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Horner's Syndrome Revisited:
With an Update of the Central Pathway

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A brief summary is presented of the life of Johann Friedrich Horner, the eminent Swiss ophthalmologist, renowned for describing the effects of paralysis of the human cervical sympathetic nerves. His early education, the quality of his professional training, and the influence of his mentors, notably Carl Ludwig and Albrecht von Graefe, contributed to his discovery of the syndrome. The full text of Horner's original work (translated by J. F. Fulton, 1929a, Arch. Surg. 18:2025–2039) is cited. The history of clinical and experimental work carried out on the autonomic nervous system prior to Horner's discovery is reviewed, including the studies of Pourfour du Petit (cited in Fulton, 1929a and Singer and Underwood, 1962, Clarendon); Hare, 1838, Lond. Med. Gaz. 23:16–18; Bernard (cited by Singer and Underwood); Budge (1853, Acad. de Sci., p.377–378); Mitchell et al. (1864, Lippincott). Hare and Mitchell et al. came close to making the discovery but were apparently hindered by their inability to interpret the signs they elicited in their patients. The experiments of Claude Bernard gave succinct accounts of the effects of damage to the cervical sympathetic nerves in animals, although there appears to be no evidence that he made similar observations in humans. Horner was the first to give a detailed, scientifically supported account and accurately interpret the signs of cervical sympathetic nerve damage in a human subject. The anatomy of the pathway is reviewed and the detailed structure of its central part updated. Evidence from computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon-emission computerized tomography (SPECT) studies have confirmed that reciprocally connected centers in the insular cortex, central nucleus of amygdala, hypothalamus, mesencephalic and pontine tegmentum, nucleus of tractus solitarius, and the ventrolateral medulla form the central pathway. The nucleus of tractus solitarius is probably the main reflex center for the sympathetic system, whereas the ventrolateral medulla serves as the pathway through which the central neurons influence the preganglionic neurons of the thoracolumbar outflow. Emotional and sensory inputs from the frontal and somatosensory cortices provide the inputs needed by the insula to drive the sympathetic nervous system to produce appropriate responses. Clin. Anat. 12:345-361, 1999.

Key words: cervical sympathetic paralysis; Johann Friedrich Horner

INTRODUCTION

The International Anatomical Nomenclature Committee voted, in 1955, to reject the use of eponyms in anatomy on the grounds that they were not descriptive and could lead to confusion, especially where one discovery or achievement is credited to more than one person. The weight of current anatomical opinion supports that view (Moore, 1988; Organ, 1991). Nevertheless, there is little doubt that in the nosology of medical syndromes, eponyms still have a place because they convey meanings with brevity and, as Wilkins and Brody (1968) pointed out, each eponym is a lesson in the history of medicine, keeping alive the names of those who have contributed to medical progress. One eponymic syndrome that aptly illustrates these points is Horner's syndrome. The complex syndrome, consisting of ipsilateral miosis, ptosis, enophthalmos, cutaneous facial vasodilatation, transitory rise in facial temperature, and anhidrosis resulting from paralysis of the sympathetic nerves of the neck, face, and eye, can be conveniently denoted by the eponym. Additionally, the syndrome (or rather, the name Hor-

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ner attached to it) probably engenders more debate than any other syndrome about who should be given the credit for the original discovery.

Horner's syndrome involves virtually the entire anatomy of the head, neck, and brain (including the brainstem) because of the close relationship of different parts of the pathway to the various structures within the head and neck. Although the literature is replete with reports of lesions of structures in the head and neck region causing Horner's syndrome, studies of the complex anatomy of the central pathways influencing the activity of the cervical sympathetic system appear to have received relatively less attention, mainly because tracing of precise routes, decussations, and fiber terminations is difficult with standard physiological and neuroanatomical techniques. Over the past decade, advances in the technologies of computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon-emission computerized tomography (SPECT) have facilitated anatomical and functional neuroimaging of areas that give rise to selected physiological responses when they are excited. The studies of Stone et al. (1986), Sacco et al. (1993), Nagy et al. (1997), and Williamson et al. (1997) have contributed significantly to the understanding of the central pathways by providing images of the brainstem and cortical centers associated with Horner's syndrome and the regulation of the sympathetic system.

In this review, the anatomical pathway involved in Horner's syndrome is re-examined with a view to updating the central part of the pathway. A clear understanding of the pathway should help the clinician not only to identify, with confidence, the causative pathology of Horner's syndrome, but also to facilitate the choice of diagnostic procedures and further management.

JOHANN FRIEDRICH HORNER: BIOGRAPHICAL SKETCH

Johann Friedrich Horner (1831–1886) (Fig. 1) had a propensity for writing. A methodical and very thorough man, he began a detailed autobiography on March 15, 1885, 2 weeks before his 54th birthday. Unfortunately, it remained unfinished when he died a year later. The original manuscript in his own handwriting, entitled *Notizen zu meiner Biographie (März 1885 begonnen),* is cited in full by Koelbing and Mörgeli (1986).

The second of six children, Horner was born in Zurich on March 27, 1831, to Dr. Salomon Horner (1801–1852), a practicing physician, and Magdalena Zeller (1804–1852). The rest of the family included Konrad (born 1829), Anna (1836), Luise (1838), Marie (birthday unknown), Elisabetha (1843), and Sophie (1845). Magdalena Horner, an intelligent and well-educated woman, ensured that all her children were trained in languages.

Fig. 1. Friedrich Horner shortly before his death. Reproduced from *Johann Friedrich Horner (1831–1886), Verlag Hans Rohr (1986).* With kind permission of Hans Rohr, publisher.

Horner began his elementary education in May 1836, and continued to secondary school (1845–1847) where he studied mathematics, natural history, and classics. After completing Switzerland's compulsory military training in 1849, he entered the University of Zurich to read medicine. He soon became a popular figure on campus because he took a lot of interest in other aspects of student life, notably political discussions and debate. His early training in medicine was especially shaped by Carl Ludwig, his teacher in anatomy and physiology. Ludwig, a strong believer in investigation of physiological phenomena on a basis of sound knowledge of structure, inculcated his scientific philosophy in his students. Other lecturers who inspired Horner at the early stages of his training were Ewald Hasse, professor of pathology, therapeutics, and

clinical medicine; Heinrich Locher Zwingli (a friend of Horner's father) in surgery; Georg Hermann von Meyer, anatomy teacher; Heinrich Frey in histology; and Oswald Heer, professor of botany. Horner gained high academic distinctions in anatomy, physiology, and botany.

Halfway through his course, Horner suffered personal tragedies that seriously threatened his studies. His brother, Konrad, who had been suffering for about a year from "articular rheumatism" and then " heart inflammation," died in December 1851 from pneumonia. The following January, his father died from "apoplexy." In the summer of that year (1852), he lost his mother. Horner worked through these difficult times, with the encouragement and supervision of Professor von Meyer, to complete and present his doctoral dissertation in February 1854. His thesis, on curvature of the spine in the seated position, was titled "Über die Krümmung der Wirbelsäule im aufrechten Stehen." He received his degree in medicine, with commendation, in 1854 and began to travel.

After a brief visit to Munich, Horner went to Vienna in April 1854 to begin postgraduate studies, attending lectures on a great variety of clinical subjects and taking courses from some of the most distinguished physicians and surgeons in Austria in the midnineteenth century. These included Johann Ritter von Oppolzer (internal medicine), Joseph Skoda (medicine), Ferdinand Ritter von Hebra (dermatology), Leopold Ritter von Dittel (surgery and orthopedics), Johann Klein (orthopedics), Franz Schuh (surgery), Johann von Dumreicher (surgery), and Friedrich Jäger Ritter von Jaxtthal (ophthalmology).

By this time Horner had become interested in ophthalmology. His first training post was with Eduard Jäger Ritter von Jaxtthal (1818–1884), son of Friedrich Jäger and privatdozent in ophthalmology at the University of Vienna. This was probably the turning point in his postgraduate training, ushering in his illustrious career as an ophthalmologist. In one lecture, Friedrich Jäger Ritter von Jaxtthal showed his students the first volume of *Archiv für Ophthalmologie*, published by a former student, Albrecht von Graefe, then a practicing ophthalmologist in Berlin. On seeing the journal, Horner decided to study under von Graefe, and with recommendation from Wilhelm von Zehender, ophthalmologist and founder of *Klinische Monatsblatter für Augenheilkunde*, he traveled to Berlin. He was warmly received and offered an assistantship under von Graefe, who by this time had established himself as an eminent privatdozent in surgery and ophthalmology.

Horner clearly found ophthalmology very challenging. He recalled his first experience in this way: "My first patient had paralysis of the trochlearis. The first diagnosis of this disease was published in the first volume of the "Archive." The method of examination was new to me. I gave my best, but did not make the diagnosis. I did, however, describe the condition exactly. The second case was an episcleritis, which was also something entirely new to me. I described what I saw as precisely as possible. In my thoughts I thanked Zehender for sending me to Berlin, but also smiled about the naiveté with which I had assumed I already knew something about ophthalmology...."

Von Graefe was, arguably, one of the best ophthalmologists in mid-nineteenth century Europe. The clinic he started in 1850 grew, in less than a decade, into an international center for ophthalmologic research and clinical ophthalmology. His research communications, published in *Archiv für Ophthalmologie*, contributed markedly to knowledge of the physiology of the eye and enhanced the understanding of the eye in systemic disease (Talbott, 1970). It is noteworthy that as a student of Claude Bernard, Von Graefe had had firsthand experience with Bernard's experiments on the cervical sympathetic nerves. He possessed a deep understanding of the autonomic innervation of the eye and eyelid as evidenced by his discovery of the von Graefe sign in thyrotoxicosis.

Horner's stay in Berlin was a positive learning experience. He became very close friends with von Graefe, who exerted a tremendous influence on his professional career. He also interacted with the élite of Europe's ophthalmologists, notably Hermann von Helmholtz, who, 3 years before Horner's arrival in Berlin, had published his celebrated description of the ophthalmoscope.

In his quest for wider experience, Horner traveled to Paris in 1855 to spend a few months in the eye clinic of Louis-Auguste Desmarres, where he studied surgical techniques. He returned to Zurich in 1856 to set up a private practice. During this period, he gave private lessons and talks in ophthalmology. He subsequently passed the examination for appointment to university faculty. Horner was appointed adjunct professor of ophthalmology and director of the ophthalmology clinic at the University of Zurich in 1862, with several beds for eye patients at the surgical department, which was then under the chairmanship of Theodor Billroth. Like Horner, Billroth had worked under von Graefe during the early stages of his postgraduate training. With their strong inclination for research and teaching, Billroth and Horner developed the department into an international center of excellence, which attracted patients and pupils from great distances (Talbott, 1970). Between 1860 and 1884, Horner supervised the theses of 28 students, drawn from all over Europe; their dissertations were on various topics in ophthalmology. Horner was appointed full professor in 1873.

Horner married Gattin Luise Hengeller on September 15, 1864. The couple had two children— a daughter, Anna Luise (1866–1939) and a son, Konrad Friedrich (1869–1943). Anna Luise married Colonel Hermann Steinbuch (1863–1925), and Konrad trained as a doctor in the family tradition, practicing in Zurich and Weesen.

In addition to his doctoral dissertation (1854), Horner published 37 articles between 1860 and 1885 (Koelbing and Mörgeli, 1986), most of them in Zehender's *Klinische Monatsblatter für Augenheilkunde*. Notable among them was a succinct account, in 1869, of the syndrome that bears his name. It describes a characteristic form of blepharoptosis accompanied by miosis, enophthalmos, and ipsilateral anhidrosis resulting from paralysis of the cervical sympathetic system. It is interesting to note that the dissertation of his thirteenth student, William Nicati, entitled *"La paralysie du nerf sympathique cervical,"* was published in 1873, four years after Horner's famous publication.

Other publications of Horner discussed retinal changes in Bright's disease (1863), orbital periostitis and perineuritis of the optic nerve (1863), tumors of the retina (1863), tumors of the eye and extraocular muscles (1864, 1871), coloboma of the eyelids (1864), diphtherial conjuctivitis (1869), keratoconus (1869), herpes of the cornea (1871), cataracts (1872, 1875), keratitis mycotica (1875), pterygium (1875), strabismus and congenital myopia (1876, 1881), antisepsis in ophthalmic surgery (1881), and prophylaxis of ophthalmia neonatorum (1882). He published a short biography on Albrecht von Graefe in 1875 and also wrote extensively on pharmacological agents used in ophthalmology (1872, 1875, 1876, 1877, 1881). Another notable contribution to ophthalmic literature was his account of a man with red-green color blindness who transmitted the disorder to his male grandchildren through an unaffected daughter, thus establishing sex-linked transmission. This appeared in a chapter on diseases of the eye in childhood, which Horner contributed to Gerhard's *Handbook of Pediatrics*, published in 1879.

Johann Horner continued in active practice, teaching, and research until his death in 1886. He was recognized as a member of the group of clinical scientists who had contributed to the maturation of ophthalmology in central Europe in the mid-nineteenth century (Talbott, 1970).

THE SYNDROME: HORNER'S ORIGINAL ACCOUNT

In 1869, while still adjunct professor at the University of Zurich, Johann Friedrich Horner published the work that would earn him international eponymic recognition. The article, entitled "*Über eine Form von Ptosis*" (On a Form of Ptosis), gave a detailed description of what is now known as Horner's syndrome. The translation, first published by Fulton (1929a), follows in its entirety.

On a Form of Ptosis

Many of my colleagues are familiar with long-standing cases of incomplete ptosis in adults, lacking the usual accompanying signs of oculomotor paralysis but exhibiting the striking symptoms of a miosis of the pupil on the same side. This clinical picture was not new to me when at the end of last November a woman, 40 years of age, presented herself with these symptoms; less than a week later I saw them again in a woman of about the same age, but it was not possible for me to obtain such crucial information for the elucidation of the ptosis in this case as it was in the first. I may be permitted, therefore, to report here on the first case.

Frau Anna Brändli, aged 40, a healthy-looking peasant woman of medium size seems to have suffered since adolescence from generalized headache, which in the course of recent years had rather diminished in frequency and intensity.

Six weeks after her last confinement, which occurred a year ago, she noticed a slight drooping of her right upper eyelid, which increased very gradually and for about 3 months had remained constant. The upper lid covers the right cornea to the upper edge of the pupil; the lid is not loose or wrinkled but somewhat sunken into the orbit and is still capable of movement; it is neither injected nor swollen. The upper convex furrows on the right side of the forehead indicate that the frontalis muscle is working as a substitute [for the levator palpebrae superioris].

The pupil of the right eye is considerably more constricted than that of the left, but reacts to light; the globe has sunk inward very slightly and repeated determinations showed that it was somewhat less firm than the left. Both eyes are emmetropic and have visual acuity and early presbyopia.

During the clinical discussion of the case, the right side of her face became red and warm, the color and heat increasing in intensity under our observation, while the left side remained pale and cool. The right side seemed turgid and rounded, the left more sunken and angular; the one perfectly dry, the other moist. The boundary of the redness and warmth was exactly in the midline.

The patient thereupon told us that the right side had never perspired and that the flushed feeling, and also the ptosis, had only developed in the course of the last year. The redness of the right side of the forehead

and cheek was said to be present in the evening as a rule but was also brought on more or less markedly at other times by any emotion.

By feeling the cheeks with the hand, one could perceive a marked difference in temperature. We took steps to establish this precisely and to determine its range. Dr. Julius Michel and Wilh. Von Muralt made accurate determinations, some of which I record here. Very sensitive thermometers were read after being warmed in water at about 25°C and then fastened against the cheek with a cotton compress and adhesive. The temperature was also taken in other localities—behind the ear (over the mastoid process), in the axilla, and in the groin.

I. Temperature of the Cheek - EXPERIMENT 1. Immediately after application, the thermometer on the right recorded 35°C, that on the left 30°C, the former rising in 15 minutes to 36.3°C, the latter to 34.1°C. After the temperature on the two sides had become nearly equal and the left cheek had been warmed by the compress so that no difference could be felt with the hand, the thermometers were quickly exchanged, and after 5 minutes the thermometer on the left rapidly fell to 35.3°C while that on the right rose to 36.3 °C; after 10 minutes the temperatures were equal.

EXPERIMENT *2*

	R	L
After 1½ minutes.....	35.0	29.5
After 4 minutes.....	35.8	31.4
After 6 minutes.....	36.1	32.8
After 10 minutes.....	36.1	33.6
After 14 minutes.....	36.2	33.9
After 20 minutes.....	36.4	34.4
After 26 minutes.....	36.6	35.0
After 34 minutes.....	36.7	35.7

II. Temperature Behind the Ear

Time	R	L	Time	R	L
3.36	34.0	30.0	3.46	36.2	35.4
3.38	35.0	32.0	3.48	36.4	35.8
3.40	35.4	33.8	3.50	36.6	36.2
3.42	35.8	34.6	3.52	36.8	36.3
3.44	35.9	35.0	3.56	36.8	36.6

III. Temperature in the Axilla. At first the temperature differed by only three-tenths of a degree and finally (after 20 minutes) by six-tenths, the curves being practically parallel, the left lower than the right by a constant interval.

IV. Temperature in the Groin. During the entire period of observation (20 minutes), the temperature remained the same 37.6°C on both sides. The sensation in both cheeks was exactly the same. This investigation thus proves the integrity of the sensory trigeminal nerves, transitory paralysis of the vasomotor fibers in the right trigeminal area; higher initial temperature on the right side with slowly rising (temperature) curve, a low initial temperature on the side with a rapidly rising curve: equalization of both if the observation is continued long enough with the left cheek adequately covered and protected.

Two points necessitate the conclusion that the vasomotor disturbance involves not only the trigeminal area, but also that of the fibers of the cervical sympathetic: first, the slight but distinct variation in temperature in the axillae; secondly, and more important, the small size of the right pupil.

The latter symptom prompted some investigations concerning the action of atropine and calabar. When equal quantities of atropine were instilled into each conjuctival sac, the right pupil enlarged slowly and irregularly; after 20 minutes it had not yet reached the size of the left but remained more constricted and oval, even though more drops were put into the right eye.

When, 24 hours after atropine, equal quantities of calabar[1] were put into the conjuctival sac of each eye, one noticed after 10 minutes a marked constriction on the right; and after half an hour almost maximal miosis, while on the left the action of atropine still continued, and it was only after a half an hour that an insignificant decrease of the effect of the atropine was apparent.

I have already mentioned that the right globe always appeared somewhat softer, but the difference was slight, even if constant. Measurements were made with a Dor tonometer, which is adequate for such comparisons. This difference in tension suggested comparing also the diameter of the retinal vessels. When observed during the stage of elevation of temperature, the veins of the right retina appeared wider and more tortuous than the left, a difference which did not exist when the whole right side was cool, as it was, for example, when the ophthalmoscopic examination was made in the early morning. However, the differences found were so slight that only through repeated examinations by several investigators can the results be securely established.

It is not too much to assert that this experiment with belladona and calabar speaks for the dual control of the movements of the iris in man; differences in color and caliber of the vessels of the irides have not been found,

[1]Calabar=extract from the calabar bean, seed of the woody vine *Physostigma venenosum*. The active ingredient is physostigmine. Argyll-Robertson first tested it on himself on January 17, 1863 and reported that it caused marked constriction of the pupil and "a condition of short-sightedness."

and therefore it is most probable that we are dealing with right dilator paralysis.

The explanation of the difference in the tension relations of the globe is as yet a matter of personal opinion since the various functional components of what the anatomist calls the trigeminus cannot yet be accurately distinguished by experimentation.

Let us now turn to the question of the causation of the ptosis. I believe that nobody who had seen all the foregoing symptoms would be surprised at my considering this ptosis, which comes on gradually but remains incomplete, to be a paralysis of the musculus palpebrae superioris supplied by the sympathetic nerve (H. Müller, Harling), and the appearance of the upper lid as part and parcel of the whole symptom-complex. It would thus appear to be the opposite of the condition in exophthalmic goiter in which the upper lid is drawn upward, or better into the orbit, which, by von Graefe and Remak, is described as due to the stimulation of the muscle fibers of the lid.

Finally, I may mention that our patient was treated with the constant current, but only for a short period and, therefore, without effect.

THE PATHWAY: ANATOMICAL BASIS AND UPDATE

Accounts of the pathway generally recognize three sets of neurons and two relay centers. The neurons are central, preganglionic (intermediate), and postganglionic. The relay centers are the ciliospinal center of Budge and the superior cervical ganglion.

The central pathway has components within the brain, brainstem, and spinal cord. The preganglionic neurons begin from the intermediolateral horn of the eighth cervical and upper two or three thoracic segments of the spinal gray matter and terminate in the superior cervical ganglion. The postganglionic neurons begin from the superior cervical ganglion and terminate in the orbit, eyeball, skin of the face, head, and neck. Lesions involving any component of this pathway, irrespective of the nature of the lesion, will result in the symptom complex described by Horner.

Central Neuron(s)

The structure of the central segment of the pathway has not received as much attention as the preganglionic and postganglionic segments because the older neuroanatomical and neurophysiological techniques often entailed destruction of tissue or the experimental animal and were, therefore, not suitable for studying the central nervous system (CNS) in human subjects. The advent of CT, MRI, PET, and SPECT within the past decade has enabled investigations of the CNS to be carried out in patients with Horner's syndrome.

Accumulating evidence suggests that the central pathway includes neurons from the cerebral cortex. In one patient presenting with Horner's syndrome after a transient ischemic episode, Nagy et al. (1997) used coronal MR images to confirm a solitary lesion in the ipsilateral insular cortex.

Stone et al. (1986), Bassetti and Staikov (1995), and Nagy et al.(1997) confirmed reports by Maloney et al. (1980) and Carpenter (1985) that the hypothalamus is involved in the central segment. Maloney et al. (1980) suggested that the central neuron was located in the posterolateral region of the hypothalamus. Carpenter (1985) amplified the observation of Maloney et al. (1980) by clarifying that hypothalamic neurons projecting to spinal levels arose from three nuclei, namely, the parvicellular part of the paraventricular nucleus, dorsal part of the lateral hypothalamic nucleus, and the posterior hypothalamic regions dorsal to the mamillary bodies. Hypothalamospinal fibers arising from these nuclei descended ipsilaterally through the brainstem and lateral funiculus of the spinal cord to terminate in relation to cells of the intermediolateral column of the spinal gray matter. The precise location of the hypothalamospinal tract has not been clearly defined, but the medial forebrain bundle has been proposed as a link (Moore and Klein, 1974). Information on the topography of the central pathway involved in Horner's syndrome in humans is incomplete. Electrophysiological and axoplasmic transport studies of experimental animals suggest that several well-defined brainstem nuclei may be involved, working in parallel to the hypothalamospinal fibers. It is tempting to hypothesize that the direct hypothalamospinal fibers may subserve the responses related to emotion, whereas the other brainstem centers would subserve the reflex vasomotor, sudomotor, and thermoregulatory responses.

Update of the Central Neuronal Pathway

The central neuronal pathway in Horner's syndrome is polysynaptic. The weight of experimental evidence suggests that the spinal sympathetic centers are controlled by a series of reciprocally connected neuronal cell groups in the medulla oblongata, pons, diencephalon, and telencephalon (Hilton,1975; Amendt et al., 1979; Spyer, 1994; Mosqueda-Garcia, 1996). Centers that make up the relay include the insular cortex, amygdala, hypothalamus, parabrachial nucleus, nucleus of tractus solitarius, and ventrolateral medulla. The pathway is essentially ipsilateral. Multiple neuro-

transmitters are involved (Spyer,1994; Mosqueda-Garcia,1996; Thomas and Spyer, 1997). A possible pathway is suggested in Figure 2

Insular cortex. The role of the insula in gustatory functions and gastric motility is well known, and it is also an important center for cardiovascular regulation (Ruggiero et al.,1987; Oppenheimer and Cechetto, 1990 ; Yasui et al., 1991; Oppenheimer et al.,1992) Stimulation of the insular cortex causes, among other effects, pupillary dilatation, increase in blood pressure and heart rate, piloerection, and respiratory effects (Yasui et al., 1991; Oppenheimer et al., 1992; Mosqueda-Garcia, 1996). Electrophysiological evidence suggests that the insula exhibits lateralization of functions and species specificity in relation to cardiovascular effects. Oppenheimer and Cechetto (1990) noted that there was an area of cardiac representation on the posterior part of the left insular cortex of the rat. Stimulation of the left insula in the rat elicits sympathetic effects (Oppenheimer and Cechetto, 1990; Yasui et al., 1991). In humans, direct stimulation of the posterior region of the left insula led to bradycardia, whereas stimulation of the right insula resulted in tachycardia and a pressor response (Oppenheimer et al., 1991,1992). The insula receives afferents from the somatosensory and frontal cortices, the lateral hypothalamic area, and parabrachial nucleus. Its efferents project to the lateral hypothalamic area, parabrachial nucleus, thalamus, the central nucleus of amygdala, and nucleus of tractus solitarius (NTS).

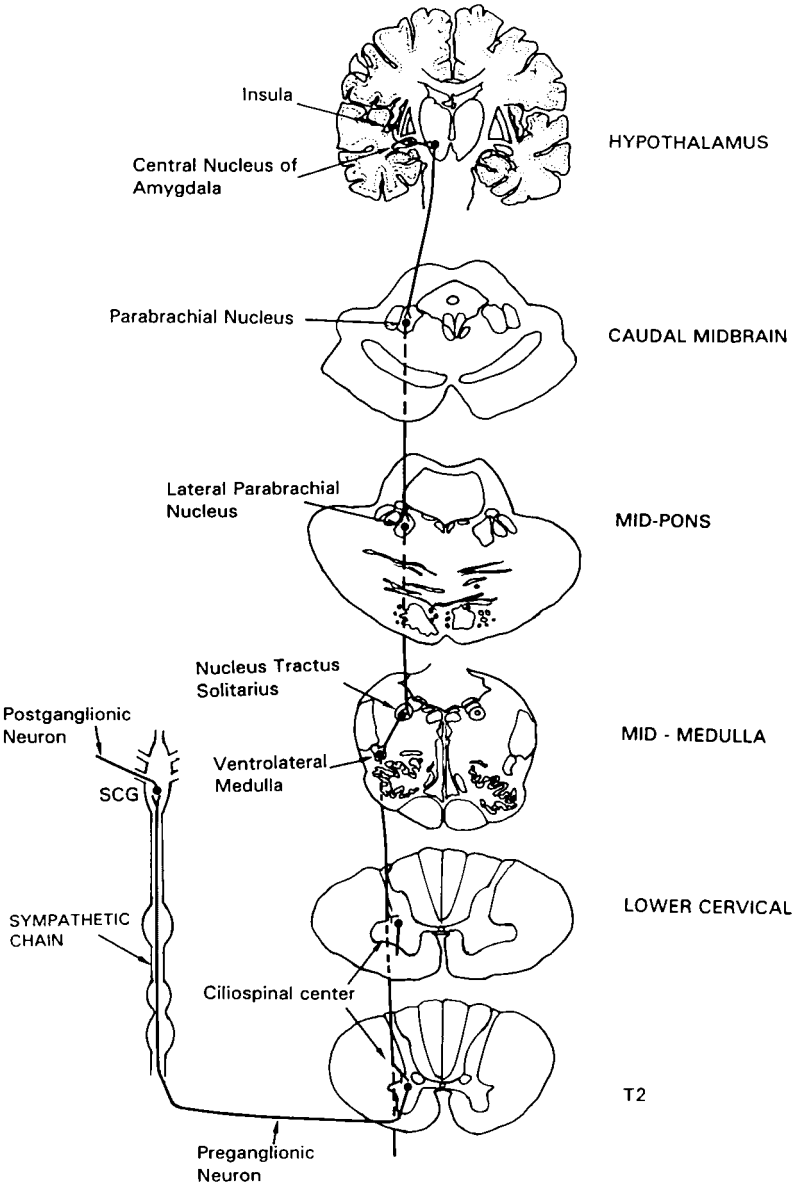

Fig. 2. Schematic diagram showing the components of the central pathway in Horner's syndrome. T2, section of the spinal cord at the level of the second thoracic segment. SCG, superior cervical ganglion.

Amygdala. The amygdaloid nuclear complex plays a major role in emotional behavior and the central nucleus may also be involved in autonomic control (Spyer, 1994; Mosqueda-Garcia, 1996). The central nucleus receives afferents from insula. It projects to the posterior hypothalamus (Krettek and Price, 1978; Yoshimoto et al.,1989) and to the lateral hypothalamic area, parabrachial nucleus, nucleus of tractus solitarius, and rostral ventrolateral medulla (Mosqueda-Garcia, 1996).

Hypothalamus. The hypothalamic nuclei involved in the pathway are the parvicellular cells of the paraventricular nucleus (Swanson,1977; Armstrong et al., 1980; Carpenter, 1985; Mosqueda-Garcia, 1996), dorsal parts of the lateral hypothalamic nucleus and the posterior hypothalamic regions dorsal to the mamillary bodies (Maloney et al., 1980; Carpenter, 1985).

The paraventricular nucleus receives afferents from the parabrachial nucleus, nucleus of tractus solitarius (NTS), rostral and caudal ventrolateral medulla (Norgren, 1978; Armstrong et al., 1980; Mosqueda-Garcia, 1996). The lateral and posterior hypothalamic regions receive afferents from the central nucleus of amygdala (Krettek and Price, 1978; Yoshimoto et al.,1989; Mosqueda-Garcia, 1996). These hypothalamic nuclei in turn give rise to autonomic pathways projecting to the brainstem and intermediolateral cell column of the spinal cord (Carpenter, 1985; Mosqueda-Garcia, 1996). The brainstem projections include central gray matter, parabrachial nucleus, and NTS. Stimulation of the lateral and posterior hypothalamic regions activates the thoracolumbar outflow (Carpenter, 1985). Computerized tomographic and magnetic resonance images published by Stone et al. (1986) and Nagy et al. (1997), respectively, showed that infarctions of the hypothalamus resulted in Horner's syndrome.

Lateral parabrachial nucleus. The parabrachial nucleus is located rostrally in the dorsolateral part of the pontine tegmentum embracing the motor nuclei of facial nerve and trigeminal nerve (Williams et al., 1995). The superior cerebellar peduncle is lateral to it, whereas the locus ceruleus is medial. It extends rostrally to the caudal part of midbrain, anterior to the periaqueductal gray matter (Woolf and Butcher, 1989). Medial, lateral, and ventral subdivisions of this nucleus have been described (Mosqueda-Garcia, 1996). General visceroceptive information from the NTS projects to the lateral nucleus. The lateral parabrachial nucleus has reciprocal connections with insula, lateral hypothalamic area, paraventricular nucleus, and central nucleus of amygdala. Efferents from the nucleus project to the NTS and ventrolateral medulla (Katayama et al., 1984; Lovick, 1986; Spyer, 1994). The projections from this nucleus run in the dorsal tegmental tract and medial longitudinal fasciculus. In cats, stimulation of the parabrachial nucleus resulted in vasoconstriction, increase in blood pressure, and tachycardia (Mraovitch et al., 1982). Askari et al. (1993) reported a patient with Horner's syndrome associated with giant cell arteritis in whom the only apparent lesion on computerized tomographic scanning was involvement of the medial longitudinal fasciculus. In studies reported by Nagy et al. (1997), MR images from a subject presenting with a left-sided Horner's syndrome associated with an ipsilateral midbrain lesion (attributed to toxoplasmosis) and contralateral trochlear nerve palsy showed destruction of tegmental areas around the fourth nerve nucleus. This area corresponds to the location of the rostral end of the lateral parabrachial nucleus (Woolf and Butcher, 1989).

Medulla. Two prominent integrative centers in the sympathetic relay have been identified at the level of medulla oblongata. These are ventrolateral medulla (VLM) and the nucleus of tractus solitarius (McAllen et al., 1982; McAllen, 1985; Doroshenko and Maiskii, 1987; Lin et al., 1989). These centers are connected functionally (Ciriello and Caverson, 1986; Chai et al., 1988) and anatomically (Loewy et al., 1981; Lovick, 1986).

Nucleus of tractus solitarius (NTS). This complex nucleus is probably one of the most important in the central pathway. It projects to, and receives afferents from, brainstem and telencephalic nuclei that regulate preganglionic sympathetic and parasympathetic as well as neuroendocrine functions. It is located in the dorsomedial part of medulla oblongata, rostral to the obex. It is ventral to the medial vestibular nucleus and lateral to the dorsal motor nucleus of vagus. The caudal ends of the left and right NTS merge at the level of area postrema to form the commissural subnucleus (Estes et al., 1989; Mosqueda-Garcia, 1996). The nucleus possesses eight other distinct subnuclei (see Loewy and Burton, 1978; Estes et al., 1989 for details). The rostral part of the NTS is primarily involved with gustatory functions (Hamilton and Norgren, 1984), whereas the caudal part plays an important role in integration of visceral and hormonal mechanisms involved in cardiovascular regulation (Estes et al., 1989). It acts as a relay area for reflexes that control circulation. Cardiovascular afferents predominantly terminate in the dorsal areas of the medial and lateral subnuclei of the NTS (Spyer, 1994). The NTS has reciprocal connections with the central gray matter, parabrachial nucleus, ventrolateral medulla, and paraventricular and lateral hypothalamic areas. It also sends efferents to the middle third of the spinal gray matter through the solitariospinal tract in the ventrolateral funiculus (Loewy and Burton, 1978; Norgren,

1978). These reciprocal connections have functional selectivity. Sympathetic vascular activity can be altered by NTS projections terminating in the rostral or caudal part of the ventrolateral medulla (Norgren, 1978; Ciriello and Caverson, 1986; Lin et al., 1989). Immunocytochemical and horseradish peroxidase studies (Nomura et al.,1984; Zhang et al., 1991) firmly established that fibers from all divisions of trigeminal nerve project to the caudal part of NTS. This may explain the cutaneous reflexes, related to facial temperature, elicited by Horner (1869) and corroborated by Weinstein et al. (1980) and Morrison et al. (1997). NTS can initiate multiple medullary reflexes that directly affect blood pressure, heart rate, respiration, and other autonomic functions (Spyer, 1994).

Ventrolateral medulla (VLM). This group of catecholaminergic and glutaminergic neurons is located near the ventrolateral surface of the medulla, at about the level of the obex (Smith and Clarke, 1964; Coote and Macleod, 1974; Lovick et al., 1984; Ross et al., 1984; Doroshenko and Maiskii, 1987). It is ventrolateral to the inferior olivary nucleus and medial to, and partially intermingled with, the lateral reticular nucleus. The nucleus is a major target for highly processed output from the NTS. It acts as a relay in the efferent pathway from several structures that initiate different patterns of sympathetic activity (Lovick, 1986; Spyer, 1994). The rostral part (RVLM) consists mainly of glutamate neurons, whereas the caudal (CVLM) neurons are catecholaminergic (Doroshenko and Maiskii, 1987). The RVLM has reciprocal connections with the central gray matter, lateral hypothalamic area, paraventricular nucleus, and parabrachial nucleus. Its main afferents, however, come from the parabrachial nucleus (Mraovitch et al., 1982) and the NTS (Andrezik et al., 1981; Ciriello and Caverson, 1986; Lovick, 1986; Su et al., 1989; Gatti and Gillis, 1991). One of the main outputs from the RVLM goes to the thoracolumbar intermediolateral cell column, which is the origin of preganglionic fibers modulating sympathetic tone (Su et al., 1989; Gatti and Gillis, 1991; Mosqueda-Garcia, 1996). The CVLM does not project directly to the spinal cord. It inhibits sympathetic activity through short inhibitory projection to the RVLM. Sacco et al. (1993), evaluating 33 patients with lateral medullary syndrome, noted that Horner's syndrome was the most frequent neurological finding. Other associated findings were ataxia and contralateral hypalgesia. Ipsilateral posterior inferior cerebellar artery thrombosis was angiographically confirmed. MR images showed typical lateral medullary infarcts involving NTS and vestibular nuclei. These findings were confirmed by Nagy et al. (1997).

Ciliospinal Center

Preganglionic neurons that innervate the cervical sympathetic ganglia originate from the intermediate area of the gray matter of the spinal cord at the level of C8 to T3 segments (the ciliospinal center of Budge). In cats and rats, preganglionic fibers from levels down to T7 have been identified in the cervical sympathetic ganglia (Dalsgaard and Elfvin, 1979; Wesselman and McLachlan, 1984; Reuss et al., 1989).

Localization of function in the ciliospinal center. In electrophysiological studies on guinea pigs, Njå and Purves (1977) found that different sympathetic functions were probably represented in different parts of the ciliospinal center; sympathetic effects elicited after stimulation of the ventral roots of the rostral segments (mainly C8, T1, and T2) consisted, primarily, of dilatation of the pupil and widening of the palpebral fissure, whereas stimulation of caudal segments, mainly at T3 and T4, resulted in vasoconstriction of the ear and piloerection on the face and neck. Dalsgaard and Elfvin (1979) and Rando et al. (1981) clarified that at each segmental level, the cell bodies of preganglionic neurons were located in one of several areas, namely, intermediolateral (IL), lateral funiculus (LF), central - near the central canal of spinal cord (C), intercalated (IC), and intermediomedial (IM). In the cat, cells of IL zone have type B axons, whereas neurons of IC zone have the thinnest (type C) axons (Lebedev et al., 1976). Dalsgaard and Elfvin (1979) noted that in the proximal segments of the ciliospinal center, preganglionic fibers mainly originated from IL neurons, whereas in caudal segments, preganglionic fibers originated mainly from IC neurons. They suggested that the preponderance of IL and IC preganglionic fibers in rostral and caudal segments, respectively, could be related to the functional localization reported by Njå and Purves (1977). Within individual segments, the neurons projecting to the superior cervical ganglion from the IL zone have been shown to be grouped into discrete longitudinal (i.e., cephalocaudal) clusters. Each cluster consists of about 14 neurons. Several clusters could be identified in each segment (Petras and Cummings, 1972; Rando et al., 1981; Gilbey et al., 1982). At each segmental level, different cell groups in the column and different clusters are thought to influence different sympathetic functions (Rando et al., 1981).

The ciliospinal center receives (A1 noradrenergic and glutaminergic) efferents from the rostral ventrolateral medulla (Smith and Clarke, 1964; Loewy et al., 1981; Lovick et al., 1984; Doroshenko et al., 1987; Gatti and Gillies, 1991; Mosqueda-Garcia, 1996). Direct projections from NTS (Norgren, 1978; Doro-

shenko et al., 1987; Mosqueda-Garcia, 1996) and A5, A6, A7 noradrenergic fibers from parabrachial nucleus (Smith and Clarke, 1964; Doroshenko et al., 1987; Spyer, 1994; Mosqueda-Garcia, 1996) also terminate on the cells of the intermediolateral horn.

Second-order (preganglionic) Neuron

This neuron is often referred to as the preganglionic neuron. It begins in the ciliospinal center and emerges from the spinal cord through the ventral roots of C8 to T3. The axons run in white rami communicantes from the ventral roots and ascend (without synapsing) through the cervical sympathetic chain to terminate in the superior cervical ganglion by synapsing with the third-order (postganglionic) neuron. Each preganglionic neuron ramifies to synapse with about 15 postganglionic neurons within the superior cervical ganglion (Maloney et al., 1980).

The preganglionic neuron has no collateral branches. It bears important relations in the root of the neck to the vertebral column, apex of the lung, cervical pleura, subclavian artery, upper ribs, common carotid artery, and internal jugular vein in the carotid sheath, thyroid gland (Fig. 3). Lesions of any of these structures could affect the neuron and produce the symptom complex of Horner's syndrome.

Third-order (postganglionic) Neuron

The cell body of this postganglionic neuron is in the superior cervical ganglion (Figs. 2 and 3), located at

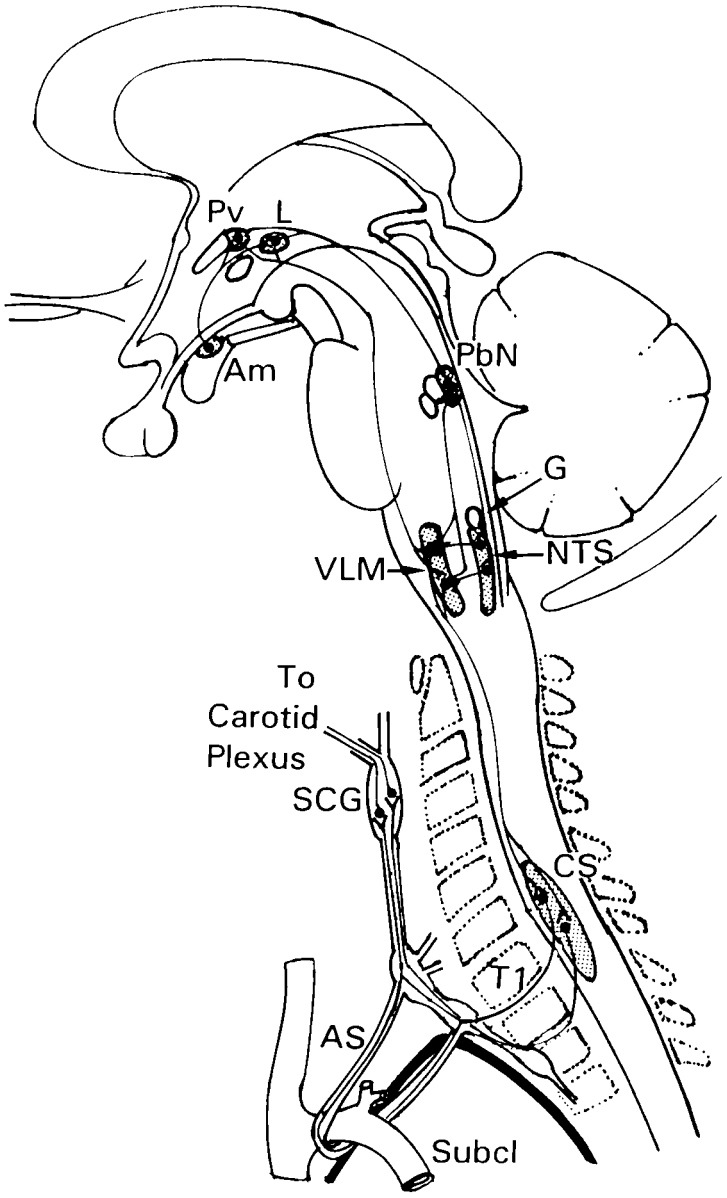

Fig. 3. Diagram of the brainstem and upper segment of the spinal cord showing the immediate relations of the central, preganglionic, and postganglionic neurons. Pv, paraventricular nucleus; L, lateral area of hypothalamus; Am, central nucleus of amygdala; PbN, parabrachial nucleus; VLM, ventrolateral medulla; NTS, nucleus of tractus solitarius; G, gustatory part of tractus solitarius; CS, ciliospinal center of Budge; AS, ansa subclavia; SCG, superior cervical ganglion; Subcl, subclavian artery.

about the level of the second and third cervical vertebrae. The ganglion measures about 2.5 cm long and lies posterior to the carotid sheath, between the internal carotid artery and the longus capitis muscle. Lateral branches from it are distributed to the glossopharyngeal, vagus, hypoglossal and upper four cervical nerves, the meninges of the posterior cranial fossa, and the jugular bulb. The medial (laryngopharyngeal) branches go to the pharynx, carotid body, and the cardiac plexus. Anterior branches are distributed along the external and internal carotid arteries. Most of the sudomotor fibers to the face course along the external carotid artery; lesions of the third neuron *distal* to the bifurcation of the common carotid artery, therefore, would not be associated with significant impairment of sweating in the face. Postganglionic nerves to the eyeball, eyelid, and orbit run in the internal carotid nerve and plexus (in the adventitia of the artery). These are particularly vulnerable in cases of aneurysm or dissecting lesions of the artery. As it passes into the cavernous sinus, the internal carotid artery is located medial to the trigeminal ganglion. Postganglionic sympathetic fibers to the pupillary dilator muscle pass from the internal carotid plexus through the abducent nerve to the trigeminal ganglion at this point; they travel in the ophthalmic division and ultimately in the long ciliary nerves to the iris. Lesions of the postganglionic neuron in this region, associated with irritation of the trigeminal nerve, are regarded as a separate clinical entity known as Raeder's (paratrigeminal) syndrome (1924). The main features of the syndrome are ptosis, miosis, enophthalmos (due to oculosympathetic paralysis), and ipsilateral facial pain (from trigeminal irritation). Facial sweating is preserved. The syndrome has been associated with head trauma, hypertension, vasculitis, migraine, parasellar masses, dissections of internal carotid artery, aneurysms of internal carotid artery (Vega et al., 1994; Selky and Pascuzzi, 1995; Zournas et al., 1995; Murnane and Proano, 1996). According to Zournas et al. (1995), there are two clinical subgroups of Raeder's syndrome. They defined Group I as cases with parasellar cranial nerve involvement. Group II cases are those arising from lesions distal to the bifurcation of common carotid artery. These are painless and without parasellar cranial nerve involvement, but are always accompanied by facial anhydrosis. Group II Raeder's syndrome cases are, clearly, difficult to differentiate from postganglionic Horner's syndrome.

Clinical anatomical evidence reported by Mariniello (1994) suggested that in some individuals the main branch to the pupillary dilator muscle was given off in the parasellar region (within the cavernous sinus) and passed directly to the ophthalmic division. Lesions of the nerve in this region ("parasellar syndrome"; Mariniello, 1994) were characterized by Horner's syndrome and ipsilateral sensory disturbance over the distribution of the ophthalmic division of the trigeminal nerve.

Within the cavernous sinus, postganglionic fibers from the internal carotid plexus are given off to arteries supplying the hypophysis cerebri (as the internal carotid artery passes lateral to the sella turcica) to oculomotor, trochlear, ophthalmic, and abducent nerves. Motor branches to the smooth muscles of the eyelids (Müller's muscle) leave the internal carotid plexus within the cavernous sinus and join the oculomotor nerve close to its bifurcation.

Lesions of any part of the sympathetic pathway described will result in Horner's syndrome. The injury could be due to mechanical (or traumatic), vascular, inflammatory, or neoplastic disorders involving the structures related to the central, preganglionic, or postganglionic neurons. A clear understanding of the topographic anatomy not only facilitates the differential diagnosis, but also helps in the choice of appropriate investigation and management strategies. Symptoms and signs referable to related structures (e.g., trochlear nerve paralysis in midbrain lesion or ataxia and nystagmus associated with Horner's syndrome, as in lateral medullary syndrome) are helpful in localization of the level of the lesion. There are also a wide variety of techniques available for the investigation of the central segment of the pathway. These range from clinical tests of cranial or spinal nerve function, physiological tests, biochemical tests, doppler studies, through to imaging techniques such as plain radiography, angiography, CT, MRI, PET, and SPECT.

Determination of Level of Lesion

In the clinical assessment of his case, Horner used atropine to establish anisocoria and pupillary dilatation lag, and calabar to confirm that the effects of the parasympathetic system were unopposed on the side of the lesion. The diagnosis of Horner's syndrome may be confirmed or refuted by pharmacological or physiological testing (Pilley and Thompson, 1975). The pharmacological tests are based on the ability of the normal (unimpaired) sympathetic postganglionic nerve to synthesize and release norepinephrine at its terminals. These tests may be used to localize the level of the lesion.

To establish that the lesion is Horner's syndrome. One or two drops of a weak solution of cocaine (4–10%) are instilled into the conjuctival sacs of the normal and affected eyes. The pupils are observed at 15-minute intervals for 45 minutes. Cocaine inhibits the re-uptake of synaptic norepinephrine. In the

normal eye, therefore, this will result in marked dilatation of the pupil. In the affected eye, no mydriatic effect is seen if there is a lesion of the second or third neuron. This is because (with interruption of the final common pathway) these neurons will not elaborate norepinephrine. If the lesion is central, there will be a slight dilatation, although much less than on the normal side.

To differentiate a preganglionic from a postganglionic lesion. Hydroxyamphetamine hydrobromide (Paredrine - 1% solution) enhances the release of norepinephrine from sympathetic terminals and therefore cause mydriasis. In a postganglionic lesion, owing to degeneration of terminals, no pupillary dilatation will occur. Intact postganglionic neurons will have the potential to produce the neurotransmitter. A normal response to Paredrine in a patient with Horner's syndrome suggests that the lesion is in the first- or second–order neurons.

Jaffe (1950), Maloney et al. (1980), and Moses and Hart (1987) have described additional pharmacological tests to help in identifying the nature of postganglionic lesions. However, as Maloney et al.(1980) and Moses et al.(1987) pointed out, these tests have limitations that make them less reliable. The known pharmacological tests cannot clearly separate central from preganglionic lesions (Moses and Hart, 1980). Localization of the lesion is, therefore, based on clinical features, associated conditions, and judicious choice of ancillary investigations based on a clear understanding of the anatomy of Horner's syndrome.

WHOSE SYNDROME IS IT?

Various views have been put forward as to whose name should be attached to the syndrome (Bonnet, 1957; Singer and Underwood, 1962; Geeraets, 1976; Pearce, 1995). There appears to be considerable support for the view that it should have been named for Claude Bernard (Bonnet, 1957; Geeraets,1976). Other published accounts of the syndrome (Fulton, 1929a; Lebensohn, 1969; Talbott, 1970; Pearce, 1995) have drawn attention to the contributions of Pourfour du Petit (1727), Hare (1838); Claude Bernard (1852), and Mitchell et al. (1863). In the French medical literature, the syndrome is commonly referred to as Claude Bernard-Horner syndrome (Bonnet ,1957; Lebensohn, 1969). Geeraets (1976), however, names the syndrome for Horner and gives Bernard-Horner syndrome, Claude-Bernard-Horner syndrome, and cervical sympathetic paralysis syndrome as synonyms. Notwithstanding the excellence of the accounts of Pourfour du Petit, Hare, Bernard, and Mitchell and colleagues, both Fulton (1929 a,b) and Lebensohn (1969) argued that none of these earlier workers had any claim to priority over Horner, because, as Lebensohn (1969) pointed out, "Horner was the first to fully describe a clinical case of paralysis of the cervical sympathetic". In his work, Horner (1868) did not refer to any of the earlier reports, save for passing reference to von Graefe, Remak, and Müller; nevertheless, the quality of his presentation leaves one in no doubt that the works of many scientists contributed to his understanding of the patient's condition. His close association with von Graefe, who had first-hand knowledge of the experiments of Claude Bernard, also helped.

In order to put Horner's work in proper perspective, therefore, a brief account follows of the chronology of published work on the autonomic nervous system in general, and the cervical sympathetic system specifically, prior to his account in 1869.

HISTORICAL REVIEW OF WORK ON THE SYMPATHETIC NERVOUS SYSTEM PRIOR TO THE DISCOVERY OF HORNER'S SYNDROME

Eustachio (1520–1574) was among the first to document the existence of the sympathetic nervous system. In anatomical plates first published in *Opuscula Anatomica* in 1564 (cited by Talbott, 1970), Eustachio gave "complete and precise" illustrations of the sympathetic nervous system. Nearly a century later, in 1664, Thomas Willis (1621–1675) gave a detailed account of the thoracic chain of ganglia in his treatise entitled "Cerebri Anatome" and named it the "intercostal nerve." In 1710, François Pourfour du Petit (1664–1741), published the results of his observation in individuals with gunshot wounds of the head and neck. He reported that injury to the "intercostal nerve" (cervical sympathetic) was followed by ptosis of the eyelid, constriction of the pupil, and enophthalmos. He clarified that the "intercostal nerve" originated from the spinal cord and that it was not a cranial nerve as had been suggested by earlier workers. In 1727, Pourfour du Petit published, in the *Histoire de l'Academie Royale des Sciences"* of Paris, the findings of experiments on dogs showing that section of the vagosympathetic nerve resulted in "depression of the globe, diminished convexity of the cornea, narrowing of the palpebral fissure, injection of the conjunctiva and relaxation of the nictitating membrane" (cited by Fulton, 1929a).

In 1938, Robert Remak (1815–1865) gave a detailed description of the topography of the autonomic system in his doctoral thesis, "*Observationes Anatomicae et Microscopicae de Systematis Nervosi Structura,*" published in Berlin (cited by Talbott, 1970). He showed

that the "organic nerve fibers" originated from the sympathetic ganglia and suggested that sympathetic ganglion should be regarded as the real center of the "organic nervous system" (referring to the autonomic system). In a subsequent publication in 1840, Remak clarified that the organic nervous system was concerned with all involuntary muscle movement, with secretion and possibly with the skin.

In the same year that Remak published his thesis, Edward Selleck Hare (1812–1838), then a house-surgeon to the Staffordshire County General Infirmary, UK, addressed a letter, dated September 11, 1838, to the editor of the Medical Gazette, London, describing the case of a 40-year-old man who had died of a tumor in the neck. Hare noted that the patient exhibited marked constriction of the left pupil and inability of the levator palpebrae "to perform its office." The autopsy report stated that the carotid artery, jugular vein, the origins of the brachial plexus, the phrenic nerve, vagus nerve, and the sympathetic with its lowest cervical ganglion all "passed into the substance" of the tumor. Hare explained that the signs elicited in the upper limb could easily be explained by the location of the tumor and the manner in which it had infiltrated the neighboring structures. He stated in his discussion, however, that ... "The paralysis of the levator palpebrae..., the contraction of the pupil; the pain of the teeth; the distressing sensation across the upper part of the chest; the paraplegia; the sense of pulsation in the various parts of the body..., cannot, ...be referred to any direct communication between the structural disease and these several affections, but rather they must be regarded as an instance of that remote sympathy which is found to exist between distant parts of the same individual...." It appeared from his admission, that Hare (unlike Pourfour du Petit) was unaware that cervical sympathetic nerves innervated the eyelid, eyeball, and vasculature of the face. Hare died on September 28, 1838, a day before the communication was published.

Serafino Biffi, in 1846, noted that following section of the sympathetic trunk, the constricted pupil could be made to dilate by galvanic stimulation of the central end of the cut sympathetic nerve. Two years later, Ruete (cited by Fulton, 1929a) reported that in paralysis of the third nerve, the dilated pupil could be made to dilate still further by the use of belladonna. He consequently suggested that there were two kinds of motor nerves to the pupil. He inferred that the sympathetic innervated the radial fibers, which dilated the pupil, whereas the oculomotor nerve supplied the circular fibers, which caused the iris to contract.

In 1852, Claude Bernard described experiments in the rabbit in which section of the cervical sympathetic chain resulted in an appreciable increase in the temperature of that side of the head. Later in the same year, he repeated the experiments in the dog. He showed that section of the nerve was followed by miosis, ptosis, retraction of the eyeball into the orbit, relaxation of the nictitating membrane, diminution of intraocular tension, diminution of the size of the nares, and an increase in temperature. Lecturing on the experiments of Claude Bernard, Charles Edouard Brown-Séquard, in 1852, confirmed that following galvanic stimulation of the cut end of the cervical sympathetic chain, the overheated skin became paler and cooler.

These experiments clearly increased the understanding of the function of the cervical sympathetic nerves. It is noteworthy that Albrecht von Graefe (1828–1870), a student of Remak's, worked in the laboratory of Claude Bernard during this period.

Budge (1853) extended an earlier discovery that he had made jointly with Augustus Waller in 1851 by showing that the fibers of the cervical sympathetic chain originated from C8, T1, and T2 segments of the spinal cord. Describing this center, he wrote : " I have found that, in the spinal cord, there is a certain region, extirpation of which augments considerably the warmth of the head. This region is situated between the last cervical vertebra and the third dorsal vertebra, and the phenomenon is transmitted by the eighth cervical nerve and the first two dorsal."

In 1864, Mitchell et al. described the case of an American Civil War soldier who took a blast of gunshot in the right side of his neck. They noted that the pupil of the right eye was very small, whereas that of the left eye was unusually large. There was "slight but very distinct ptosis of the right eye..." The conjuctiva of the right eye was somewhat redder than that of the left and the pupil of the right eye was a little deformed. They found that "the face became distinctly flushed on the right side and pale on the left." They did not discuss the possible causes of the signs they elicited. Nevertheless, they ended their report by asking: "Was this a case of wound or injury of the cervical sympathetic nerve?"

Although Mitchell et al. (1864) were unable to correlate their patient's signs with the lesion, they appeared to know about the effects of injury to the cervical sympathetic nerves. It seems reasonable to infer, therefore, that Horner, who was appointed professor of ophthalmology in 1862, might have been equally well informed about previous work on the cervical sympathetic nerves.

Horner's strong basic sciences background, his extensive travels, and his close association with von Graefe gave him a much broader understanding of the

symptoms he elicited in his patient. Ophthalmological research work at von Graefe's laboratory was intensive and scientifically sound. There is little doubt that the academic influence of von Graefe inspired both Argyll-Robertson (who studied under von Graefe from 1857 to 1858) and Horner to their various ophthalmologic discoveries.

The fact that Horner did not refer to previous reports, although intriguing, was the norm at that time; neither Hare (1838) nor Mitchell et al. (1864) referred to previous reports. The comprehensiveness of Horner's account reflected his deep understanding of the anatomy and physiology of the cervical sympathetic nerves.

Comment

Johann Friedrich Horner was obviously not aware at the time he was writing his paper that he was making history. The publication that earned him the credit as the originator of the syndrome of paralysis of the cervical sympathetic system in humans was a report of an isolated case. Indirect evidence gleaned from his work suggests that Horner was very conversant with the literature and with state-of-the-art scientific techniques. The physiological methods he used were a combination of techniques published by du Petit in 1727, Biffi in 1846, Claude Bernard in 1852, and Brown-Séquard in 1852. The pharmacological test employing atropine (belladona) was described by Ruete in 1847, and the use of calabar (physostigmine) was pioneered by his colleague, Argyll-Robertson, in 1863. In 1851, 3 years before Horner's arrival in Berlin, Helmholtz had published his famous description of the ophthalmoscope. On arrival in Berlin in 1854, Horner became a close associate of von Graefe, Helmholtz, and Donders. It seems reasonable to presume that he acquired firsthand experience in the use of the ophthalmoscope from Helmholtz, an experience that clearly contributed significantly to the quality of his work.

Horner knew the clinical picture of "incomplete ptosis" following damage of the cervical sympathetic nerves. As evidenced by his opening statement in the report, he assumed that his readers were equally familiar with the condition. This may be one reason why he omitted references to previous work.

A detailed analysis of Horner's report and comparison with the reports by previous workers reveals the impact that sound anatomical knowledge has on the ability of a clinician to gather and interpret information. Hare (1838) gave an excellent clinical account of the case of a 40-year-old man with a rapidly growing tumor in the neck, compressing the brachial plexus and showing signs suggestive of damage of the cervical sympathetic nerves. Like Horner, Hare (1838) did not cite any references. It appeared that he was not aware of the earlier work of Pourfour du Petit. He was unable to correlate the ocular and cardiovascular signs with the original lesion. His report predated the important advances in the anatomy and physiology of the sympathetic nervous system published by Biffi in 1846, Claude Bernard in 1852, and Budge in 1853. Had he had the benefit of this information, he probably would have made the discovery. He may have been dealing with what is now known as Pancoast's syndrome.

Even though Horner did not discuss the cause of his patient's symptoms, he gave such a meticulous, scientifically substantiated account of the effects of paralysis of the cervical sympathetics that the syndrome is now regarded more as a "clinical sign" of the disruption of the cervical sympathetic nerves than as a disease entity (Moses and Hart, 1987; Conn, 1995).

Horner's account showed that there were signs of impairment of sudomotor function, general visceral functions, and cardiovascular regulation. Whereas the pathways for these functions may converge on the intermediolateral horn cells, the higher centers controlling them may involve quite diverse and complex nuclei and tracts. The simplified pathway suggested in Figure 3 shows how emotional and other inputs could be integrated with the sympathetic drive to the head, face, and neck regions. Spyer (1994) made clear that much of the basic structure for reflex cardiovascular control is contained in the medulla, but the level of integration provided there is rudimentary. The reciprocal connections between the centers in medulla, pons, midbrain, and hypothalamus ensure integrated and behaviorally significant responses. The suprabulbar areas, namely, central nucleus of the amygdala and the insula, are essential in patterning the behavioral and underlying cardiovascular and autonomic features (Hilton 1975; Spyer, 1994). Electrophysiological studies have confirmed that stimulation of the lateral and posterior hypothalamic regions results in dilatation of the pupil, acceleration of the heart rate, elevation of blood pressure, piloerection, and increase in rate and amplitude of respiration (Carpenter, 1985). These are typical features of emotional excitement that are not normally expressed when the hypothalamus is under full cortical control. If those nuclei of the hypothalamus function as part of the central segment of the pathway, it follows that they should normally be subject to cortical control. In Horner's original account of the syndrome, he noted that there was an emotional element involved. The patient's symptoms were "brought on more markedly....by any emotion." This observation has been confirmed by Durham (1958), Weinstein et al., (1980), and Morrison et al. (1997).

They found that in infants and children with congenital Horner's syndrome, a physiological facial vasodilatation was observed during normal crying or when the children became distressed. There was a characteristic hemifacial flushing, in which the line of demarcation was exactly in the middle of the face (the "harlequin" sign; Morrison et al.,1997). This emotionally driven response is thought to be regulated by the amygdala. Studies in which the central nucleus of amygdala was stimulated in intact living animals (Cox et al., 1985) reported that a complete repertoire of behavioral responses ranging from flight or rage to "playing dead" was produced. The responses were associated with appropriate cardiovascular adjustments.

There appears to be lateralization of function with respect to the contribution of insular cortex (Oppenheimer et al., 1991, 1992). Sympathetic activity in humans is controlled by the right insula. Evidence from electrophysiological studies showed that stimulation of the left insula produced bradycardia (Oppenheimer et al., 1991). Questions arise as to whether the insula is the highest center regulating sympathetic activity. If it is, then at what level do behavior and emotion become integrated with sympathetic responses?

The insula is known to receive a heavy input of processed sensory information from the somatosensory and frontal cortices. Studies of conscious human subjects using positron emission tomography and single photon emission computerized tomography have shown that activation of the insular cortex may be induced by painful stimuli (Coghill et al., 1994), phobic stimuli (Rauch et al., 1995), and by physical exercise (Williamson et al., 1997). The SPECT images obtained by Williamson et al. (1997) confirmed that insular activation depended on afferent inputs to the somatosensory cortex from peripheral receptors.

Although lesions of the insula have been shown to result in Horner's syndrome (Nagy et al., 1997), there appears to be no information in the literature linking Horner's syndrome with isolated lesions of other areas of the cerebral cortex. Until firm evidence becomes available, it can only be presumed that the frontal and sensorimotor cortices serve to enrich the behavioral and sensory inputs used by the insula to drive the sympathetic system.

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