at first *left* exophthalmos, subsequently palpitation and *right* goître came on, and, still later, *right* exophthalmos and *left* goître were added to the symptoms.

<sup>a</sup> Trans. Ophthalm. Soc. Vol. II., p. 241.





