THE CENTRAL TEGMENTAL BUNDLE

AN ANATOMICAL AND EXPERIMENTAL STUDY IN THE MONKEY [1]

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THREE FIGURES

INTRODUCTION

In the brainstem of higher mammals there exists a very conspicuous and important tract linking the diencephalon to the inferior olivary nucleus. This system, that reaches its highest development in primates and man, was described for the first time by von Bechterew (1885) who called it "centrale Haubenbahn" indicating its origin and termination. It is a fact, however, that nowadays the origin of this system is the object of discussion and controversy among anatomists. This is the reason we prefer to use the name "central tegmental bundle" because the name does not imply any specific origin or termination and yet, nevertheless, emphasizes a most important relation of the tract, that is, that it courses through the central portion of the tegmentum of the brainstem.

For many years, only its anatomical structure and relations attracted the attention of investigators, but its functional activity and its clinical significance met with little interest. Foix et al. ('26) established a direct relationship between a lesion of this system at pons levels (with the consequent degeneration of the inferior olive) and a curious syndrome called palatal nystagmus or palatal myoclonus. The work of Foix et al. inaugurated a fruitful period of clinico-anatom-

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ical studies upon the central tegmental bundle and the syndrome of palatal nystagmus. As a result of their work very interesting and ingenious physiopathological theories have been proposed.

The advance in the clinico-anatomical field brought new questions to mind that neither the clinical nor the anatomical investigations were able to solve satisfactorily. The discovery and application of stereotaxic instruments to the study of the physiological activity of the central nervous system opened new horizons along the lines of neurophysiological research. The neurophysiological methods have been applied to the study of the central tegmental bundle. The works of Ranson et al. ('42), and many others, demonstrated that the tegmental gray of the brainstem and the tracts which course through it seem to constitute coordinating centers for the activity of the facial, glossal, palatal and laryngeal musculature. Either destruction or stimulation of the central tegmental bundle resulted in the production of abnormal rhythmic movements similar to those seen in patients with a lesion of the central tegmental bundle or inferior olive, offering a very important contribution to the understanding of this curious syndrome.

In spite of the all important advances in the anatomical, physiological and clinical aspects of the central tegmental bundle and the palatal nystagmus syndrome, multiple other questions remain unanswered. What are the anatomical relations between the central tegmental bundle, the cranial nuclei and the reticular gray? What is the physiological significance of the central tegmental bundle? What is its role in the so-called palatal nystagmus? These problems have been the source of our curiosity and interest in making this experimental and anatomical study of the central tegmental bundle in an attempt to understand the complex functions of this system.

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MATERIALS AND METHODS

The animals used in this study were Macaca mulatta and Macacus cynomolgus. The normal anatomy of the brain of Macaca mulatta was studied in preparations from the Huber Comparative Neurological Collection stained by the Weil technique. The experimental material was prepared by the Marchi method using the Swank and Davenport ('35) modification. This technique reveals only degenerating myelinated fibers. The technical difficulties and apparent optimal staining times for various fiber systems, of necessity, limits the conclusions which can be drawn from a study of this nature. Ten lesions were placed, 4 animals being used for the experiments. The McCulloch stereotaxic instrument was employed for making the lesions under ether anesthesia.

The stimulation of the central tegmental bundle was carried out under variable depths of ether anesthesia using a minimal faradic current from the Grass stimulator. The results of electrical stimulation are modified by many factors such as temperature, blood supply, shock, flow of cerebrospinal fluid, type and depth of anesthesia and type and intensity of stimulating current (see also Hines, '44). The lesions of the central tegmental bundle in the tegmentum of the brainstem were produced by an insulated needle through which a mild cauterizing electric current was passed.

In all instances, preoperative and postoperative testing of the animals was carried out and included examination of reflexes, muscle tone, cranial nerves and careful inspection of the mouth and palate. All the monkeys studied were sacrificed between the 14th and 20th postoperative days. After inducing surgical anesthesia with ether or sodium pentothal, the thoracic cavities were rapidly opened bilaterally and the arterial systems perfused with 500 to 1000 cm^3 of

10% formalin. The brains with attached cervical cords were removed carefully; in all instances the fixation was excellent.

SURVEY OF LITERATURE

In 1885 von Bechterew, working at Flechsig's Laboratory, described a system of fibers connecting the cerebrum to the inferior olive which he called the "centrale Haubenbahn." This is a system of fibers the course of which can be followed longitudinally through the brainstem from the caudal part of the diencephalon to the inferior olivary nucleus. This system had been previously mentioned by others, such as Stilling (1846), Schroeder van der Kolk (1859) but without giving a precise description. According to von Bechterew, this bundle begins in the caudal end of the diencephalon, around the gray substance of the third ventricle; from this point it follows a descending course through the central portion of the tegmentum of the brainstem. It is situated, first, ventromedial to the medial longitudinal fasciculus, then, at pontine levels, dorsal to the medial lemniscus and superior olivary nucleus, and finally, at the medulla levels, in the olivary capsule and hilus of the inferior olivary nucleus. Some of the fibers probably continue caudally in the olivo-spinal system.

Since the description by von Bechterew, we find numerous anatomical studies in the medical literature which add very little to clarify our understanding of this bundle. Its existence is generally accepted, but the number of fibers included in it by the different writers varies from the components given in the original description, and the name has changed from writer to writer. "Fasciculus thalamo-olivaris" was the name used by Edinger ('11), Beccari ('43), Rasmussen ('45); "fasciculus thalamo-bulbaris" was Castaldi's ('23) term; and "fasciculus anulo-olivaris" was Mettler's ('44) name for it; Woodburne, Crosby and McCotter ('46) called it the "pallido-incerto-olivary system." These different terminologies indicate the disagreement among writers as to the exact place of origin of this system. This disagreement is

easily understood, since human cases of the degeneration of this complete system have not been observed, and the histological methods have not been successful in clarifying its origin in normal human material.

Several hypotheses dispute the origin of the system but they fall into 4 fundamental groups. The first hypothesis places the origin in the corpus striatum, the second in the thalamus, the third in the tegmentum of the midbrain, and the fourth in the red nucleus of the midbrain.

Regarding the first hypothesis, Flechsig ('20) was one of the early workers to offer the opinion that the central tegmental bundle derived most of its fibers from ansa lenticularis. Probst ('03) advanced the idea that some of the fibers of this bundle emanated from the diencephalon and continued to the inferior olive. Winkler ('33) considered this system as a strio-olivary pathway but thought, in disagreement with Wallenberg ('22), that its fibers arose in the pallidum and not in the neostriatum. Winkler also believed that a considerable component of fibers of pallido-rubral origin coursed downward through the tegmentum of the midbrain with this system but did not end in the inferior olivary nucleus but in the reticular substance of the rhombencephalic tegmentum. This point of view was accepted by Weisschedel ('37), who based his conclusions upon an investigation of human material from subjects whose ages ranged from 19 to 40 years. He held that the central tegmental bundle is made up of several components: a main bulk of rubro-olivary, and other accessory pallido-olivary fibers, pallido-rubro-reticular fibers and reticulo-reticular fibers. Many writers deny the existence of descending striate fibers in the central tegmental bundle (Verhaart, '36; Ranson and Ranson, '42; Cardona and Macchi, '51).

Among those who regarded the thalamus as the origin of the system under consideration was Foix and Nicolesco ('25). They followed the idea previously advanced by von Bechterew and stated, more specifically, that the central tegmental bundle connected the thalamus with the inferior olive and that the

anterior nucleus of the thalamus was its place of origin. Others considered the origin of this bundle to be the subthalamic formations associated with the pallidum. Woodburne, Crosby and McCotter ('46) described this bundle as originating to some slight extent in the pallidum and zona incerta (where some pallidal fibers synapse). The small bundle runs dorso-caudalward, occupying a position close to the periventricular gray. It continues in this position after undergoing some synapse in the tegmentum to planes behind the red nucleus where it is joined ventrally by many tegmento-olivary fibers. The combined bundle passes through the pons in a position dorsal to the medial lemniscus and enters the rostral pole and the lateral side of the inferior olivary nucleus at medullary levels.

That the central tegmental bundle arises only from mesencephalic levels was advocated by Economo and Karplus ('09), Nishikawa ('23) and Poppi ('29) who emphasized the reticular component from the reticular substance of the mesencephalon. Tilney ('28) traced "the main bulk of this bundle to the region of the nucleus oculomotorius" and assumed that it served to connect the ocular nuclei to the inferior olive. Alexander ('31) subsequently endorsed this idea and attributed the origin of the central tegmental bundle to the periaqueductal gray. Ogawa ('39) appeared to regard this system as a "central tegmental fasciculus," and thought it arose in the nucleus of Darkschewitsch, nucleus interstitialis of Cajal and the nucleus of Forel's field. In the cat it is made up of fine myelinated fibers. He concluded that this bundle was less significant in the infraprimate forms than in primates. Mettler ('44) spoke of this system as the "anulo-olivary tract." He thought his data indicated that, in the monkey, the bundle, which von Bechterew described as a composite bundle carrying fibers from level to level, was not the central tegmental bundle. The area in which, according to Mettler, the central tegmental bundle has its cells of origin, is located in the anulus aqueductus, and he named it the "anulo-olivary tract." This tract is composed of thin myelinated fibers,

diffuse through most of its course, and it enters the rostral end of the inferior olivary nucleus in a very diffuse manner. No fibers enter this bundle from the lentiforme nucleus, red nucleus, or thalamus.

Dejerine ('01), Probst ('03), Ziehen ('03), Foix and Nicolesco ('25), Winkler ('33), Jacob ('42), Verhaart ('36), Monnier ('46), Weisschedel ('37) and Cardona and Macchi ('51) subscribed to the idea that the central tegmental bundle receives fibers from the red nucleus. This point of view is extensively discussed by Weisschedel, who spoke of the tract "rubro-olivary" as an important descending extrapyramidal pathway in man. Recently Cardona and Macchi, in a well-documented paper, concluded that the central tegmental bundle at the level of the red nucleus forms a heavy system of fibers which arise from this nucleus and the perirubral formation, joined by fibers from the subthalamic region (Forel's field) and nucleus of the posterior commissure without demonstrable fibers from the corpus striatum. This system of fibers descends through the tegmentum of the pons and at this level it is made up of two components: (1) a ventral or rubro-perirubro-olivary component, which, according to Cardona and Macchi, corresponds to the bundle described by von Bechterew located dorsal to the medial lemniscus and ending in the inferior olive; (2) a dorsal or rubro-perirubro-reticular component, which is situated dorsally to the ventral component through its course in the tegmentum to the upper medullary level, where it separtes from the preceding ventral bundle and ends in the reticular system. This latter is not usually considered a part of the central tegmental bundle.

Some observers regard as an important component of the central tegmental bundle fibers which arise from the dentate nucleus of the cerebellum. These fibers were described originally by Orestano ('01) and Ramón y Cajal ('03), who distinguished two separate descending tracts of cerebellar origin within the brainstem. Ramón y Cajal designated them as "vía cerebelo-espinal homolateral o externa" and "vía cere-

belo-espinal cruzada o interna," and he believed that they were formed respectively by bifurcation of some fibers within the superior cerebellar peduncle, before and after its decussation. He thought that the cells of origin were in the dentate nucleus, and perhaps, also, in the fastigial nucleus. Van Gehuchten ('05) could not demonstrate the homolateral cerebello-spinal tract of Cajal, and stated that the crossed cerebello-spinal tract should be called "cerebello-bulbaire croisée." He agreed with Ramón y Cajal that this tract arose from bifurcation of the fibers of the superior cerebellar peduncle. Rasmussen ('33) and Rand ('54), using various animals, have contributed to the knowledge of the descending cerebellar bundle. These authors concluded that the brachium conjunctivum descendens, as they called it, was a completely crossed tract lying dorsal to the medial lemniscus and that it decreased in size as it passed caudalward. These fibers arise in the dentate nucleus, and probably in the nucleus interpositus (Rand), and they can be traced into the chief inferior olivary nucleus through the extent of the nucleus and also to the medial accessory olivary nucleus. A few fibers continue medialward, as they run caudal to the chief inferior olivary nucleus, and possibly extend into the upper cervical cord levels. Jakob ('42), in human material, found secondary degeneration of the central tegmental bundle from a lesion of the dentate nucleus of the cerebellum. According to him, the central tegmental bundle in man contains crossed and uncrossed fibers from the dentate nuclei which join the pallidal fibers during its course through the brainstem. Neither the dorsal thalamus, nor the red nucleus, nor the superior colliculi contribute to the fibers of the central tegmental bundle.

It is worthy of mention that some authors described the existence of ascending trigeminal fibers in the central tegmental bundle. Von Bechterew saw trigeminal fibers joining the central tegmental bundle at pons level. This idea was later subscribed to by Sterzi ('15), and then by Mettler ('44), who spoke of the trigemino-thalamic fibers of the central

tegmental bundle. Ziehen ('3, '13, '20) made clear the distinction between the central tegmental bundle and the fasciculus dorsalis lateralis tegmenti, which represents the secondary ascending trigeminal pathways to the thalamus.

There is general agreement among authors that the central tegmental bundle is a descending pathway to the inferior olive and, nowadays, the existence of ascending fibers in this system is considered very doubtful. Winkler ('33), in his *Opera Omnia,* stated that the central tegmental bundle also carries homolateral ascending fibers from the inferior olivary nucleus and reticular substance of the medulla with destination in the corpus striatum. Verhaart ('36) wrote about the existence of olivo-fugal fibers of uncertain destination in the central tegmental bundle. Winkler based his conclusions on the fact that section of the cerebral peduncle, in an experimental rabbit was followed by degeneration of the small cells of the homolateral inferior olivary nucleus and degeneration of the large cells of the reticular substance. The results obtained in subprimate mammals cannot be applied safely to the human brain, without careful checking. Moreover, anatomico-pathologically the degeneration of the central tegmental bundle has always been described as a descending one, and there is no evidence in medical literature of ascending degenerated fibers from human lesions.

The comparative neurological studies of the central tegmental bundle have not led to a common conclusion with regard to the system. Thus Collier and Buzzard ('01), studying the brains of cats, gave the thalamus as the origin of the central tegmental bundle. Lewandowsky ('04), studying cats and dogs, indicated that the anterior quadrigeminal bodies were the origin of this tract. Economo and Karplus ('09), studying cats and monkeys, believed that the tegmentum of the mesencephalon was its origin. Verhaart ('36) studied only monkeys, and concluded that this bundle arose in the red nucleus.

Alexander ('31), in a comparative study of the central tegmental bundle concluded that it exists in all mammals, with variations in size from species to species. He indicated that

the central mesencephalic gray substance is the place of origin for this tract. From the phylogenetic studies, we may conclude that the central tegmental bundle does not exist exactly in its primate form in lower vertebrates. In the lower mammals (e.g. rodents) the existence of a discrete bundle is doubtful; in carnivores, with the development of the cerebellar hemispheres, the central tegmental bundle appears as a well-defined system; in primates the bundle is particularly well defined.

The myelinization of the central tegmental bundle, according to Flechsig ('20), begins in the fetus at 43 mm, according to Poppi ('29), at 45 mm, and according to Sterzi ('15), in the fetus at 8 months. Von Bechterew (1885) and Ziehen ('03) stated that the myelinization of this system begins only after birth and that its progression parallels the myelinization of the cortical-spinal and cortico-pontine systems during the first months of life. Langworthy ('32) found the central tegmental tract myelinated very little in the brain of a two-month old child examined by him. Cardona and Macchi ('51) stated that the fetus at 5 months shows only a partial myelinization of the dorsal portion of the central tegmental bundle through the brainstem, and practically no myelinization of fibers of the ventral portion. They further stated that at 8 months a partial myelinization of all components of the central tegmental bundle exists; at this time, a great number of fasciculi of the brainstem reached an advanced degree of myelinization (medial longitudinal fasciculus, medial and lateral lemnisci, inferior and superior cerebellar peduncles, cranial nerves from oculomotorius to hypoglossus). Somewhat retarded in their myelinization are the tecto-bulbo-spinal, ponto-cerebellar, and cortico-spinal fasciculi. In a new-born baby, Cardona and Macchi ('51) observed an increase in myelinization of the fibers of the central tegmental bundle over that in the 5 month fetus.

Very little is said of the central tegmental bundle in the classic treatises on the physiology of the central nervous system. Some valuable information on the functions of this

bundle can be obtained from anatomico-clinical studies (Foix et al., '26; Guillain et al., '33, etc.), stimulation and destruction by mediation of stereotaxic instruments (Ranson and Ranson, '42; Ingram et al., '32; Bender et al., '52; Monnier, '46; and others), or by a study of the destruction of the inferior olivary nucleus where the tracts end (V. Bechterew, 1885; Muskens, '34; Zand, '34; Wilson and Magoun, '45).

Muskens ('34) stated that a lesion of the "dorsal strio-olivaris fasciculus" produces retropulsion; lesion of the "ventral strio-olivaris fasciculus" produces propulsion; and destruction of the entire system produces decerebrate rigidity. This singular opinion has not been confirmed by further researches (Sherrington, '47; Graham Brown, '13; and others).

Ingram, Ranson and their associates ('32) evoked, by faradic stimulation of the tegmentum of the midbrain, a response similar to that elicited by its stimulation on the cut surface of the brainstem in decerebrate animals. The response consisted essentially of a bending of the head, neck and trunk toward the side stimulated, flexion of the ipsilateral and extension of the contralateral forelimb with varying movements of the hindlimbs. This response pattern, according to Ingram et al. ('32), may be obtained from the caudal part of the subthalamus, in the region of the capsula of the red nucleus, from the reticular formation of the tegmentum dorsal and lateral to the red nucleus and including the central tegmental bundle, and caudal to the red nucleus from almost anywhere in the reticular formation back to the caudal part of the pons. The responses may also be elicited by stimulation of the regions in the tegmentum occupied by various tracts such as the central tegmental bundle, the rubro-spinal, and the spino-thalamic tracts. Ingram et al. ('32) concluded that "There is no evidence that these take any special part in it and it seems more probable that it should be attributed to cells and fibers of the reticular formation through which these tracts run." The central tegmental bundle was stimulated in most of the experiments and usually gave typical responses, except at its more rostral levels where contralateral

movements of the head were common. At the more caudal levels of the explored area (pons and medulla), occasionally other responses occurred, usually accompanying the typical response. They included contraction of the orbicularis oculi muscles, slight cries and flexion of one or both hindlimbs.

Wilson and Magoun ('45) proved, in the cat, that the postural response which may be evoked by stimulation of the central tegmental bundle at midbrain levels (Ingram et al., '32) does not depend upon descending mesencephalic connections to the inferior olive, for characteristic responses to midbrain stimulation were obtained in terminal experiments in animals with uni-or bilateral olivectomy. Similarly the inhibitory effect upon decerebrate rigidity and spinal reflexes may be evoked by stimulating the bulbar reticular formation.

Monnier ('46) found by stimulating and then producing electrolytic lesions in the subthalamic region and the mesencephalic and rhombencephalic tegmentum of the monkey and the cat, that a lesion of the region where the central tegmental bundle courses is not followed by permanent hypertonicity. He considered that the central tegmental bundle is the efferent pathway of the extrapyramidal system in charge of the regulation of the fundamental motor activity and that it plays a very important role in the mechanism of the extrapyramidal dystony and dyskinesies.

Weinstein and Bender ('43), on stimulating the tegmentum of the mesencephalon in the macaque monkey with the Horsley-Clarke instrument produced a facial pattern integrated with other somatic and autonomic components into purposeful acts. The facio-ocular synkinesies of contraction of the orbicularis oculi muscles, upward rolling of the eyeballs and constriction of the pupils can be elicited from the reticular substance of the pons, lateral to the midsagittal plane. Contraction of the orbicularis oris muscle, which is a seeking, swallowing movement, is associated with elevation of the base of the tongue, raising of the uvula and inhibition of respiration in the inspiratory phase. These movements are

elicited from the reticular formation of the medulla lateral to the midsagittal plane and dorsomedial to the rostral part of the inferior olive. A facio-respiratory complex stimulating laughter, with retraction and elevation of the corners of the mouth, depression of the lower jaw, lowering of the base of the tongue and uvula and cessation of respiration in the expiratory phase, can be elicited from an area dorsomedial to the olive. In their conclusions Weinstein and Bender stated "there is no reason to believe that the responses from the brainstem were elicited from descending hypothalamic pathways and it seems that the brainstem is an important integrator of somatic functions of cranial muscles and it is also an integrating center for facial expression." In considering the exact anatomic localization of the facial pattern they considered that it is difficult to determine whether the nuclei in the reticular formation or the tracts traversing its substance are responsible for the effect of stimulation.

In 1952 Bender and his associates, in a paper in which they discussed the myoclonus of muscles of the eyes, face and throat, mentioned experiments carried out by them in the monkey using the stereotaxic technique. In this article specific reference is made to the fact that the electrical stimulation of certain regions in the brainstem produces palatal myoclonus. The specific regions stimulated were situated in the reticular system, just dorsal and medial to the inferior olivary nucleus and also within the dorsal and medial region of the olivary nucleus itself. The palatal myoclonus thus elicited was ipsilateral, and at times bilateral. Further electrical explorations showed that stimulation of the central tegmental fasciculus also produces bilateral simultaneous contractions of the face musculature and movements of the eyeballs and eyelids. This contraction, although not rhythmic, involves many of the muscles which are implicated in patients with myoclonus.

Studies of the effect of olivary lesions have been considered by many other researchers, practically all of them working on cats. Von Bechterew (1885) described a unilateral destruc-

tive lesion of the inferior olive producing forced rotation of the body, ipsilateral deviation of the eyes upward and downward, contralateral deviation of the eyes upward and lateralward and a rotatory nystagmus with deviation of the head. Those changes were not constant and diminished after a certain time, to disappear later. Bilateral lesions of the inferior olives produced general disturbance of static coordination with oscillation of the trunk toward either side, and inclination of the head. Sometimes it was impossible for the animal to maintain a normal posture.

Keller ('01) stated that the removal of the inferior olive resulted in forced rotation of the body and disturbances in equilibrium and sensibility. Luthy ('31) observed no symptoms after lesions of the inferior olive that could not be attributed to an associated injury of the rubro-spinal or pyramidal tracts. Muskens ('34) reported that the olivary lesions resulted in equilibratory disturbances associated with a compulsion to rotate.

Zand ('34, '36, '37) described a loss of decerebrate rigidity following olivary injury and concluded that the inferior olive was a center for extension hypertonus; also that it was a tonic regulatory center of muscular tonus and posture under the influence of inhibitory and excitatory centers. These reports — that decerebrate rigidity was abolished by olivary injury — were investigated by Wilson and Magoun ('45) in the cat. In some of the animals of their series, in terminal experiments, typical extension rigidity resulted in the absence of one or both inferior olives, and Zand's results would appear to have been attributable to injury of structures other than the inferior olivary nucleus. Wilson and Magoun ('45) described the results of complete or almost complete extirpation of the inferior olive in cats. Such extirpation produced inevitably some injury to adjacent structures (pyramids, medial lemniscus, reticular formation, etc.), and unilateral partial retrograde degeneration of the olive on the opposite side. After unilateral olivectomy the characteristic symptoms observed were abnormal movements of the vocal cord, pre-

dominantly on the side of the lesion. An intention tremor of the neck muscles was present and some head and body swaying occurred on standing. Decomposition of movement, together with hypermetria in the use of the contralateral legs, contributed to an ataxia in gait. As a result of these symptoms the animals frequently fell to the side of the lesion when standing or walking. With bilateral olivectomies, laryngeal myoclonus, hypermetria and extensor hypertonus of the extremities were present bilaterally. With continued survival of the animals these symptoms gradually diminished in intensity, but did not disappear within the longest interval following 4½ months. Broadly, Wilson and Magoun considered the symptoms encountered in these animals as disorders of posture associated with incoordination of movements, symptoms which resembled those following cerebellar ablation in carnivores. This is not surprising since the olivary outflow passing to the cerebellum is large.

Weisschedel ('37), basing his conclusion on anatomical, clinical and pathological considerations, questioned the physiological significance of the rubro-spinal tract as a principal descending pathway of the extrapyramidal system in man. He believed it has lost much of its importance and is a reduced fiber system. He considered that the central tegmental bundle is the most important descending pathway of the extrapyramidal system, constituting the tract which conducts the pallidal discharge to the final common pathways in the spinal cord. This idea needs further confirmation because the experimental and clinical facts demonstrated in a lesion of this tract do not appear to support such a conclusion.

Only about 50 post-mortem examinations of cases having had palatal nystagmus have been reported in medical literature. The more recent cases, those reported after the work of Foix and his associates in 1926, are of greater value than the earlier ones owing to more careful and detailed examinations of the central nervous system. As stated by Guillain and Mollaret ('31), earlier reports cannot be depended upon because the specimens were not studied in serial sections.

In a very excellent review and discussion of this problem published by Trelles ('44), the clinical pathological cases of palatal nystagmus have been grouped into three categories:

1. The first group includes the most frequent pathological processes responsible for the palatal nystagmus syndrome — a lesion situated in the tegmentum of pons. The central tegmental tract and the inferior olivary nuclei were involved in all of the specimens, but the other fiber bundles traversing the tegmentum did not regularly show any participation in the disease process. In this group can be included the 4 cases of Foix and his associates ('26); also the cases of van Bogaert ('26), Freeman ('33), Guillain, Thurell and Bertrand ('33), Lhermitte, Levy and Trelles ('35), Alajouanine, Thurell and Hornet ('35), Marinesco, Jonesco-Sisesti and Hornet ('36), and Savitsch ('36).

2. The second group includes a primary lesion of the dentate nucleus of the cerebellum and hypertrophic degeneration of the contralateral inferior olivary nucleus, without any apparent lesion in the tegmentum of the pons. In this group are the cases of van Bogaert and Bertrand ('28), Garcin, Bertrand and Frumasan ('33), Lhermitte, Levy and Trelles ('35), Lhermitte and Crouzon ('37), Savitsch and Ley ('37), Jacob and Montanaro ('42), and Murphy and Langworthy ('39).

3. The third group deals with an exceptionally rare lesion, localized to the inferior olivary nucleus. In this group we find only one case, that of Guillain, Bertrand and Mollaret ('33).

The anatomical examinations of these cases allow us to conclude that perhaps the most constant lesion responsible for the palatal nystagmus is the "hypertrophic" degeneration of the inferior olive, which is present in practically all the cases and which is secondary to a lesion in the homolateral central tegmental bundle or the contralateral dentate nucleus of the cerebellum.

The "hypertrophy" of the inferior olivary nucleus has also been described as a pseudo-hypertrophy. The affected olivary nucleus appears swollen, its outline less distinct, and the

normal convolutions obscured. Changes of the cells were accurately described by Lhermitte and Trelles ('33). According to these authors, the hypertrophic process affects not only the chief inferior olivary nucleus but also the accessory olivary nuclei. Stained with Nissl's method, its cells appear to be increased in size and deformed, and to have a great number of vacuoles in their cytoplasm. The silver impregnation methods show true proliferation and hypertrophy of the cytoplasm and dendritic processes. Some of the olivary cells show atrophy, and, in some instances, a reduction to small masses. Such a mass was called a "residual glomerulus" by Nicolesco et al. ('38). The evolution and duration of this process varies very much from case to case depending upon the etiological factor. However, it is also known that the process develops very slowly through months and years. Nevertheless, cases of palatal nystagmus followed by hypertrophy of the inferior olivary nucleus have been reported to occur in a few days: e.g. the case of Marinesco and associates ('36) which concerns a patient with an ictus who subsequently developed a palatal nystagmus and died 12 days later. The microscopic examination of this case revealed a developing hypertrophy of the inferior olive.

Before the publication of Lhermitte and Trelles ('33), this degeneration was spoken of as "pseudo-hypertrophy of the olives" or "sclerosis olivar," indicating that it was a consequence of a degenerative process of the neurones of the inferior olivary nuclei with intense proliferation of neuroglia cells and demyelinization. In 1913 Marie and Foix ascribed, as the ethiological factor in this process, two important conditions (1) a degeneration of the central tegmental tract (although not always present), and (2) a sclerosis of the olivary vessels. However, in 1933, Winkler still defended the idea that the hypertrophy of the inferior olive is due to cellular changes secondary to the degeneration of the pallido-olivary fibers. This hypothesis has very little support because of the negative findings of Marie and Foix ('13), that the lesions of the central tegmental bundle above the decussation

of the brachium conjunctivum produce only a degeneration of the olivary capsule, with atrophy of the olive. Only the lesions of the central tegmental bundle during its pontine course and associated with local vascular disturbances result in an hypertrophy of the olive.

The degeneration of the central tegmental bundle is apparently the cause of the hypertrophy of the inferior olivary nucleus of the same side; yet the olive may show the same type of degeneration following a lesion of the opposite dentate nucleus. This is easy to understand because of the crossing of the dentato-olivary fibers (Orestano, '01, Ramón y Cajal, '03; Jakob, '42; and Rand, '54) which join the central tegmental bundle. It seems that the hypertrophic degeneration of the inferior olivary nucleus is produced by a complex mechanism. It is due, on the one hand, to lesions of the central tegmental bundle, including the dentato-olivary fibers and, on the other hand, to a circulatory deficiency within the olivary complex.

Another conclusion arises from the pathological studies of cases with palatal nystagmus. The palatal nystagmus occurs on the side opposite the lesion of the inferior olivary nucleus, but on the same side as a causative lesion in the dentate nucleus of the cerebellum. In other words, the syndrome is ipsilateral in relationship to the dentate nucleus lesion and contralateral in relationship to the hypertrophy of the inferior olive.

PROTOCOLS OF EXPERIMENTAL ANIMALS

Monkey 992

OPERATION No. 1. This was a healthy young male (Macaca mulatta) of 5 pounds in which, on April 29, 1952, under ether anesthesia, a small trephine opening in the left parietal region was made just lateral to the midline. The McCulloch's stereotaxic instrument was employed and the insulated needle was directed into the left paraolivary area of the inferior olive.

Stimulation. The Grass stimulator was used. The vibratory rate was 25–40, the voltage 2–5 and the pulse duration 1 msec. During the stimulation the animal was continued under slight ether anes-

thesia. During repeated stimulation, a momentary arrest of respiration was followed by a slow respiratory rate. No contractions or abnormal movements were observed either in the face or in the mouth or palatal region.

Destruction. A cauterizing current of 4 mamp. was passed through the needle for 60 sec. before it was removed. No abnormal responses were observed.

Postoperative testing. This failed to reveal any abnormality or the presence of abnormal movements in the palate. The animal was observed periodically without discovering any abnormal signs. The muscular tonus in the extremities was normal. The monkey was able to run, climb and jump well. The examination of the cranial nerves revealed nothing unusual.

OPERATION NO. 2. On May 27, 1952, under ether anesthesia, a small trephine opening was made in the parasagittal region of the right parietal bone and, using the stereotaxic instrument, an insulated needle was directed into the right paraolivary area of the inferior olive.

Stimulation. The Grass stimulator was used, employing the same current as in the previous operation. Ether was administered. The responses to stimulation were a reduction in the frequency of respiratory movements during the passage of the current, a contraction of the muscles of the jaw and a tremor in the left hand which remained for a few minutes after cessation of the stimulus.

Destruction. A cauterizing current of 4 mamp. was passed through the needle for 60 sec. before it was removed. No abnormal responses were observed.

Postoperative testing. This did not reveal abnormal signs or symptoms. The examinations of the reflexes and the muscular tonus of the extremities were normal. The cranial nerves were normal and the examination of the palate did not reveal any abnormal movements.

OPERATION NO. 3. On June 13, 1952, while under ether anesthesia the animal was placed in the stereotaxic apparatus. Using the previous trephine opening, an insulated needle was directed into the brainstem to the supposed location of the left central tegmental bundle in the tegmentum of the pons. At this level the bundle constitutes a conspicuous mass of fibers.

Stimulation. The Grass stimulator was used; the intensity and frequency of the current were the same as in previous experiments. The ether anesthesia was held at a minimum, only enough anesthetic being given to keep the animal quiet. The results of the stimulation were as follows: the respiratory movements were reduced in frequency, there was the beginning of quivering of the musculature of the left

side of the face, then clonic contractions, predominantly in the lower part of the face but also in the left palate.

Destruction. A cauterizing current of 4 mamp. for 60 sec. was passed through the needle before it was removed. This produced an intense contraction of the musculature on the left side of the face which made difficult the inspection of the palate.

Postoperative testing. This did not reveal abnormal signs or symptoms.

OPERATION No. 4. On June 24, 1952, while under ether anesthesia the animal was again placed in the stereotaxic apparatus and, through the previous trephine opening on the right side, an insulated needle

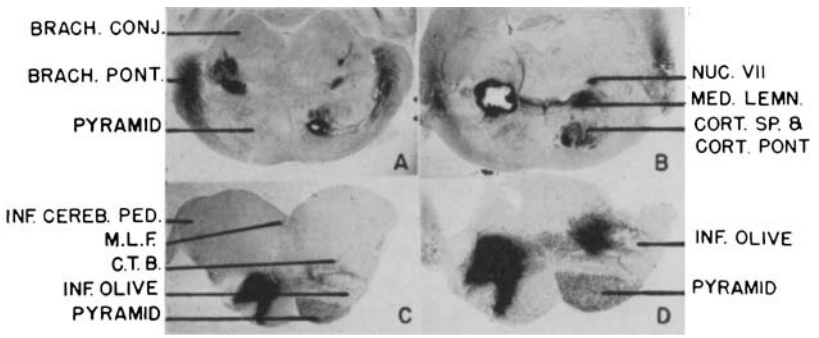

Figure 1

A and B Photomicrographs of transverse sections through the upper and midportions of the pons of the Monkey No. 992 (Macaca mulatta) showing the structures involved in the lesions. Marchi technique. × 7.

C and D Photomicrographs of transverse sections through the upper medulla of Monkey No. 992, showing lesions in both inferior olives. The left lesion extends into the ipsilateral pyramid. On the right, the degenerated fibers of the central tegmental bundle are visible. Marchi technique. × 7.

ABBREVIATIONS

BRACH. CONJ., brachium conjunctivum
BRACH. PONT., brachium pontine
C.T.B., central tegmental bundle
CORT.-SP. AND CORT.-PONT. TR., cortico-spinal and cortico-pontine tracts
DENT.-RUBR.-TH. TR., dento-rubro-thalamic tract
GENU VII, genu facialis
INF. CEREB. PED., inferior cerebellar peduncle
INF. OLIVE, inferior olive
M.L.F., medial longitudinal fasciculus
MED. GEN., medial geniculate nucleus
MED. LEMN., medial lemniscus
NUC. AMBIG., nucleus ambiguus
NUC. VI, nucleus abducens
NUC. VII, nucleus facialis
NUC. VIII, nucleus acusticus
NUC. XII, nucleus hypoglossus
PULV., pulvinar
PYRAMID, pyramid
VII N., facial nerve

was directed into the brainstem to the predetermined location of the right central tegmental bundle at the level of the tegmentum of the pons.

Stimulation. Stimulation was carried out wth the Grass stimulator while the animal was under slight ether anesthesia. The vibratory rate was 25–40, the voltage 2–5 volts and the pulse duration 1 msec. Low voltage (2–3 v.) produced quivering of the right side of the palate with a spread toward the left side. Higher voltage (5 v.) produced strong contraction of the right facial musculature and the right platysma and shoulder muscles. The contractions of the palate were more intense on the right side; they were bilateral, but much less intense on the left side. They consisted of elevation of the entire soft palate and contraction of the pillars toward the side. Respiratory changes consisting of slowing of the respiratory frequency were also present.

Destruction. A cauterizing current of 4 mamp. was passed through the needle for 60 sec. At the opening and closing of the current a strong contraction and quivering of the soft right palate was observed with a spread toward the left side.

Postoperative testing. This testing did not reveal abnormal signs or symptoms for some time. One week after the last operation it was evident that the animal had some difficulty in walking and jumping because of a weakness and a dimunition of tones of the muscles of his hindlimbs. This difficulty was present until the animal was autopsied.

Necropsy. The animal was sacrificed on July 17, 1952. Inspection of the brain, after direct infusion into the arterial system of 10% formalin, showed the exterior of the cerebrum, brainstem and cerebellum to be normal except for a very small circular area of yellowish discoloration on the surface of both upper parietal convolutions at the site where the insulated electrode had been inserted. Upon sectioning the brain it was possible to follow the needle into the brainstem. There was neither hemorrhage in nor infection of the wound.

Microscopical findings, localization of the lesions. This macaque's brain was prepared for microscopical study by the Marchi technique, and sectioned from the cervical cord through the thalamus.

The first lesion on the left side and the second on the right side resulting from the respective operations are small and localized, both involving the inferior olivary nucleus on the side. The lesion in the left olivary nucleus (first operation) is somewhat irregular in shape, partially destroys this formation and extends into the homolateral pyramid, and the lateral part of the medial lemniscus and includes the efferent roots of the XII nerve. As the lesion is followed rostrally

it decreases in size. It disappears at the level of the middle portion of the olivary nucleus being continued forward by a needle tract.

The lesion in the right olivary nucleus is as easily visualized at the same level as that in the left olivary nucleus, but is smaller, round in outline and placed at the hilus of the inferior olivary nucleus. It extends only for a very short distance and then is continued as a needle tract. Ascending degeneration of fibers such as the central tegmental bundle or other fiber systems is not present in the material studied. The degeneration of the olivo-cerebellar fibers crossing the midline to enter the inferior cerebellar peduncle is more conspicuous in those arising from the left olivary nucleus than in those arising in the right olivary nucleus. Descending degenerated fibers from the inferior olivary nuclei are present for a short distance in the upper cervical cord. They appear at the periphery, in the ventral part of the medulla oblongata and in the surrounding olivary area. They extend caudalward, in the same marginal position, to upper cervical levels. This degeneration is not very outstanding and probably involves only part of the olivo-spinal fibers and, since the lesions are bilateral, it is impossible to say whether the tract is a bilateral or an ipsilateral system. The cortico-spinal fibers severed on the left are followed as a descending degenerated bundle into the cord.

The third lesion, resulting from the third operation, is small and localized. It starts at the middle part of the left half of the tegmentum pontis, involving the lateral portion of the medial lemiscus, the horizontal fibers of the trapezoid body and the more ventral fibers of the central tegmental bundle. This lesion reaches its greatest size at the level of the superior olive at which level it involves the left facial nucleus and also the efferent roots of the left abducens and facial nerves. From this point the lesion decreases rapidly and disappears a few sections caudally. Degenerated fibers of the trapezoid body cross the midline and there is also a partial degeneration of the left lateral lemniscus. The central tegmental bundle is involved in part in the lesion but does not show evidence of ascending degeneration of its components. There is a little evidence in the slides of the caudal degeneration of the bundle toward its termination in the olivary capsule.

The fourth lesion is small and localized. It begins at upper pons levels. On the right it involves a bundle of cortico-spinal fibers and some of the transverse ponto-cerebellar fibers. This lesion on the right side extends to the midlevel of the pons. It has produced an obvious descending degeneration of the cortico-spinal fibers in the corresponding pyramid at medulla levels and crossing there are evidence of degenerated fibers in the lower part of the motor decussation.

Summary. The first experiment resulted in a lesion of the left inferior olivary nucleus and part of the homolateral pyramid without clinical manifestations resulting from the destruction (incomplete) of the inferior olivary nucleus and its afferent or efferent systems. The involvement of the cortico-spinal fibers was responsible in part for the syndrome later revealed by the animal.

The second operation produced a lesion in the hilus of the right inferior olivary nucleus and part of the incoming fibers from the central tegmental bundle. No clinical manifestations resulted from these lesions. In both experiments stimulation preceded cauterization. In neither case was there elicitation of movements or any other types of responses except a modification of the respiratory frequency.

The third experiment resulted in a lesion of the tegmentum of the pons involving the superior olive, part of the medial lemniscus and the more ventral fibers of the central tegmental bundle. This lesion did not have any clinical consequences so far as the motility of the palatal region was concerned. The stimulation that preceded the cauterizing lesion produced quivering of the musculature on the left side of the face and in the left palate, followed by clonic contractions of the lower part of the face and the left palate.

In the fourth experiment, in which there is a lesion of the cortico-spinal fibers on the right, the stimulation previous to the destructive lesion produced a contraction of the right facial musculature, the platysma and the right shoulder, and also a contraction of the soft palate bilaterally, but predominantly on the right side. The lesion of the cortico-spinal fibers was followed by a degeneration caudalward involving the right pyramid and this, together with the lesion of the left pyramid, was responsible for the final symptomatology that the animal presented.

Monkey 86

OPERATION No. 1. On July 17, 1952, under ether anesthesia, a small trephine opening was made in the left parietal region just lateral to the midline in this healthy young male Macacus cynmologus. The stereotaxic instrument was employed and the insulated needle was directed into the left half of the brainstem aiming to reach the central tegmental bundle in its descending course through the tegmentum of the lower third of the pons.

Stimulation. The Grass stimulator was used. The vibratory rate was 40, the voltage 4–7 v. and the pulse duration 1 msec. The results of the stimulation were contraction of the facial musculature on the homolateral side accompanied by a contraction of the musculature of the palate on the left side.

Destruction. A cauterizing current of 3 mamp. was passed through the needle for 60 sec. before it was removed. The closing and opening of the current produced an ipsilateral jerking of the face.

Postoperative testing. This did not reveal any abnormality or the presence of abnormal movements in the palate.

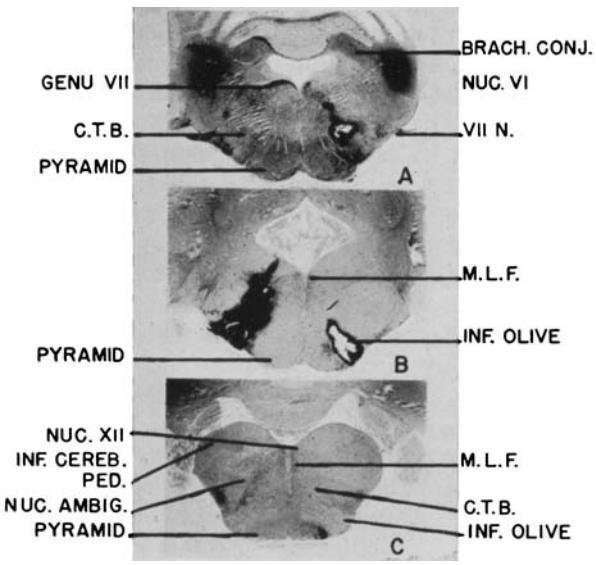

Figure 2

A and B Photomicrographs of transverse sections through the upper and mid-portions of the pons of the Monkey No. 86 (Macacus cynmologus). Marchi technique. × 7.

C Photomicrograph of a transverse section through the lower medulla of Monkey No. 86 showing the descending degenerated fibers of the central tegmental bundle entering the inferior olivary nucleus on the right. Marchi technique. × 7.

Operation No. 2. On July 24, 1952, under ether anesthesia, a small trephine opening was made in the right parietal region just lateral to the midline. Using the stereotaxic instrument, an insulated needle was directed into the right half of the brainstem to the central tegmental bundle as it descended through the tegmentum of the pons on its way to its termination in the inferior olivary nucleus.

Stimulation. The Grass stimulator was used. The intensity of current and the anesthesia (ether) were the same as in the first operation. The responses to stimulation were: contraction of the facial

musculature toward the right, deviation of the right eye laterally, slight contraction of the right side of the soft palate toward the same side. Stimulation 1 mm above and 0.5 mm medial to the original point of application of the current was carried out in order to avoid the stimulation of the neurons producing face movements but the results were the same.

Destruction. At the site of the original stimulation, a cauterizing current of 3 mamp was passed through the needle for 60 seconds before it was removed. The passage of the current produced a strong facial contraction on the right side.

Postoperative testing. On the days following the last operation, the animal showed a deviation of the face toward the right and stimulation of the animal produced an accentuation of this deviation. In the palate and in the extremities, no abnormal signs or symptoms were observed.

Necropsy. Fourteen days after the last lesion was produced the animal was sacrificed and perfused with 10% formalin. The brain appeared normal except for a very small circular area of yellowish discoloration at the site of the needle puncture. Upon sectioning the brain, only the needle tracts from the cortex into the brainstem were seen. The entire brainstem, basal ganglia and thalamus were stained using the Marchi technique.

Microscopical findings, localization of the lesions. The first lesion on the left is small and localized. It begins at the lower pons and ends at the upper medulla oblongata levels. It involves the facial nucleus and its efferent roots, part of the fibers of the central tegmental bundle, the more ventral ponto-cerebellar fibers and, to some extent, the reticular gray. No ascending degenerated system of fibers from the lesion to upper levels of the brain was present in the material studied. Descending degeneration of fibers below the lesion level are present in the medial longitudinal fasciculus and in the central tegmental bundle. The degeneration of the latter is not very marked due to the fact that the lesion only partially involved this bundle. The degenerated fibers enter the capsule of the left inferior olivary nucleus. It is also possible to follow degenerated fascicles into the reticular gray and the nucleus ambiguus on the same side.

The second lesion on the right starts at the caudal level of the pons, practically at the transition between pons and medulla oblongata, involving the medial portion of the reticular gray and some of the fibers of the central tegmental bundle. At its maximum size, in the upper medulla oblongata, the lesion also includes some cortico-spinal fibers and the upper pole of the right inferior olivary nucleus. No evidence of ascending degenerated fibers was found in the material

studied. Descending degenerated fibers are present in the central tegmental bundle, which can be followed to its termination in the olivary capsule. There is a clear descending degeneration of fibers of the central tegmental bundle into the homolateral nucleus ambiguus and the reticular substance. Also there is some degeneration in the medial longitudinal fasciculus and the cortico-spinal fibers. A reduced number of degenerated fibers from the inferior olivary nuclei is present at the periphery in the ventral part of the medulla oblongata. Such fibers are more marked on the right side than on the left; and these degenerated fibers extend caudalward into the upper cervical cord.

Summary. The first experiment on this monkey resulted in a lesion which destroyed the nucleus and the roots of the left facial nerve, part of the component fibers of the central tegmental bundle and the more ventral ponto-cerebellar fibers. The severed fibers of the central tegmental bundle can be followed into the capsule of the inferior olivary nucleus and a few into the nucleus ambiguus on the left side. The stimulation that preceded the destructive lesion produced contraction of the left side of the face and contraction of the musculature of the homolateral side of the palate. The lesion of the facial nerve and of its nucleus was responsible for the left facial paralysis that the animal showed later. No abnormal signs or symptoms were observed in the palate.

The second experiment resulted in a localized lesion which involved part of the right central tegmental bundle, some cortico-spinal fibers, the right facial roots, the right abducens roots and the superior pole of the right olivary nucleus. The descending degeneration of the central tegmental bundle and cortico-spinal fibers involved in the lesion can be followed into the right inferior olivary nucleus and the right pyramid respectively. The descending degenerated fibers of the right central tegmental bundle can also be clearly followed into the homolateral nucleus ambiguus and the near-lying reticular gray.

The stimulation that preceded the destructive lesion produced contraction of the face, and a deviation of the right eye and the palate toward the right. The postoperative examination did not reveal any symptoms except the left facial palsy mentioned above.

Monkey 941

OPERATION No. 1. This was a healthy Macacus cynmologus on which, on July 3, 1952, under ether anesthesia, a small trephine opening into the left parietal region was made just lateral to the midline. The stereotaxic instrument was employed and the insulated

needle was directed into the brainstem toward the descending central tegmental bundle in the tegmentum of the midbrain at a plane cutting the posterior commissure dorsally and the oculomotor nuclei below the aqueduct and lateral to the periaqueductal gray.

Stimulation. The Grass stimulator was used. The vibratory rate was 25–40, the voltage 2–7 v. and the pulse duration 1 msec. During the stimulation the animal was continued under light anesthesia. The results of the stimulation were: a deviation of the eyes in the horizontal plane toward the opposite side (right) and a slight contraction of the palate on the same side as the stimulation (left). During the stimulation a rhythmic contraction of the palate synchronous with the respiratory movements was produced. At the maximum of stimulation, an arrest of the respiratory movements occurred. When the position of the needle was modified to 9 mm above and 1 mm lateral to the original point of application, neither eye deviation nor palate movements were elicitated.

Destruction. A cauterizing current of 3 mamp was passed through the needle for 60 sec. before it was removed. At the opening of the circuit only jerking of the eyes was observed

OPERATION No. 2. On July 10, 1952, under ether anesthesia, a small trephine opening was made in the right parietal region just lateral to the midline. Using the stereotaxic instrument, an insulated needle was directed into the right half of the brainstem, toward the central tegmental bundle in its descending course through the tegmentum, just outside of the periaqueductal gray at approximately the same region as before.

Stimulation. The Grass stimulator was used. The intensity of current and anesthesia, ether, were the same as in the first operation. The responses to stimulation were the following: elevation of the right lid, elevation of the right lid and the right eye, elevation of the right lid and both eyes and elevation of both eyes, but more intense for the right eye than the left and pupillary contraction in the former. The position of the needle was modified 1 mm laterally and 1 mm above the original position. Stimulation at this new placement of the needle produced an elevation and deviation of the palate musculature toward the right side. No ocular responses were observed.

Destruction. A cauterizing current of 3 mamp was passed through the needle for 60 sec. before it was removed. At the opening of the circuit, a contraction of the right half of the palate was observed.

Postoperative testing. Two days after the last operation, the animal began to show a spasmodic torticollis. Its head was inclined toward the left shoulder with some rotation of the mandible toward the right side. In walking and running, the monkey fell to the left

side. The left pupil appeared smaller than the right. The palate did not show any abnormal movement or deviation. The monkey continued without change in the signs above mentioned until the day of the necropsy.

Necropsy. This was performed on July 24, 1952, 14 days after the second operation. The animal was sacrificed and perfused with 10% formalin. The brain appeared normal except for a very small lesion at the site of the needle punctures. The entire brainstem, basal ganglia, thalamus and cervical cord were stained using the Marchi technique.

Microscopical findings, localization of the lesions. The first lesion on the left is small and localized. It reaches its maximum at midbrain level involving partially the left red nucleus, some of the efferent roots of the oculomotor nerve and some of the descending fibers of the central tegmental bundle, the medial longitudinal fasciculus and other descending systems. This lesion diminishes in size above and below this point. Rostrally it extends to the back end of the left thalamus and it involves also the Edinger-Westphal nucleus. Caudally it invades some of the fibers of the decussation of the brachia conjunctiva.

No evidence of ascending degenerated fibers was found in the section. Descending degenerated fibers were clearly visible in the medial longitudinal fasciculus and much less conspicuously, in the central tegmental bundle. The former can be followed caudalward to lower medulla levels in its usual situation, close to the ventricle and midline; the latter reaches the capsule of the inferior olivary nucleus and the homolateral nucleus ambiguus.

The second lesion on the right is small and localized. It includes, at its maximum size in the tegmentum of the midbrain, the dorsal portion of the red nucleus, the nucleus of the right oculomotor nerve, the medial tacto-spinal fibers, the medial longitudinal fasciculus and some of the component fibers of the central tegmental bundle and the dento-rubro-thalamic radiations. From this point the lesion decreases in size caudalward and rostralward. Rostrally it involves some of the more ventral fibers of the posterior commissure. Caudally it invades the efferent roots of the right oculomotor nerve and fibers of the decussation of the brachium conjunctivum.

Ascending degenerated fibers were found in the rubro-thalamic radiations and in the thalamic fasciculus which can be followed into Forel's Field H. Descending degenerated fibers of the medial longitudinal fasciculus and central tegmental bundle and a few rubrospinal fascicles can be traced to medulla levels. The most conspicuously degenerated fibers are those of the medial longitudinal fasciculus. De-

generated descending fibers of the central tegmental bundle end in the inferior olivary nucleus and nucleus ambiguus of the same side although they are not very numerous.

Summary. The first experiment on this monkey resulted in a lesion in the tegmentum of the midbrain which destroyed partially the left red nucleus, some of the efferent roots of the left oculomotor nerve, the medial longitudinal fasciculus and some of the descending fibers of the central tegmental bundle. The stimulation that preceded the destructive lesion produced deviation of the eyes in the horizontal plane toward the opposite side, slight contraction of the left side of the palate and modification of the respiratory frequency. On changing the position of the electrode needle to 1 mm above and 1 mm lateral to the original reading, no responses were elicitated. Partial descending degeneration of the central tegmental bundle could be followed into the homolateral olivary nucleus and the nucleus ambiguus.

The second experiment resulted in a localized lesion which involved the tegmentum of the midbrain, the most dorsal portion of the red nucleus, the nucleus of the oculomotor nerve, the medial longitudinal fasciculus, part of the rubro-thalamic radiations and part of the component fibers of the central tegmental bundle.

Ascending degenerated fibers (rubro-thalamic) were followed into the Forel's Field H. Descending degenerated fibers of the medial longitudinal fasciculus and central tegmental bundle, and a few fascicles of the rubro-spinal system were traced to medulla levels. The degenerated fibers of the central tegmental bundle appear to end in the olivary nucleus and nucleus ambiguus of the homolateral side. The stimulation that preceded the destructive lesion produced oculomotor responses (elevation of the eyelid and the eye together with pupillary constriction). On modifying the original position of the electrode, no ocular responses were obtained but the palate musculature showed elevation and deviation toward the right.

Two days after the second operation, the animal showed a spasmodic torticollis which lasted until the sacrifice of the animal 14 days later.

Monkey 631

OPERATION No. 1. Under ether anesthesia a small trephine opening was made in the left parietal region just lateral to the midline in this healthy young male Macacus cynmologus on January 15, 1953. The stereotaxic instrument was employed and the insulated needle was directed into the left paraolivary area where the central tegmental bundle turns into this nucleus.

Stimulation. The Grass stimulator was used. The vibratory rate was the same as in previous experiments ('40), the voltage 4–7 v. and the pulse duration 1 msec. The results of the stimulation were a slight facial contraction and a slight contraction of the platysma. On displacing the electrode 1 mm medially, the facial and platysma contractions disappeared and then a slight contraction of the palate musculature toward the left side was observed.

Destruction. A cauterizing current of 3 mamp was passed through the needle for 60 sec. before it was removed. No movements were observed. At the end of the operation the monkey was in good condition and it did not show any abnormal signs. The animal continued in a similar condition until the second operation.

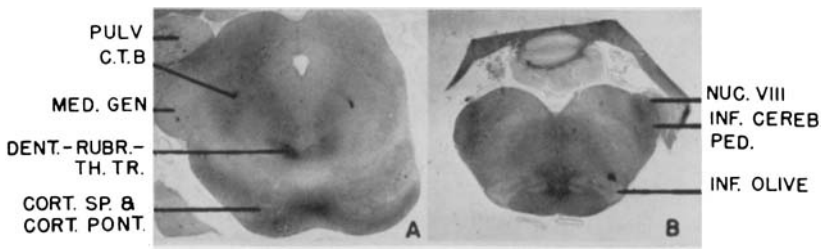

Figure 3

A and B Photomicrographs of transverse sections through the lower midbrain and lower medulla respectively of Monkey 631 (Macaca mulatta) showing the needle tracts through the tegmentum into the inferior olivary nucleus on the right. Marchi technique. × 7.

Operation No. 2. On January 21, 1953, under ether anesthesia, a small trephine opening was made in the right perietal region just lateral to the midline. Using the stereotaxic instrument, an insulated needle was directed into the right paraolivary area.

Stimulation. The Grass stimulator was used. The intensity of current and of the anesthetic, ether, were the same as in the first operation. The responses to stimulation were: slight contraction of the facial musculature toward right side, contraction of the right palate and some quivering of it. The electrode was moved up and down to avoid the facial responses and, when these ceased, a destructive lesion was made.

Destruction. A cauterizing current of 3 mamp was passed through the needle for 60 sec. before it was removed. At the time of the make and break of the current there was an elevation and deviation of the right half of the palatel musculature toward the homolateral side.

Postoperative testing. After the operation the animal was in good condition and recovered rapidly from the anesthesia. On the following days the animal was tested with negative results.

Necropsy. Ten days after the last lesion was produced the animal was sacrificed and perfused with 10% formalin. The brain appeared normal except for the small lesion produced by the needle punctures in the parietal lobes. The entire brainstem, basal ganglia and the thalamus were stained using the Marchi technique.

Microscopical findings, localization of the lesions. The first cauterizing lesion intended for the left paraolivary area is not visible in the sections. Instead of it, there is a punctiform lesion produced by the needle which can be followed through the brainstem from the subthalamic region to lower medulla levels in the neighborhood of the left inferior olivary nucleus. This needle tract in the tegmentum of the midbrain involves some of the most lateral fibers of the central tegmental bundle and it appears to follow caudalward the course of this fasciculus. At the level of the tegmentum of the pons it passes close to the nucleus of the left VII nerve and perhaps through its edge. As was mentioned before, the needle tract ends in the neighboring paraolivary area. No evidence of ascending degenerated fibers was found in the material examined. Descending degenerated fibers are visible in the left nucleus ambiguus and left inferior olivary nucleus, although they are not very numerous.

The second lesion on the right is very small, punctiform and localized. It involves a small area of the dorsal part and the capsule of the right inferior olivary nucleus. This lesion is continued rostrally by a needle tract throughout the tegmentum of the brainstem. At midbrain levels it occupies a position similar to that of the lesion on the left side, and it descends likewise in the most lateral portion of the central tegmental bundle to reach the inferior olivary nucleus. During its course it passes through the lateral part of the nucleus of the facial nerve.

Ascending degenerated fibers were not present in the sections. Descending degenerated fibers were followed into the right nucleus ambiguus and the right inferior olivary nucleus. Although these fibers are few in number, they are more numerous than those observed in the corresponding nuclei of the other side.

Summary. The first experiment on this monkey, contrary to expectation, did not result in a visible lesion of the left paraolivary area. We can only follow a needle tract throughout the tegmentum of the brainstem into the mentioned area. The stimulation produced a slight contraction of the facial musculature and a contraction of the palate toward the homolateral side. No ascending degenerated

fibers were seen in the slides and a very few descending degenerated fascicles could be followed into the left nucleus ambiguus and the left inferior olivary nucleus.

The second experiment resulted in a very small localized lesion involving a portion of the dorsal part and the capsule of the right inferior olivary nucleus. A needle tract similar to the one described on the left side extends rostrally from the lesion. No evidence of ascending degenerated fibers was found but a few descending degenerated fibers were followed into the right nucleus ambiguus and the right inferior olivary nucleus.

In both experiments facial and palatal responses were obtained which depended upon the stimulation of the facial nuclei, through which the needle tract coursed, and the nucleus ambiguus. The descending degenerated fibers in both ambiguus nuclei and in both inferior olivary nuclei were due to the involvement of the fibers of the central tegmental bundle by the needle tract along the course of this fasciculus.

RESUMÉ OF RESULTS AND DISCUSSION

The review of the literature on the central tegmental bundle leads to the almost inevitable conclusion that this system has often been misinterpreted from the very first description of it given by von Bechterew. Evidence for this conclusion is derived from many sources, including the almost general disagreement as regards its origin.

In the preceding text we have discussed extensively the different hypotheses regarding the origin of the central tegmental bundle in the striatum, in the thalamus, and in the mesencephalon (either in the tectum or the tegmentum). The study of the normal anatomy of the brain of Macaca mulatta in preparations from the Huber Comparative Neurological collection stained by the Weil technique and our experimental material permit us to present the following description of the central tegmental bundle which, in our opinion, is in agreement with the actual knowledge of this important tract.

We consider the central tegmental bundle to be made up exclusively of descending fibers, a fact almost unanimously accepted, with the exception of the isolated descriptions of Winkler ('33) and Verhaart ('36), who believed there were

also ascending fibers in the system. Another fact worth remembering is, that the central tegmental bundle has multiple components, each of them with different significance. It is a complex bundle of varying lengths, partly a chain of neurons including a system of fibers which link the diencephalic centers and the mesencephalic centers, and partly a group of long fascicles forming a very conspicuous bundle enriched with the mesencephalic components between the tegmentum of the brainstem and the inferior olive.

In accordance with Woodburne and associates ('46), we believe that the most rostral component of the central tegmental bundle comes from the pallidum and the zona incerta, where the fibers establish a first synapse and receive new fibers. These run caudalward into position very close to the mesencephalic periventricular gray, where they establish new synapses. Increased by many new fibers the bundle continues its descending course. At the level of the red nucleus, the central tegmental bundle is joined ventrally by a heavy contingent of rubro-olivary fibers which increase the system. At this level, the central tegmental bundle reaches its maximum development. During its further course, the bundle is joined by fibers from the brachium conjunctivum descendens, which arises in the contralateral dentate nucleus of the cerebellum. The combined bundle then passes through the tegmentum of the pons, where it has a dorsomedial position in relation to the medial lemniscus. At this level some authors (Jakob, '42; Cardona and Macchi, '51) identify in the system a dorsal and a ventral part which continue their descending course spinalward to the medullary centers. Perhaps, as Cardona and Macchi maintain, it should be possible to separate this system into two different portions: (1) a ventral rubro-perirubro-olivary bundle which ends in the inferior olivary complex; and (2) a dorsal rubro-perirubro-reticular bundle which terminates in the reticular substance of the medulla oblongata. We confess that we were unable, in our material, to distinguish between these two different divisions at medullary levels. However, we verified the ter-

mination of the majority of fibers of the central tegmental bundle in the olivary nucleus, in its capsule as well as in its hilus. We were fortunate in being able to follow in Marchi preparations some of the fibers of the system to their termination in the accessory olivary nuclei, the central reticular substance, and particularly the nucleus ambiguus. A few fibers appeared to continue a descending course into the cervical cord with the olivo-spinal fascicle, but examination of our preparations does not allow us to reach a definite conclusion on this point. In summary we may conclude then that, anatomically speaking, the central tegmental bundle is formed by a chain of neurons which includes palido-incerto-tegmento-rubro- and dentato-olivary fibers.

The experimental results may be summarized and correlated as follows. On monkey No. 992, there were 4 experiments in which stimulation was used and electrolytic lesions were placed in the central tegmental bundle. In the first two experiments the insulated needle of the stereotaxic instrument was directed into the paraolivary region at the inferior third of the medulla oblongata with the purpose of reaching the central tegmental bundle immediately above its termination. The last two experiments had for an objective the stimulation and then destruction of the central tegmental bundle in its descending course through the tegmentum of the pons, immediately below the decussation of the brachia conjunctiva. Of the first two attempts, the one made on the left side resulted in a partial lesion of the left olive and the ipsilateral pyramid. The stimulation that preceded the lesion elicited a momentary reduction in the respiratory frequency, and the lesion produced only symptoms indicative of injury of the cortico-spinal fibers. The lesion on the right side resulted in an involvement of the hilus of the inferior olive and fibers of the central tegmental bundle. The stimulation that preceded the lesion elicited similar changes in the respiratory frequency, jaw movements, and a fine tremor of the fingers of the left hand. No further manifestations resulted from these lesions. The third experiment resulted in a lesion of the

tegmentum of the pons, involving the superior olive, part of the medial lemniscus, and the more ventral fibers of the central tegmental bundle on the left. The stimulation that preceded the cauterizing lesion produced quivering of the musculature of the left side of the face and left side of the palate, followed by a rhythmic clonic contraction of the lower part of left side of the face and left side of the palate. Changes in the respiratory frequency were also observed. The 4th experiment resulted in a lesion in the base of the pons on the right involving some cortico-spinal fibers. The stimulation that preceded this lesion elicited right facial contraction, contraction of the platysma and shoulder on the right side, and also contraction of the entire palate, but predominately on the right, accompanied by a modification of the respiratory frequency.

In monkey no. 66, we intended to place a lesion in the central tegmental bundle at the lower pontine levels. The lesion on the left side destroyed partially the nucleus of the facial nerve, and some fibers of the central tegmental bundle, for descending degeneration could be followed into the capsule of the inferior olive, reticular substance, and nucleus ambiguus. The stimulus that preceded the destructive lesion elicited a contraction of the facial musculature on the left side and contraction of the soft palate toward the left. The lesion on the right was more extensive than the preceding one, and included the medial portion of the tegmental reticular gray, some descending fibers of the central tegmental bundle, some of the cortico-spinal fibers, and the upper pole of the inferior olive. On this side a clear descending degeneration of the central tegmental bundle into the inferior olive, reticular substance and nucleus ambiguus was found. The stimulation that preceded the destructive lesion elicited contraction of the facial musculature, deviation of the right eye toward the same side, and contraction of the right half of the soft palate. No further neurological sign was observed and only facial palsy resulting from the injury of the facial nerve was persistent.

In monkey no. 941, it was the intention to place the lesions in the tegmentum of the midbrain, dorso-lateral to the oculomotor nuclei and periaqueductal gray, where the central tegmental bundle courses. The lesion on the left side partially destroyed the red nucleus, the efferent fibers of the oculomotor nerve, the medial longitudinal fasciculus and the central tegmental bundle. In the microscopic material, we were able to follow the descending degeneration of the medial longitudinal fasciculus and of the central tegmental bundle. The degenerated fibers of the latter end in the capsule of the inferior olive, and in the nucleus ambiguus. The stimulation that preceded the lesion elicited a deviation of the eyes in horizontal plane and pupillary constriction. Correcting the position of the needle, it was possible to avoid the ocular responses and then only contraction of the palatal musculature was observed. The lesion on the right included a small portion of the red nucleus, the nucleus of the oculomotor nerve, the medial longitudinal fasciculus, some fibers of the central tegmental bundle, the rubro-thalamic radiations and the posterior commissure. The microscopic material shows an ascending degeneration of the rubro-thalamic radiations into the area of Forel's field and a descending degeneration of the fibers of the central tegmental bundle, the medial longitudinal fasciculus, and a few fibers of the rubro-spinal tract. The descending fibers of the central tegmental fasciculus end in the inferior olivary nucleus and the nucleus ambiguus. No further symptoms were observed.

In monkey no. 631, in which we intended to place a lesion in the left paraolivary area, at medullary levels, the microscopic study of our material revealed that, contrary to what we had expected, there was no well-defined lesion, and we could only follow the needle tract through the tegmentum of the brainstem into the paraolivary area. A few degenerated fibers of the central tegmental bundle were followed into the inferior olive and nucleus ambiguus. The stimulation that preceded this lesion elicited slight facial contraction and contraction of the left half of the palate. On the right side there

was a very small and localized lesion in the capsule of the right inferior olive, from which a needle tract could be followed rostrally in the course of the central tegmental bundle through the brainstem. The stimulation that preceded the lesion elicited slight facial responses, palatal response consisting of quivering, followed by rhythmic contractions of the right half of the soft palate. The facial responses were avoided by changing slightly the position of the needle. No further symptomatology was observed in this animal.

In summary, stimulation of the central tegmental bundle in the monkey elicited, as its most frequent responses, modification of the respiratory rhythm and frequency, mainly a diminution of the latter and sometimes periods of apnea. Frequently ocular responses were obtained, particularly when the stimulation was carried out in areas in the neighborhood of the oculomotor nuclei. Likewise facial responses were obtained when the stimulation was in the proximity of the facial nucleus. In most of the experiments, movement of the palatal musculature were observed. The responses of the palatal musculature were a raising and deviation of the uvula, elevation and contraction of the soft palate toward the side stimulated, and sometimes bilaterally. The palatal responses were mainly ipsilateral, but occasionally included both sides. In the latter case, eventually, a rhythmic contraction of the musculature of the palate, similar to the palatal nystagmus seen in human patients, was observed, but this was of short duration and ceased immediately after cessation of the stimuli. In very few instances accompanying responses of the skeletal musculature were observed; for instance, monkey no. 992, during stimulation, showed contraction of the jaw, tremor of the fingers and movement of the shoulders associated with the palatal responses.

Our findings are in agreement with the reports of Bender and Weinstein and others referred to previously. However we did not observe in our experimental material the "typical" pattern of responses elicited by faradic stimulation of the tegmentum of the midbrain described by Ingram et al. ('32),

nor the responses to stimulation of the central tegmental bundle described by the same authors. Perhaps this discrepancy is due to the extent of the regions stimulated by Ranson and associates which may have included other structures with the central tegmental bundle. Also we did not verify the results of Wilson and Magoun ('45) referred to earlier (p. 298). This fact may be due to incomplete destruction of the olivary nuclei (its more medial portions particularly being spared) and probably also to the short period of observation, for Wilson and Magoun ('45) obtained this symptomatology only some time after the operation.

The facts described above indicate that the central tegmental bundle is a pathway for the integration of somatic functions of muscles innervated by cranial nerves to which it brings the coordinatory impulses of the basal ganglia, reticular substance and cerebellum.

Since the studies of Foix and associates ('26), clinicians in general have related the so-called palatal nystagmus (palatal myoclonus) to a lesion of the central tegmental bundle. Like Weisschedel ('37), who considered the central tegmental bundle the most important pathway of the extrapyramidal system we have been surprised not to find for man accounts of some specific disease or hereditary process, or lesion which affected this system in a selective manner. Though Cardona and Macchi ('51) have suggested that the central tegmental bundle is affected electively in cerebellar rubro-olivary atrophy. Such a joint degeneration of the central tegmental bundle and the brachium conjunctivum conceivably could exist for these fiber paths approach each other in the midbrain tegmentum, but that such a condition does occur needs further documentation.

The patho-anatomical problem of palatal nystagmus can be reduced to the following alternatives: (1) lesion of the tegmentum of the pons including the central tegmental bundle and secondary "hypertrophic" degeneration of the ipsilateral inferior olive; (2) primary lesion in the dentate nucleus of the cerebellum and secondary "hypertrophic" degeneration

of the controlateral inferior olive; and (3) primary "hypertrophy" of the inferior olive, an extremely rare condition.

Patho-anatomical data suggests that the most constant lesion found in this syndrome is "hypertrophic" degeneration of the inferior olive (Lhermitte and Trelles, '33). This, in almost all instances, is a consequence of a lesion of the central tegmental bundle, or a lesion of the contralateral dentate nucleus of the cerebellum with degeneration of the dentato-olivary fibers included in the central tegmental bundle.

Van Bogaert and Bertrand ('28) and others called attention to the frequent involvement of the inferior olive and dentate nucleus in cases of palatal nystagmus. They regarded these abnormal movements as the result of an anatomic or functional release of infra-nuclear motor centers from the control of more cephalically situated motor mechanisms. They believed that the movements characteristic of this syndrome may result from lesions which effect any one of the following structures: (1) the superior cerebellar peduncle; (2) the tegmental reticular substance; (3) the central tegmental bundle; (4) the inferior and accessory olivary nuclei; (5) the dentate nucleus. One link of the chain of neurons being involved in some instance, and a different link in other instances. Guillain and Mollaret stated that the mechanism responsible for palatal myoclonus includes a vast system which constitutes a triangle including the inferior olive, the dentate nucleus and the red nucleus. Disturbances in equilibrium in the forces acting through these nuclei and over the pathways connecting them, produces the characteristic abnormal movement. This results from a "short circuit in the central coordinators." Years later ('33) correcting their earlier ideas, these observers stated that the more important elements in their "circuit" were the inferior olive and the dentate nucleus of the cerebellum directly interconnected by the olivo-dentate fibers through the inferior cerebellar peduncle. However, the cases in which the inferior cerebellar peduncle are involved (e.g. Wallenberg's syndrome, syndrome of the corpus restiforme, etc.) failed to show a palatal nystagmus. In 1944

Trelles, in a monograph upon the inferior olive, stated that the fundamental patho-anatomical abnormality in the syndrome of palatal nystagmus is the "hypertrophy" of the inferior olive. This olivary hypertrophy may be primary (Guillain, Mollaret and Bertrand, '31), or secondary to a lesion of the system of fibers connecting this nucleus with the dentate nucleus of the cerebellum which are included in the central tegmental bundle. Trelles, in 1935, stressed the significance of the cerebello-olivary fibers in the superior cerebellar peduncle (brachium conjunctivum descendens) which had been described previously by Cajal and confirmed later as a component of the central tegmental bundle by Jakob ('42). Thus it seems clear why only the lesions affecting the central tegmental bundle below the decussation of the brachium conjunctivum, or a lesion of the contralateral dentate nucleus, produce the "hypertrophic" degeneration of the inferior olive and consequently palatal nystagmus. Lhermitte and Trelles described the olivary "hypertrophy" in detail and considered the inferior olive a "coordinating mechanism" in charge of integrating the motor activity of the rhombencephalic nuclei. The disturbance of this "coordinating mecanism" is responsible for the palatal nystagmus. This opinion led these authors to admit connections between the inferior olivary nuclei and the motor nuclei of the cranial nerves, particularly nucleus ambiguus, innervating the musculature involved in this syndrome. However this anatomical relationship had not been demonstrated.

In the beginning of this discussion a description of the central tegmental bundle was given which we consider more in agreement with what is actually known about this system. It is well established now that the central tegmental bundle, by its fibers from the brachium conjunctivum descendes, connects the dentate nucleus with the contralateral inferior olive. This clarifies part of the clinical findings, mainly why the palatal nystagmus, when it is unilateral, appears ipsilateral in relation to the lesion on the dentate nucleus. Since the discharge path from the olive to the cord crosses in the in-

ferior olive, it is evident that the palatal nystagmus will be contralateral to the olivary lesion.

The syndrome of the palatal nystagmus produced under pathological and experimental circumstances may be compared to the ocular nystagmus which can be elicited either by a destructive lesion or by an irritative focus in the vestibular system. Both conditions produce a disturbance of the normal equilibrium with imbalance of the system producing the symptoms. In the same manner, we may consider that the coordinating impulses from the basal ganglia, from mesencephalic reticular substance and particularly from the cerebellum (dentate nucleus), transmitted by the central tegmental bundle to the cranial nuclei and inferior olivary nuclei maintain a perfect equilibrium in the palato-pharyngeal-laryngeal musculature. In the event anyone of the elements of this "system" (central tegmental bundle, dentate nucleus, inferior olive) is the site of a destructive or an irritative lesion, the normal balance of the "system" as a whole is upset, and the remaining impulses aroused from the intact structures produce the abnormal movements (palatal nystagmus).

FINAL SUMMARY

1. The central tegmental bundle is a complex of fibers of varying lengths, partly chains of neurons linking to some extent the diencephalic and mesencephalic centers, and chiefly a group of long fasciculi enriched with the mesencephalic components, between the tegmentum of the brainstem and the inferior olive. During their course, these fascicles are joined by rubro-olivary, tegmento-olivary and dentato-olivary fibers. The combined bundle ends in the inferior olivary complex, in the central reticular substance and in the nucleus ambiguus. A few fibers continue into the cervical cord.

2. The stimulation of the central tegmental bundle by mediation of the stereotaxic instrument elicited movements of the palatal musculature, raising and deviation of the uvula and elevation and contraction of the soft palate toward the

side stimulated. These movements were sometimes accompanied by a bilateral rhythmic contraction of the palate similar to the palatal nystagmus seen in human patients. These responses were frequently associated with changes in respiratory frequency, and occasionally with ocular or facial responses.

3. On the basis of the experimental and patho-anatomical data available, one may postulate that the palatal nystagmus results from an imbalance in the "system" (dentate nucleus, central tegmental bundle, inferior olive) an imbalance produced by destructive or irritative lesions which disturb the normal discharge patterns from these centers. If the lesion is destructive (human cases) the syndrome appears on the side contralateral to the lesion in the inferior olive and on the ipsilateral side if the dentate nucleus is injured. If the lesion is irritative (experiments on animals) the syndrome appears on the ipsilateral side in relation to the tegmental structures stimulated.

LITERATURE CITED

ALAJOUANINE, TH., TH. HORNET AND R. THURELL 1935 Un cas de myoclonies velopharyngées et oculaires. Rev. Neur., *64:* 853–872.

ALEXANDER, A. 1931 Untersuchungen über die zentrale Haubenbahn. Arb. a.d. neurol. Inst. a.d. Wien. Univ., *33:* 261–288.

BECCARI, N. 1943 Neurologia comparata. Sansoni Edizione Scientifiche, Firenze, 777 pp.

BECHTEREW, W. v. 1885 Ueber eine bisher umbekannte Verbindung der grossen Oliven mit dem Grosshirn. Neur. Centralblt., *3:* 194–196.

BENDER, M. B., M. NATHANSON AND G. E. GORDON 1952 Myoclonus of muscles of the eye, face and throat. Arch. Neur. and Psychiat., *67:* 44–58.

BOGAERT, L. VAN 1926 Syndrome de la calotte protuberantielle avec myoclonies et troubles du sommeil. Rev. Neur., *1:* 977–988.

BOGAERT, L. VAN AND I. BERTRAND 1928 Sur les myoclonies associees sinchrones et rhytmiques par lesions on foyer du tronc cérébrale. Rev. Neur., *1:* 203–214.

BROWN, T. GRAHAM 1913 On postural and nonpostural activities of the midbrain. Proc. Roy. Soc., *87B:* 145–163.

CARDONA, F., AND G. MACCHI 1951 La "vie centrale della calotta." Arch. ital. Anat. Embriol., *55:* 84–124.

CASTALDI, L. 1923 Studio sulla struttura e sullo sviluppo del mesencefalo. Arch. ital. di anat. e di embriol., *20:* 23–225.

COLLIER, J., AND F. BUZZARD 1901 Descending mesencephalic tracts in cats, monkeys and man. Brain, *24:* 177–221.

DEJERINE, J., AND A. DEJERINE 1901 Anatomie des centres nerveux. 2 vols., J. Rueff, Paris.

EDINGER, L. 1911 Vorlesungen über den Bau der nervösen Zentralorgane des Menschen und der Tiere. F. C. W. Vogel, Leipzig, 530 pp.

ECONOMO, C. v., AND J. P. KARPLUS 1909 Zur Physiologie und Anatomie des Mittelhirns. Arch. f. Psychiat., *46:* 275–356, 377–499.

FLECHSIG, P. 1920 Anatomie des menschlichen Gehirns und Rückenmarks auf myelogenetischer Grundlage. G. Thieme, Leipzig, 68 pp.

FOIX, CH., AND J. NICOLESCO 1925 Les noyaux gris centraux et la région mesencephalo-sousoptique. Masson et Cie, Paris, 582 pp.

FOIX, CH., A. CHAVANY AND P. HILLEMAND 1926 Le syndrome myoclonique de la calotte. Rev. Neur., *1:* 942–957.

FREEMAN, W. 1933 Palatal myoclonies. Report of two cases with necropsy. Arch. of. Neur. and Psychiat., *29:* 742–755.

GARCIN, R., I. BERTRAND AND P. FRUMASAN 1933 Étude anatomo-clinique d'un cas de syndrome de Parinaud et de myoclonies rhythmiques du voile du palais. Rev. Neur., *2:* 812–820.

GEHUCHTEN, A. VAN 1905 Les pedunclès cérébelleux supérieurs. Le Nevraxe, *7:* 29–86.

GUILLAIN, C., AND P. MOLLARET 1931 Deux cas de myoclonies synchroniques et rhytmées velo-laryngo-oculo-diaphragmatiques. Le problème anatomique et physiopathologique. Rev. Neur., *2:* 545–566.

GUILLAIN, C., R. THURELL AND I. BERTRAND 1933 Examen anatomo-pathologique d'un cas de myoclonies squeletiques synchroniques. Rev. Neur., *2:* 801–802.

GUILLAIN, G., I. BERTRAND AND P. MOLLARET 1933 Sur la lésion responsible du syndrome myoclonique du tronc cérébral. Étude anatomique d'un cas démonstratif sans lesions focales. Rev. Neur., *2:* 666–674.

HINES, M. 1944 Significance of the precentral motor cortex. Ch. XVIII (pp. 459–494) in Precentral Motor Cortex (edited by P. C. Bucy) Ill. Monographs in Med. Sciences, 4. Univ. of Ill. Press, Urbana.

INGRAM, W. R., S. W. RANSON, F. I. NANNETT, F. R. ZEISS AND E. W. TERWILLIGIER 1932 Results of stimulation of the tegmentum with the Horsley-Clarke stereotaxic apparatus. Arch. Neur. and Psychiat., *28:* 513–541.

JAKOB, CHR. 1942 La sistematizacion del haz central de la calota como via neuronal cerebelosa eferente olivo-bulbar. Rev. Neur., Buenos Aires, *7:* 1–24.

JAKOB, CHR., AND F. C. MONTANARO 1942 Miclonias oculo-laringo-faringo-velopalatinas en el sindrome bulbo-protuberancial. Rev. Neur., Buenos Aires, *7:* 85–188.

KELLER, R. 1901 Ueber die Folgen von Verletzungen in der Gegend der unteren Olive bei der Katze. Veit a Co, Leipzig, 77 pp.

LANGWORTHY, O. R. 1932 Development of the behavior patterns and myelinization of tracts in the nervous system. Arch. Neur. and Psychiat., *28:* 1365–1382.

LEWANDOWSKY, M. 1904 Untersuchungen über die Leitungsbahnen des Truncus cerebri. G. Fischer, Jena, 99 pp.

LHERMITTE, J., G. LEVY AND J. O. TRELLES 1935 Un nouveau cas de myoclonies velopalatines et laryngées avec étude histologique. Rev. Neur., *63:* 238–247.

LHERMITTE, J., AND J. O. TRELLES 1933 L'hypertrophie des olive bulbaires. L'Encéphale, *28:* 588–600.

LHERMITTE, J., AND O. CROUZON 1937 Un noveau cas de myoclonies du voile du palais, de la tongue, des levres et des globus ocularies. Lesions limitées aux noyaux denteles et aux olives bulbaires. Rev. Neur., *67:* 390–396.

LUTHY, F. 1931 Ueber anatomische Verbindungen zwischen unterer Olive und Kleinhirn. Proc. Intern. Neur. Congr., 239–240, Berne.

MARIE, P., AND C. FOIX 1913 Sur la dégéneration pseudo-hypertrophique de l'olive bulbaire. Rev. Neur., *2:* 48–52.

MARINESCO, G., N. JONESCO-SISESTI AND TH. HORNET 1936 Nystagmus velopalatin à la suite d'une lesion récente du faisçeau central de la calotte. Etude anatomoclinique. Rev. Neur., *66:* 541–547.

METTLER, F. A. 1944 The tegmento-olivary and central tegmental fasciculi. J. Comp. Neur., *80:* 149–175.

MONNIER, M. 1946 Les formations réticulées tegmentales. Rev. Neur., *78:* 422–452.

MURPHY, E. L., AND O. R. LANGWORTHY 1939 Palatal myoclonies; clinical and anatomical report of two cases. South. Med. Journal, *33:* 1035–1039.

MUSKENS, L. 1934 Experimentelle und klinische Untersuchungen über die Verbindungen der unteren Olive und ihre Bedeutung für die Fallrichtung. Arch. Psychial. Nervenkr., *102:* 558–613.

NICOLESCO, J., O. SAGER AND TH. HORNET 1938 Réflexions à propos d'un cas de myoclonies vélo-palatines consécutives à une lesion cérébelleuse droite avec hypertrophie des cellules nerveuses de l'olive gauche. Rev. Neur., *70:* 302–317.

NISHIKAWA, Y. 1923 Experimentelle Untersuchungen über einige Bahnen des Hirnstammes des Kaninchens. Arb. a. d. neur. Inst. a. d. Wien. Univ., *24:* 357–396.

OGAWA, T. 1939 The tractus tegmenti medialis and its connections with the inferior olive. J. Comp. Neur., *70:* 181–190.

ORESTANO, F. 1901 Le vie cerebellari efferenti. Riv. di Pat. Nerv. Ment., *6:* 49–69.

POPPI, V. 1929 Sulla mielinizzazione dei principali sistemi di fibre del mesencefalo dell'uomo e sulla constituzione della guaina mielinica. Riv. Pat. Nerv. Ment., *34:* 242–282.

PROBST, M. 1903 Zur Kenntnis der Hirnlues und über die Zwischenhirn-Olivenbahn. Jahrb. f. Psychiat. u. Neur., *23:* 350–381.

RAMÓN Y CAJAL, S. 1903 La double via descendente nacida del pedúnculo cerebeloso superior. Trab. Lab. Invest. Biol. Univ. Madrid, *2:* 23–29. N. Moya, Madrid.

RAND, R. 1954 An anatomical and experimental study of the cerebellar nuclei and their efferent pathways in the monkey. J. Comp. Neur., *101:* 167–224.

RANSON, S. W., AND S. W. RANSON, JR. 1942 Efferent fibres of the corpus striatum. Res. Publ. Asso. Nerv. Ment. Dis., *21:* 69–76. The Williams and Wilkins Co., Baltimore.

RASMUSSEN, A. T. 1933 Origin and course of the fasciculus uncinatus (Russell) in the cat, with observations in other fiber tracts arising from the cerebellar nuclei. J. Comp. Neur., *57:* 165–197.

———— 1945 The principal nervous pathways. The Macmillan Co., New York, 73 pp.

SAVITSCH, E. 1936 Étude anatomique d'un cas myoclonies vélo-palato-laryngées avec nystagmus myoclonique rotatoire. J. Belge de Neur., et Psychiat., *36:* 291–297.

SAVITSCH, E., AND R. A. LEY 1937 Myoclonies palato-pharyngo-laryngées au cours d'un neurinome de la region latero-bulbaire. Rev. Neur., *67:* 585–604.

SCHROEDER VAN DER KOLK, J. L. C. 1859 Bau und Funktionen der medulla spinalis und oblongata. F. Vieweg u. Sohn, Braunschweig, 274 pp.

SHERRINGTON, C. S. 1947 The integrative action of the nervous system. Cambridge University Press, 433 pp.

STERZI, G. 1915 Anatomia del sistema nervoso centrale dell'uomo. 2 vols., A. Draghi, Padova.

STILLING, B. 1846 Ueber den Bau der Hirnknotens oder der varolischen Brücke. F. Maukii, Jena, 183 pp.

SWANK, R. L., AND H. A. DAVENPORT 1935 Chlorate-osmic formalin method for staining degenerating myelin. Stain Tech., *10:* 87–90.

TILNEY, F. 1928 The brain from ape to man. 2 vols. P. Hoebner, New York.

TRELLES, J. O. 1935 Les ramollisments protuberantiels. G. Doin, Paris. Thèse 308 pp.

———— 1944 La Oliva Bulbar. Ed. Lumen, Lima. 109 pp.

VERHAART, W. J. C. 1936 Die zentrale Haubenbahn bei Affen und Menschen. Schweiz. Arch. f. Neur. u. Psychiat., *58:* 270–283.

WALLENBERG, A. 1922 Beitrag zur Kenntnis der zentrifugalen Bahnen des Striatum und Pallidum beim Menschen. Z. f. d. ges. Neur. u. Psychiat., *30:* 388–389.

WEINSTEIN, E. A., AND M. B. BENDER 1943 Integrated facial patterns elicited by stimulation of the brainstem. Arch. Neur. Psychiat., *50:* 34–42.

WEISSCHEDEL, E. 1937 Die zentrale Haubenbahn und ihre Bedeutung für das extrapyramidale motorische System. Arch. f. Psychiat., *107:* 443–579.

WILSON, W. C., AND H. W. MAGOUN 1945 The functional significance of the inferior olive in the cat. J. Comp. Neur., *83:* 69–77.

WINKLER, C. 1933 Le Corps strié et le diencéphale. Vol. 10 of *Opera Omnia:* 155–162. De Erven F. Bohn, Haarlem.

WOODBURNE, R., E. C. CROSBY AND R. E. MCCOTTER 1946 The mammalian midbrain and isthmus regions. Part II. The fiber connections. A. The relation of the tegmentum of the midbrain with the basal ganglia in Macaca Mulatta. J. Comp. Neur., *85:* 67–92.

ZAND, N. 1934 Étude experimentale sur la rigidité decerebrée. Arch. neerl. de Phys., *19:* 166–175.

———— 1936 Le rôle des olive bulbaires. L'Encephale., *31:* 270–292.

———— 1937 De la sémiologie des olives bulbaires. Rev. Neur., *67:* 746–749.

ZIEHEN, TH. 1903, 1913, 1920 Makroskopische und mikroskopische Anatomie des Gehirns. In: Handbuch des Anatomie des Menschen, K.v. Bar deleben, ed. G. Fischer, Jena.