1951

The extrapyramidal pathways and motor function

https://hdl.handle.net/2144/4447

Boston University
which epitomizes adaptive nature of organism. The red nucleus, for example, will be seen to have entirely different connections and functions in different animals; and what is more to the point, its relationship to other motor centers will be different. This evolutionary shift of anatomical and functional status is another facet of the problem which is to be treated here. The purpose of this paper is not
Approved by

First Reader  Arthur M. Lasike  Professor of Anatomy

Second Reader  Henry Waller  Associate Professor of Anatomy
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>A Brief History</td>
<td>3</td>
</tr>
<tr>
<td>The Reticular Formation</td>
<td>8</td>
</tr>
<tr>
<td>Connections of the Reticular Formation</td>
<td>13</td>
</tr>
<tr>
<td>The Red Nucleus</td>
<td>22</td>
</tr>
<tr>
<td>The Corpus Striatum</td>
<td>26</td>
</tr>
<tr>
<td>a. Gross Anatomy</td>
<td>31</td>
</tr>
<tr>
<td>b. Myeloarchitecture</td>
<td>35</td>
</tr>
<tr>
<td>c. Fiber Connections</td>
<td>36</td>
</tr>
<tr>
<td>d. Experimental Work on the Striatal Connectors</td>
<td>38</td>
</tr>
<tr>
<td>e. Physiology of the Corpus Striatum</td>
<td>44</td>
</tr>
<tr>
<td>The Substantia Nigra</td>
<td>48</td>
</tr>
<tr>
<td>The Subthalamic Nucleus of Luys</td>
<td>51</td>
</tr>
<tr>
<td>The Cortex</td>
<td>53</td>
</tr>
<tr>
<td>Conclusions and Summary</td>
<td>55</td>
</tr>
<tr>
<td>Bibliography</td>
<td>iii</td>
</tr>
<tr>
<td>FIGURE</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Figure 1.</td>
<td>Interegmental Spinal Connections (from Lloyd)</td>
</tr>
<tr>
<td>Figure 2.</td>
<td>Connections of Anterior Horn Cells (from Lloyd)</td>
</tr>
<tr>
<td>Figures 3-8.</td>
<td>Evaluation of the Vertebrate Telencephalon (from Kappers, Huber and Crosby)</td>
</tr>
<tr>
<td>Figure 9.</td>
<td>The Telencephalon of a 25 mm. Human Embryo</td>
</tr>
<tr>
<td>Figure 10.</td>
<td>Cortico-striatal Connections (from Dusser de Barenne, Carol and Mc Culloch)</td>
</tr>
</tbody>
</table>
One of the major problems which neurology has to consider is the mechanism by which nervous impulses are delivered to a complex musculature in such a way that orderly and appropriate movements result. This thesis is concerned with that part of the motor nervous system which acts through pathways other than the corticospinal: the so-called extrapyramidal pathways. It becomes important to understand this older (phylogenetically) motor system when an attempt is made to analyse the motor mechanics in primates, in which animals another system of direct motor fibers co-exists and cofunctions with the extrapyramidal.

The approach will be predominantly anatomical, in the belief that any substantial theories must grow out of a knowledge of structure. This means that comparative, embryological, and histological aspects will form the core of the material, while physiological and pathological information will be considered more or less secondarily.

The isolation of the pyramidal from the extrapyramidal system is arbitrary in the sense of function, for it is apparently a principal of nervous activity that functionally related parts are related anatomically as well. The justification of this division lies in the fact that these two systems represent distinctly different stages in vertebrate phylogeny. Such a classification tends to emphasize the comparative anatomy of the nervous system, but it also fails to emphasize the functional interdependence that most probably exists. Another weakness of this artificial approach is that the homologies do not necessarily imply analogies, especially with regard to the brain,
which epitomizes adaptive nature of organism. The red nucleus, for example, will be seen to have entirely different connections and functions in different animals; and what is more to the point, its relationship to other motor centers will be different. This evolutionary shift of anatomical and functional status is another facet of the problem which is to be treated here. The purpose of this paper is not only to isolate the significance of extrapyramidal structures in non-pyramidal animals, but also to attempt a statement of their status in primates.

The rewards of such an inquiry are attractive: to understand how anatomical and functional changes are reflected in each other would be to gain a great insight into the nature of the nervous system. More particularly, though, the comprehension of nervous diseases of motor function would be "a consequence devoutly to be wished".

There are good reasons for the present lack of knowledge in this subject; the questions that have just been posed were asked by competent neurologists a century ago, but there has been surprisingly little advancement in the field. The very nature of nervous mechanics is elusive; the compactness of a tissue which is so sensitive to the environment; the minuteness of the structures involved: these are factors which prevent easy inspection of the central nervous processes, and there are other limitations in the experimental methods being used. Most of the fiber connections have been worked out upon certain assumptions which may prove to be false, such as the degeneration phenomenon in nerve cells (Gudden's law and Wallerian degeneration).
Questions of trans-synaptic degeneration and of the maintainance of injured cells by remaining collaterals have been raised. The classification of cells into functional types is also unsettled. Malone (1912), Marinesco (1909), and Hunt (1924) have advanced several ideas that imply cell types, and many have based their thinking upon such premises.

As a result of these and other difficulties neurology is a relatively undeveloped field; and the extrapyramidal system, having been even more hidden anatomically and otherwise, is understandably a poorly known subject.

A Brief History

From what has already been said it should not be too surprising to find that the extrapyramidal system has received very little attention. There are long periods during which little or no work was done on the system, and the advent of cortical research did much to overshadow this and other topics.

The earliest reference to an extrapyramidal motor system seems to be that of Prus (1898) in a lecture to the Medical Society of Lemberg, Poland. Prus had set out to determine whether epileptic movements were cortical or medullary in origin. His experimental design, it is worth noting, was not very much different from used by Tower almost forty years later in another classical experiment. The technic involved
cortical stimulation of unnarcotized dogs in which the pyramidal tracts had been sectioned at the level of the internal capsule, the peduncles, the pons, the medullary pyramids, or the lateral funiculi of the spinal cord; none of these lesions prevented the cortical induction of epilepsy. Only upon section of the mesencephalic tegmentum did cortical stimulation fail to give epileptic movements, from which Prus concluded that certain extrapyramidal pathways travel through the tegmentum and the substantia nigra:

"...the extrapyramidal tracts conduct excitations mainly for the associated movements and not the special movements in Munk's disease..........."

Regarding the possible reflex (involuntary) nature of these associated movements, Prus says (55):

"It is difficult for me to give a definite answer to this question as well as to the questions whether the extrapyramidal tracts can transmit voluntary excitation, whether the extrapyramidal tracts have any influence on muscle tone, and whether, during voluntary movement, both pyramidal and extrapyramidal tracts are active. However, it is my opinion that a mechanism as complicated as is the execution of a voluntary movement probably requires both pathways, for it can hardly be assumed that only one transmitter between cerebral cortex and spinal cord—namely the pyramidal tract—could be sufficient for the harmonious coordination of different muscles in the execution of even the most simple movements."

The next systematic treatment of the extrapyramidal system does not appear until 1914, when Wilson's famous paper forwarded an elaboration of Sherrington's concept of an old motor system being masked by a new one. The substance of Wilson's work will be referred to later,
but it is interesting to note here that his efforts mark an important milestone in the development of modern experimental neurology. Wilson and other workers of that day began to evaluate the voluminous work which had been done, and at the same time they repeated experiments and to verify details.

Wilson suggested that the extrapyramidal system acted through descending striorubrospinal tracts to effect striped muscle tone. In a lecture series (1925), he gave a detailed analysis of the motor symptoms in cases of choreoathetosis, pointing out that the only true signs were weakness, poverty of voluntary movement, and changes in muscle tonus. The so-called associated movements were quite in tact.

During the years following the work of Wilson and preceding Tower's, there were few basic studies done on the extrapyramidal pathways. Hunt had theorized on the old and new motor systems (1924) and Jacob's pathologically oriented article was contemporary (and almost identical) with Wilson's Croonian lectures.

Tower and Hines provided fresh impetus to the stagnant subject with their observations of cortically induced movements despite the destruction of the pyramidal tracts, just as Prus had seen (1935). Tower published a more thorough study of the same material in 1936, in which she further noted the thresholds and distribution of extrapyramidal cortical inhibition. Tower found that the extrapyramidal movements were slow in starting and massive in distribution, whereas pyramidal movements (according to stimulations of pyramidal cortex) were fast and more isolated.

Verhaarts 1938 paper on the corpus striatum and the red nucleus presented a different approach to motor physiology. He emphasized what Tower had omitted in her discussion: the autonomic effects of extra-
pyramidal action. This author suggested that the extrapyramidal component of movement is an autonomic drive which regulates the level of activity.

Papez's paper of 1942 was a valuable review of anatomical research to that date; and several theoretical interpretations of the extrapyramidal pathways were given on the basis of the fiber connections as they were understood then. Papez traces pathways into the cerebellum and back to the cortex, which circuits are said to be extrapyramidal.

Finally, the voluminous work of Mettler should be mentioned (1935—the present). Mettler's publications have included anatomical and physiological investigations of the extrapyramidal systems. He has been historian as well as researcher for the problem.

Histologically, then, we see that the present topic of discussion has suffered from periods of neglect, and that pertinent investigations have been all too few and far between. As in any intellectual pursuit, the early stages of inquiry into the extrapyramidal systems have reflected the influence of individuals. The case of Prus is striking as an example of scientific precocity and prescience. Wilson's observations on a neuroanatomical and on a clinical level were both sweeping and accurate to a remarkable degree.

For the present, there are several individuals whose energies have already left their impression on the contemporary world of neurology. In the field of the extrapyramidal functions the names of Magoun and Mettler are well known.
The discussion will revolve around those anatomical entities which are known to be associated with the extrapyramidal pathways or which have been included in the various extrapyramidal schemas to be presented.

The divisions to be treated include the reticular formation, the red nucleus, the corpus striatum, the substantia nigra, the subthalamus, and the extrapyramidal cortex. The last mentioned topic is only briefly reviewed, since it really forms an entirely different, more general problem which is out of the scope of this thesis.

Each area is discussed in terms of gross anatomy, microscopic anatomy, embryology (when possible), comparative anatomy, fiber connections, and physiology.
Areas of diffusely arranged cells found in the medulla, pons, mesencephalon, and diencephalon are loosely termed the reticular formation. There is general agreement upon the sensory-motor coordinating function of these cells in the lower vertebrates, and it has been suggested that the marked phylogenetic increase in the volume of reticular cells in primates reflects an adaptation to the complex extrapyramidal systems in these animals.

There are some very large, motor-type cells in the reticular formation, but most of the cells are medium or small sized. Kappers (25) states that these cells are responsible for the correlation of numerous sensory pathways with lower motor centers. The phylogenetic differentiation of the reticular elements in lower vertebrates is certainly suggestive of such a function; and, as von Hoevell pointed out (1911), the relatively underdeveloped reticular formation in such sheltered animals as turtles (in which somatic sensory pathways are reduced) attests to this integrative action.

The following account, based on the work of Kappers, Huber, and Crosby (1936), briefly illustrates the parallel development of reticular nuclei and various sensory modalities.
The Muller cells of the Cyclostomes are large and small reticular elements associated with lower motor centers through the medial longitudinal fasciculus. In Selachians, large multipolar cells are scattered along the medial longitudinal fasciculus, in addition to the ventral a ventral nucleus of the vagus and a nucleus at the entrance of the vestibular nerve. There is further differentiation in the Ganoids and Teleosts, in which reticular cells are discretely arranged about lateral line, vestibular, gustatory, and visceral centers.

The only special reticular nucleus found in Amphibians is a motor mass firing into the medial longitudinal fasciculus.

Anlagen of the red nucleus and of the interstitial nucleus of Cajal are said to be present in the adult Reptiles, lying lateral and cephalic to the oculomotor nucleus in these animals. The inferior reticular nucleus becomes well defined in this group.

In birds there is a definite red nucleus, as well as an interstitial nucleus of Cajal and two nuclei associated with the medial longitudinal fasciculus.

The Mammalian reticular formation shows an increase in both volume and differentiation. Superior, medial, lateral, and inferior reticular nuclei are readily seen; the medial nucleus is interposed in the acoustic pathways and sends fibers into the reticulo-spinal tract, while the lateral nucleus is a link in the spinocerebellar systems.
The reticular formations of Rodents, Carnivores, and Man were systematically described by Roussy and Mosinger, who included many mesencephalic and diencephalic structures which had not hitherto been associated with the reticular formation. These authors are convinced, in fact, that their reticular formation represents a functional system, a "vegetative-motor system" of an extrapyramidal type. Other authors, notably Verhaart (71), have also emphasized the autonomic nature of the extrapyramidal functions; but the exact status of the reticular formation as a part of the extrapyramidal system is still an unsettled question. For purposes of anatomical description the classification of Roussy and Mosinger (64) is used here, with the reminder that it has little more than a theoretical foundation.

The evidence for Roussy and Mosinger's conception of a reticular system deserves attention, however, because many basic problems concerning the nature of the extrapyramidal system revolve about the possible truth of their premises.

The following considerations are offered as evidence of functional unity in the reticular formation and its derivatives:

1- characteristic large, medium, and small multipolar cells rich in yellow pigment and having well developed dendrites are found in all "reticular" structures; 2- rubriform and nigriform cells are also characteristic;
3—sub-pallidal extrapyramidal formations develop from reticular cells; and, 4— the reticular formation of the suprasegmental apparatus is apparently an anatomical continuation with the reticular substance of the spinal cord, which is acknowledged to have autonomic functions. None of these facts or interpretations are positive enough to be convincing, but the implications will be seen to reappear in numerous papers which will be discussed in this review. An account of the reticular "system" (formation, for our present purposes) is given in the following paragraphs.

The diencephalic reticular formation is divided into anterior and posterior divisions. The anterior division includes most of the optic recess, the parataenial nuclei, the anterior thalamic nuclei, and the anterodorsal part of the hypothalamus. The taenia thalami carry impulses from the anterior division of the diencephalic reticular formation to the habenular ganglion in the so-called reticulo-habenular fasiculus.

The posterior division is continuous with the anterior, and is itself divisible into external, middle, and internal segments.

The internal segment is continuous with the metathalamus and includes the posterior reticular thalamus, the reticular metathalamus, and almost the entire subthalamus.

The middle segment is made up of the zona incerta and the nuclei of Forel's fields H-1 and H-2.
The internal segment borders the reticular substance of the hypothalamus and includes the pre-\(\text{ro}r\)oral field, the periventricular gray matter, and the nuclei of Forel's field \(H\).

The mesencephalic reticular formation is rather widespread and is best considered as several groups; 1- a medial group, continuous with the subthalamic reticular formation, consists of the interstitial nucleus of Cajal, the nucleus of Darkesheiwitsch, and the nucleus of Gudden: These areas have connections with the medial longitudinal fasiculus and with the nucleus of the central tegmental tract. 2- a ventromedial group, continuous with Forel's field, comprising the red nucleus and the retro-\(\text{rub}r\)bral field.
3- the median and paramedian groups, lying between the red nuclei (called the cupuliform formation by Foix and Nicolesco 1927), include the nucleus of the central tegmental tract and the nucleus of the medial longitudinal fasiculus. 4- the medial group includes almost all of the peduncular tegmentum. 5- the paraleminiscal area, surrounding the medial leminisci, and finally, 6- the entopeduncular region, which is the substantia nigra.

Pontine and medullary reticular formations fall into median, paramedian, lateral, and middle segments.

The median and paramedian segments are made up of the superior central nucleus of Bechterew, the medial reticular nucleus of the tegmentum, the inferior central nucleus of Roller, and the reticular nucleus of the hypoglossal nerve (Kolliker).
The middle segment lies next to the motor nuclei of the ninth, tenth, and twelfth cranial nerves; and is also closely related to the central tegmental tract and to the sensory decussation.

The lateral segment consists of the lateral tegmental nucleus, the peri-trigeminal and peri-facial substances, and the inferior olive with its surrounding reticular cells: This completes the description of the reticular formation as given by Roussy and Mosinger (see above).

The connections of the reticular formation

Because of the diffuse arrangement of cells, the fiber connections of the reticular formation are difficult to study, and information is exceedingly sparse.

Roussy and Mosinger (above) classified these connections as associational, commissural, afferent, and efferent; but they did not quote the source of their statements.

The associational fibers, running caudo-rostrally, are long and short bundles connecting the thalamus, subthalamus, and hypothalamus with caudal parts of the brain stem reticular formation by way of the central tegmental tract and through a diffuse pathway, as well.

Commissural pathways are subdivided into inter-reticular, reticulo-vegetative, and other more doubtful connections which will not be mentioned here. The inter-reticular connections are carried in the
supramammillary commissure, the posterior commissure, Meynert's
decussation, and the ventral tegmental decussation. The reticulo-
vegetative fibers are in the fasiculus of the tuber cinereum and in
Ganser's commissure, which is reduced in man.

Afferents to the reticular formation include endings from all the
sensory cranial nerves, cerebellar fibers in the brachium conjunctivum,
pallidal and striatal fibers in the anse lenticularis and in "le
fasceau pallidal de la pointe", and in the lenticular fasiculus.

Efferents descending from the reticular formation are found in the
posterior longitudinal bundle of Schutz, which carries fibers from
the hypothalamus, the subthalamus, and from the nucleus of Darkeschewitsch
and the interstitial nucleus of Cajal. Reticulospinal fibers and the central
tegmental tract are main bundles of reticular efferents (64).

The existence of reticulospinal tracts in man has been demonstrated
by Peers, Bodian, and others (51). Barnhart, Rhines, McCarter, and
Magoun (quoted by Papez) traced these fibers into the spinal cord
in cases of bulbar poliomyelitis. Papez refers to the similar
findings of Kohnstamm (1899), Probst (1902), and van Geguchten (1903),
who reported reticulospinal tracts in birds, mice, rabbits, cats,
and man. Papez confirmed these observations for the cat (51) and also
found some reticular cell fibers entering the medial longitudinal
fasciculus; but the search for ascending reticular fibers gave only negative results.

The importance of the reticular formation as a part of the extrapyramidal motor system has been a subject of increasing interest and importance; and certain groups of experimental findings indicate that the reticular formation may turn out to be an important extrapyramidal outflow channel which so many workers have searched for. Although the types of experimental approach contributing to this new viewpoint are varied, they are considered together here so that the proposed evidence for reticular mediation of extrapyramidal action can be appraised as a unit.

Tower, in a paper which is now well known (67), observed that stimulation of the cat’s cortex caused inhibition of cortically induced movements, and that the inhibition was not eliminated by sectioning the medullary pyramids; in her conclusions Tower speculated that this was an extrapyramidal phenomenon which was carried out by the bulbar reticular formation and its reticulospinal tracts.

Magoun and Rhines (31) describe bulbar inhibitory and facilitatory areas in the ventromedial and dorsolateral portions of the medullary reticulum, respectively. They would inhibit reflex movement bilaterally by stimulating the appropriate area of the medulla.

A cortico-bulbo-reticular pathway has been traced by Dusser de Barenne, who strychninized area 4-s and recorded strychnine spikes in the bulbar reticular formation and in the caudate nucleus. He deduces that
a direct pathway from the extra pyramidal cortex to the medulla is involved in the spike transmission. Destruction of the caudate nucleus did not alter this response.

Electroencephalography has become another important source of information concerning neural circuits and the behavior of the reticular formation. Several contributions have come forth during the past fifteen years through the efforts of Forbes, Jasper, Morison, Rose, Magoun, and Moruzzi, and others. Their observations stem from the classical observations of Bergeer (1930), Bremer (1935), and Gerebtzoff (1941).

The fundamental facts of brain waves, as they are understood at present, are these: there is a slow wave of electrical activity (8-12 per second) which emanates from the brain, the occipital cortex according to Berger. Visual, auditory, or mental concentration interrupts this alpha rhythm, as it is called, and replaces it with a faster wave of lower voltage; this transformation has been termed the arousal reaction. An experimental reproduction of the alpha rhythm is obtained by stimulation of the anterior or intralaminar thalamic nuclei, which stimulation rouses a gradual spreading over the cortex of this cortical activity: the so-called recruiting reaction.

Magoun finds these waves limited in distribution to areas of cortex which are usually referred to as associational (1949). The same worker produced desynchronization of cortical waves (arousal?) by stimulating the bulbar, pontine, mesencephalic, and diencephalic reticular formations. Using isolated brain preparations Magoun made lesions of the tectum, cerebral peduncles, and the lateral mesencephalic
 tegmentum, none of which interfered with the electrical response he described. The inference is that impulses are being carried orally in the brain stem reticular formation, reaching the cortex through the thalamus perhaps, although destruction of the thalamus does not alter the response.

Jasper (1949) confirms Rose's report (1943) of a diffuse reticular thalamic radiation to the cortex, suggesting that these fibers form the anatomical substrate for thought integrations (23).

Starzl and Magoun (1951) have modified the conception of a diffuse thalamic radiation, since they find a definite topographical distribution of cortical impulses from thalamic stimulation (66). According to these authors the arousal response was obtained from the stimulation of the central median and anterior ventral thalamic nuclei as well as from the intralaminar and anterior nuclei.

The parts of the thalamus which are reported to be involved in these reactions are known to have afferent connections with the olfactory system through the mammillothalamic tract (which also carries impulses from the reticular nuclei of the hypothalamus) and efferent connections with the globus pallidus through the interior thalamic peduncle. Furthermore, Papez has forwarded a very logical theory which explains the mechanism of emotion by pathways connecting the olfactory tract to the hypothalamus, hippocampus, and the cingulate cortex: if this theory were true, then there would be
greater justification for the idea that the thalamic radiations from reticular nuclei are concerned with the emotional content of arousal and attention. In fact, Papez has called the gyrus cinguli the "seat of dynamic vigilance by which environmental experiences are endowed with an emotional consciousness". Such an assumption is in agreement with the reticulo-vegetative theory of Roussy and Mosinger, as well (cited above). (63) (81).

Magoun has summarized his elaborate conception of the reticular formation in a recent article (1951) which alludes to more concrete evidence (below) for caudal and cephalic reticular effects. He prefaces his discussion with a brief interpretation of the phylogenesis of the reticular formation, which is characterized as an internal addition to the nervous system, in response to such externals as the cortex and the cerebellum. The caudal effects of bulbar reticular stimulation have already been described above, but it should be added that certain neurologists, notably Denny-Brown (1950), have submitted Magoun's methods and conclusions to a very vigorous criticism on the grounds that electroencephalographic and other electrical technics are entirely outside the realm of present understanding of the nervous system. He concludes that the results are not comprehensible and that no valid conclusions can be drawn. These criticisms have the virtue that they emphasize the possibilities of artifact, such as might be involved in stimulation of
the bulbar reticular formation; but the refusal to entertain the hypotheses based on these observations is surprisingly dogmatic. The logic of these negative criticisms is also weak if one takes the trouble to analyze it. The implication is that where no absolutely valid conclusions can be drawn, no conclusions should be attempted. This attitude denies the value of hypothesis and theory, which methods of scientific thinking are too well established in physics and biology to require any further justification. Finally, it might be pointed out that the requirement of absolute control in biological experiment is naive; for the most striking feature of living systems is interaction and interdependence.

Although the writings of Roussy and Mosinger (1935) were almost purely hypothetical, Magoun (1950) has given some concrete evidence which puts his conception of the reticular formation functions on a more than theoretical plane (81). Lloyd's work, for example, has given strong indications of a reticulospinal mechanism for the mediation of inhibition and facilitation (1941). He stimulated the ventrolateral white column of the spinal cord and read spike potentials of the motor cell pool from the anterior roots. From the records of latency and spike characters the conclusion is made that reticulospinal and long propriospinal fibers (Ad) carry impulses which weakly effect the motor cell pool directly, and which have powerful effects on the anterior horn cells through internuncials. Spikes read in the spinal gray show
prolonged, heightened activity in the internuncial pool corresponding to action potentials in the anterior roots (i.e. the motor pool). When the stimulus in the ventrolateral white column is three centimeters oral to the anterior root from which records are being taken, then the latency indicates that one synapse is involved, or that there is direct anterior horn cell stimulation. At distances greater than three or four centimeters the spike amplitude and latency of the anterior root response are greater, so that internuncial mediation must be active. Lloyd (1941) has shown that dorsal roots, corticospinals, vestibulospinals, and reticulospinals all effect the anterior horn cells most powerfully through the internuncial pool of the spinal cord. The diagrams on the next page are taken from Lloyd's paper (84), and will serve to summarize his findings.

Lettvin (82) found that stimulation of the bulbar reticular formation in the cat caused spikes in the intermediate cell pool of the spinal gray (internuncials) and in no other place. Likewise, stimulation of this site (checked histologically) caused inhibition of the knee jerk.

Lettvin and Dell (83) reported recording a large positive potential in the motor neuron pool during bulbar stimulation.

Woodburne, Crosby, and McCotter (80) have described connections between the reticular formation and the corpus striatum (see below) which might be involved to explain Magoun's theory.

Clinically, Magoun (1950) cites a host of diseases which might be understood on the basis of reticular cell pathology, including bulbar poliomyelitis. Tremors and spasticity might be malfunctions of reticular inhibition, for example. Tremors at rest have been produced in Monkeys by lesions of the medial mesencephalic tegmentum, between the red nucleus and the substantia nigra, in the subthalamus, and in the cerebellum (Ranson-quoted by Magoun) (81).
Figure 1
Redrawn from Lloyd—
showing reticulospinals
and short propriospinals
ending in the cord.

Figure 2
Redrawn from Lloyd (Journal of
Neurophysiology, volume 30, 1941)
Diseases causing abnormal cephalic reticular function may include changes in somnolence and cataleptic states. Ranson, Ingram, Barris (quoted by Magoun - 1950) obtained cataleptoid states in cats by lesions of the caudal hypothalamus, tegmentum, and the cephalic mesencephalon. The same results were duplicated in monkeys by Ranson, Peterson, Magoun, McCulloch, and Lindsley. The implication of these studies is that the reticular formation has some energizing and necessary effect upon voluntary movement.

Provisionally, then, the reticular formation may be looked upon as a mechanism for extrapyramidal motor effects of a facilitatory and an inhibitory nature, as well as for cephalic cortical effects of the same kinds.

The Red Nucleus

The red nucleus is a large, ovoid column of cells extending (in man) from the caudal margin of the superior colliculi to the caudal limit of the diencephalon. Small-celled and large-celled masses can be distinguished, although the caudally situated large-celled group becomes less conspicuous in Man and higher mammals.

The gross and microscopic anatomy of this nucleus was carefully described by Foix and Nicolesco (12) from whose book the following account is taken. The cells are predominantly small, being more densely aggregated dorsomedially. A rich dendritic network which is evenly distributed, intermingled with the cells, gives the red nucleus
its peculiar appearance. The cells are triangular and appear to be suspended on their thick dendrites, which show heavily staining neurofibrils in silver preparations, surrounded by lighter staining neurofibrils.

The cytoplasm stains weakly, showing fine granulations which are pigmented in the adult. Glial elements are predominantly satellite and microglial cells.

Foix and Nicolesco classify the connections of the red nucleus into "principal" and "accessory" tracts (1927): the principal connections are:

1. afferents - dentatorubrals, striorubrals, and possible corticorubrals.
2. efferents - the rubrospinal tract (doubtful in Man), rubrothalamics, and the central tegmental tract - composed of thalamic and fronto-rubro-olivary fibers.

Accessory connections include: optic fibers from the fountain decussation of Meynert, fibers from the medial longitudinal fasciculus, endings from the fasciculus retroflexus, and from the tegmental fasciculus of Gudden, the medial leminiscus, the mammillary peduncle, the substantia nigra, and finally from the prerubral field of Forel.

Hatschek (quoted by Kappers, Huber, and Crosby - 1936) interpreted the red nucleus as a derivative of two separate nuclei which he named parvocellular and magnocellular. Von Monakow (quoted by Verhaart - 1938) identifies the red nucleus in Man as the parvocellular mass.

Until 1946 the embryology of the red nucleus was not clearly understood. Foix and Nicolesco state that the nucleus is probably from the mesencephalon and the diencephalon, but they do not venture to give the exact cite of origin. Cooper (2) finds that the cells from the mid-
ventral proliferation migrate ventrolaterally towards the developing cerebellar fibers during the twelfth foetal week. Regarding pallido-rubral relations it may be significant that the putamen and the globus pallidus first begin to appear during the twelfth week. Cooper (1946) failed to find any striorubral fibers in his material.

It is well recognized that the red nucleus undergoes a phylogenetic progression in which the large-celled nucleus - first appearing birds - gives way to the small-celled mass which develops with the corticospinal system and becomes quite prominent in Man.

Weisschedels (quoted by Verhaart - 1938) states that the central tegmental tract has taken over the motor functions of the older rubrospinals, which theory Verhaart - 1938 questions since this latter tract does not end on anterior horn cells, and since it does have major connections with the inferior olive.

Verhaart's studies (1938) on the connections of the red nucleus in the Java monkey and in Man gave these results: 1. there are no direct connections between the globus pallidus and the red nucleus. Lesions of the ventral thalamus, the H_2 bundle, the combsystem, the globus pallidus, and the medial thalamus gave no rubral degeneration. 2. The frontorubral radiation is composed mainly of cerebellar fibers, while the medial radiation consists of fibers ascending from the interstitial nucleus of Cajal going to the thalamus (?). 3. Corticorubrals exist, but may not be direct. 4. The rubrospinals are inconstant in Man. 5. Lesion of the central tegmental tract in cats causes slight degeneration in the olivary capsule, while the same lesion in monkeys and in Man causes complete cellular degeneration of the inferior olive (Winkler). Verhaart concludes that the old red nucleus is a primitive
reflex motor system and that the small-celled nucleus of Man is a crossed-link in the frontal corticocerebellar pathway, independent of the corpus striatum. This independence is evidenced by the evolutionary transformations of the red nucleus as compared to the static nature of striatal phylogeny.

Papez and Stotler (54) studied the red nucleus in the baboon, the Mangabey and Macaque monkeys, the chimp, and in Man. They describe three efferent tracts: the uncrossed rubroreticular-olivary pathway, the crossed rubrospinal, and the crossed oculomotor connections. The magnocellular portion was found to be prominent in the subhuman primates studied, while the lateral and medial small-celled parts were well defined, but considerably smaller than in Man. The rubro-oculomotor tract, the shortest of these efferent tracts, originates in the medial segment and follows the medial longitudinal fasciculus closely, lying dorso-medial to the capsule of the red nucleus. It fires upon the oculomotor, trochlear, and perhaps the abducens nuclei. The authors suspect that tectal (visual) impulses may reach the medial rubral segment through the tract which Ogawa has called the tractus tegmenti medialis. The pretectal nuclei are not well developed in Man, however.

The rubrospinal tract arises from the caudal part of the lateral segment and receives some fibers from the large cells. It crosses the midline caudal to the red nucleus and descends in a lateral position close to the motor nuclei of the fifth, seventh, ninth, tenth, and eleventh cranial nuclei. In the spinal cord it lies ventral to the crossed pyramidal tract. Whether this tract is functional in Man is uncertain. Papez and Stotler cite the case of a senile woman with left sided spasticity, which, at autopsy, revealed marked reduction in the head of
the right caudate nucleus and in the medial segment of the red nucleus of the same side; while the caudal part of this nucleus was preserved bilaterally. They relate the patient's normal voluntary motor functions to the rubrospinal tracts—the corticospinals were severely damaged.

The rubroreticulo-olivary tract is large in Man, issuing from the lateral segment and descending to the inferior olive. Papez's view (1942) is that this tract carries accessory impulses to the cerebellum, reciprocal to the pathways of voluntary action—such as the corticostriatonigrostriate—olivary. He concludes that "the red nucleus occupies a central position in the tegmentum, connected on the one hand with the pallidum and on the other with the oculomotor centers and the motor nuclei of the spinal cord, and that, in addition, it has a separate action through the inferior olive to the cerebellum. This does not exclude the possibility of a rubro-reticulospinal connection with the motor nuclei of the spinal cord."

To explain the action of the red nucleus Papez applies a theory (54) of reciprocal motor innervation by the striatum and the cerebellum, such as the pallidorubral and pallidonigral pathways, which might indicate simultaneous excitation and inhibition in different parts of the cerebellum (an idea which is born out by cerebellar stimulation).

---

The Corpus Striatum

Various ideas concerning the significance of the corpus striatum (the caudate and lentiform nuclei) in brain physiology date back to the earliest descriptions of the basal ganglia; but systematic and experimental information did not begin to influence the subject until the end of the
last century, when technics of ablation and electrostimulation came into use. These methods were of the crudest sort and the results were understandably conflicting. It wasn't until some time after the turn of the century that the anatomical independence of the corpus striatum from the cortex was generally recognized, for Ferrier, whose book had a profound influence upon neurological thinking (1875), tacitly assumed that the basal ganglia were linked to the corticospinal pathway; and it was only with Fleschig, Charcot, and Wernicke that the actual anatomy became known. Since that time, as Wilson (1914) points out, opinion on striatal function has been somewhat divided and confused. It has been variously considered as a cortex-like motor organ, a center for "automatic movements", and as an autonomic center by different workers.

Certain facts seem to have been established before Wilson's systematic study (1914). Minor (1889) had convinced himself that the caudate and lentiform nuclei were electrically inexcitable and that the other effects had been due to irradiation of current into the internal capsule. Ziehen (1890) showed, also, that ablation of the motor cortex abolishes any muscular response to striatal stimulation. Bechterew repeated many earlier experiments and concluded that no automatic movements resided in the caudate and putamen, but that the pallidum was an extra-pyramidal motor nucleus.

Wilson's (1914) paper (76), from which the above history is taken, marks the beginning of a more refined type of experiment, using improved stimulators, the Horsely-Clarke stereotaxic instrument, and the method of histological controls. Although Wilson was clinically minded, his neuroanatomical research seems to have been the most careful of the period. His observations were followed, however, by a period which
neglected neuroanatomical investigation in preference for the clinico-pathological approach; and only recently has this basic weakness been rectified.

Wilson's findings (1914) make for a logical starting point in our discussion. Checking previous reports, he confirmed the fact that the caudate and lentiform do not give movement when stimulated, and he noted that the only lesion symptoms of the corpus striatum were contralateral clumsiness and a slight preference for the ipsilateral hand in voluntary movements. Regarding the fiber connections, he described striopetal connections with the subthalamus and the thalamus; striofugal fibers to the red nucleus, and the substantia nigra, and the optic thalamus. No corticostriate fibers were found, and it was concluded that the corpus striatum was a noncortical-like motor center controlling muscle (striped) tone through such extrapyramidal pathways as the striorubro-spinal. Wilson could find no reason to suppose that the corpus striatum acts vicariously in cases of cortical damage.

One of the important reasons for the dearth of results in striatal experiments seems to be that animals with a well developed cortex are used, so that striatal signs are masked by the intact neural mechanisms. It should be especially instructive, then, to consider the anatomical and physiological status of the organ in lower animals... A brief history of the telencephalon is included here because of embryological and possibly functional relationships between pallium and striatum. This material is based, for the most part, on the account of Kappers, Huber and Crosby (see above).

The prosencephalon of Amphioxus remains a simple, undifferentiated structure. The progressive developments in the Craniotes are represented
in the diagrams on the next page (from Kappers, Huber, and Crosby – 1936).

As the telencephalic wall differentiates, a dorsal pallium and a ventrolateral striatum are said to be distinguishable, as shown in the diagrams.

The corpus striatum of various fishes are connected to the dorsal thalami and to tertiary olfactory fibers, according to Herrick (1911), who calls the teleost striatum an olfacto-somatic organ. The globus pallidus arises from the area somatica of certain authors.

The lateral forebrain bundle of Reptiles contains thalamostriate, striotegmental, and striomesencephalic connections with the somatic striatum, though the polarity of these fibers is not certain.

Striotegmental, striorubral, striocerebellar, and striohypothalamic fibers have been described in Birds. Edinger divides the Bird striatum into ekcto-striatum, meso-striatum, and hyper-striatum (quoted by Rogers).

Rogers (61) studied instinctual patterns of behavior in pigeons whose corpora striata and cortices had been variously ablated. He found that only lesions involving both striate bodies caused behavioral changes.

It is generally agreed that the paleo-striatum is an olfactory structure represented in mammals by the head of the caudate nucleus, which is said to arise from the pallial (dorsal) telencephalon or perhaps from the ventral pallium (Kappers). The mammalian putamen arises ventral to the original site of the caudate and prior to it in time, while the globus pallidus arises before both of these nuclei, from the area somatica of the primitive ventral telencephalon.
Figures 3-8, from Kappers, Huber, and Crosby

TYPES OF VERTEBRATE TELENCEPHALONS

**Figure 3**

**Figure 4**

**PETROMYZONT**

**HOLUCEPHALAN**

**Figure 5**

**Figure 6**

**AMPHIBIAN**

**HOLOSTEAN**

**Figure 7**

**Figure 8**

**REPTILE**

**TELEOST**

Key:
- LDP - lateral dorsal pallium
- MDP - medial dorsal pallium
- S - septum
- ST - striatum
- EPI, ST - epistriatum
In Johnston's article on forebrain evolution (24) the dual origin of the vertebrate caudate nucleus from lateral and ventral (olfactory) telencephalon is shown. The dorsal caudate (neo-) is interpreted as the first phylogenetic thickening of the dorsal, pallium; a derivative of the area somatica.

Winkler (1930) described the embryology of the corpus striatum in Man. The figure appearing on the next page (from Winkler's article - Jf) shows the telencephalon of a 25 mm. embryo with three pairs of fissures, labelled according to Winkler's terminology.

The putamen and the globus pallidus are developed by the 55 mm. stage, but the caudate nucleus does not appear until the embryo has reached 87 mm., the posterior part differentiating and myelinating before the anterior. The oral direction of myelinization indicates that the putamen may rightfully be part of the paleo-striatum, or older than the neo-striatum at any rate.

**Anatomy**

**Gross Anatomy** — The caudate nucleus is commonly described as a comma-shaped gray mass with a long arching tail which ends in the ventral part of the amygdaloid nucleus. The head of the caudate bulges into the anterior horn of the lateral ventricle forming its lateral wall, and continuing in the same relative position to the body of the lateral ventricle posteriorly. At the collateral trigone it bends downward to become the tail. The tail passes around the posterior border of the internal capsule, curving downward and forward to form the roof of the
THE TELECEPHALON OF A 25MM. HUMAN EMBRYO
(redrawn from Winkler)

Figure 9

Key: 1-the fissure of Monro
2-fissure "x"
3-the lateral fissure (y)

Explanation—the classification of the basal ganglia has been based upon the supposed homologies of one of the above fissures with the sulcus limitans. See Kappers Huber and Crosby for a discussion of the problem.
inferior horn. Medially it is separated from the thalamus by the stria thalamus (terminalis) and the terminal vein. The internal capsule separates the head of the caudate from all but the anterior part of the putamen, with which part it is continuous. The anterior extremity of the head of the caudate is/with cerebral gray matter in the region of the anterior perforated substance. The Lentiform Nucleus lies embedded in the white substance of the cerebral hemispheres. It is a pear-shaped mass which does not extend as far anteriorly as does the caudate. Inferiorly it is separated from the inferior horn by the tail of the caudate and by the white substance of the roof of the inferior horn of the lateral ventricle. The lateral surface conforms closely to the shape and extent of the insular cortex, from which it is separated by the external capsule and the claustrum. The oblique surfaces are in intimate relation to the internal capsule superiorly and medially. In coronal and horizontal sections the lentiform nucleus resembles a bi-convex lens, the medial aspect being much more convex than the lateral. An external medullary lamina divides the lentiform into a lateral putamen and a medial globus pallidus.

The globus pallidus is a yellowish nucleus whose medial surface lies at the angle of the internal capsule.

The putamen is darker than the globus pallidus in gross appearance and is continuous anteriorly with the caudate. It is a concave-convex shape in horizontal section, the lateral surface being related to the external capsule.

Microscopic anatomy - Foix and Nicolesco (cited above) accepted the widely held view that the caudate and putamen comprised the neo-striatum; they describe the histology of these nuclei together since there are no differences.
In the caudate and putamen there is a dense arrangement of large and small nerve cells, which are in the approximate ratio of 1:20. The large cells are usually polygonal, with numerous dendrites which leave the cyton in various planes. The nucleus is pale and ovoid, revealing a large nucleolus. Irregular masses of chromatophil substance are found in the cytoplasm and neurofibrils are readily demonstrated in silver preparations. Some ten satellite cells are normally seen next to the cyton.

The small cells are densely packed triangular or polygonal cells with dark nucleoli inside pale nuclei. The cytoplasm has dust-like chromatin and no neurofibrils are seen with silver stain. These cells are normally pigmented in the adult.

The globus pallidus is entirely different in its cellular structure from the caudate nucleus and the putamen. There is a single type of large nerve cell which is diffusely distributed. These cells differ from the large cells of the caudate and putamen in that they are more fusiform and triangular; they have regular nissl granules; the dendrites are strikingly thick and travel in the same plane directly after leaving the cell; and finally, the dendrites form rich plexuses which are also joined by axons. Functionally, the fiber network of the globus pallidus is probably of the greatest importance. Satellite cells are rare and the neurofibrillar structure is not especially notable.

The neuroglia are mostly fibrous; and in general, the cells of the internal pallidal segment are larger than those of the external segment.
Myeloarchitecture

Bundles of myelinated fibers which pass through the corpus striatum, becoming more numerous medially, give this structure its familiar appearance for which it is named. The lentiform nucleus has a much more complex fiber composition, however, than does the caudate, in addition to which are two or more medullary lamina which divide the lentiform into its named parts.

The fibers crossing and originating in the caudate nucleus enter the internal capsule perpendicularly, to reach the lentiform nucleus. The externally situated fibers go along the dorsal external surface of putamen and enter the external medullary lamina by curving again at the ventral part of the putamen. The medial fibers of the caudate cross the internal capsule and follow the dorsal external surface of the globus pallidus to enter the internal medullary lamina. The internal fibers follow still another course, running along the capsular surface of the globus pallidus and joining the fibers leaving its apex.

The fibers from caudate to lentiform do not all run through the full extent of the medullary lamina; some of them end in the globus pallidus, while others turn medially to become radiating pallidofugal bundles. Fibers from the head of the caudate travel along the medial surface of the internal capsule to join the ansa lenticularis; others go directly to the thalamus and the infundibulo-suboptic region.

Radiating bundles are seen in the putamen, also, including paler fibers which are supposed to originate from the putamen itself. Some bundles enter the medullary lamina to terminate in the globs pallidus, while others join the ansa lenticularis.
The medullary laminae are usually two in number (external and internal), but accessory laminae are not uncommon in both parts of the lentiform nucleus. The external medullary lamina consists of a concentrated bundle of parallel fibers, some of which travel its whole length, while a greater number enter the radiating bundles of the globus pallidus.

The internal medullary lamina, dividing the globus pallidus into two segments, is larger and more complex than the external lamina. Its fibers contribute to the dorsal superior part of the internal pallidal segment as well as to the ansa lenticularis.

Before leaving the classical description of striatal fibers it is well to recall that the unmeyelinated fibers, which do not form definite bundles, are still to be elucidated.

Fiber Connections

Although no account of experimental sources is given by Foix and Nicolesco, their description of striatal connections is used here as a starting point in a historical discussion. A more detailed review of the experimental findings follows.

These authors (1926) preface their information with a reminder that the nature of the corpus striatum, the compact and intermingling fibers, makes an exact knowledge of fiber origins and terminations difficult to obtain, not to mention the presence of unmyelinated fibers.

1. The ansa lenticularis originates from the medullary laminae, collects into a bundle at the inferior pallidal surface, and runs medially to cross the posterior brachium of the internal capsule. Having crossed the capsule, the bundle turns caudally and spreads out fanwise. The medial fibers end in the outer thalamic nuclei, the hypothalamus, and the red nucleus, as well as in the mesencephalic reticular formation.
2. The lenticular fasiculus (H2 bundle) originates from radiating pallidal fibers (for the most part), the ansa lenticularis, and from the apex of the globus pallidus. These fibers from a compact bundle which arches medially, crossing the internal capsule and then turning caudally to lie dorsomedially to the subthalamic nucleus, the capsule of which it forms. The terminations of these fibers are mainly in the capsule of the subthalamus anteriorly, in the anterior periventricular nuclei, the hypothalamus, the zona incerta, and in the anterior pole of the red nucleus.

3. Strio-thalamic fibers include direct connections from the head of the caudate and from the globus pallidus, ending in the ventral external thalamus.

4. Strio-subthalamic fibers come directly from the radiating pallidal bundles, crossing the internal capsule and entering the external surface of the Subthalamic nucleus.

5. A bundle from the apex of the globus pallidus ("le faisceau pallidal de la pointe") runs directly to the supero-external pole of the substantia nigra and the stratum intermedium.

6. The thalamic fasiculus of Forel originates in Forel's field near the midline, in the angle formed by the mammillothalamic tract and the fasiculus lenticularis. After crossing the internal capsule it enters the ventral thalamus.

7. Commissural fibers travel in the commissure of Meynert, the anterior commissure, and the suboptic commissure of Forel.

8. Cortico-striatal fibers may exist, according to Cajal and Marinesco.

These are the connections of the corpus striatum, then, according to Foix and Nicolesco.
EXPERIMENTAL WORK ON THE STRIATAL CONNECTIONS

As in many problems concerning the extrapyramidal system, the connections of the corpus striatum are largely undetermined. Mettler has summed up the situation this way (1942):

"If one attempts to compare the most contemporary plans of extrapyramidal connections, such as those of the Vogts, Jacob, Kappers, Huber, and Crosby, Papez, Ranson, Bucy, and others, it is immediately obvious that many of these arrangements are mutually exclusive and a laborious task is imposed upon the investigator who personally attempts to determine the validity of any particular pathway."

Since the time of Foix and Nicolesco surprisingly few striatal connections have been elucidated, but some of the pathways which were suspected have been confirmed by more dependable methods. There has been a great deal of repetition in these confirmations, so that a complete review would be unduly long and unnecessary; an attempt will be made here to present the most significant findings which will indicate the status of each supposed tract at the present time.

Afferent connections. 1. the presence of corticostriatal fibers have been weakly indicated by slight degenerations in the caudate nucleus following cortical lesions. Cajal and Luys had supposed that delicate collaterals from the cortico-thalami might account for the fine neuropil in the caudate
nucleus. Verhaart and Kennard (1939) described what they called a questionable degeneration in the caudate nucleus and in the globus pallidus following thermocoagulation of area 4-s, and a heavy degeneration in the putamen following thermocoagulation of area 6 (72). Paul Glees (1944) confirmed these connections by the method of terminal bouton degeneration. In his material ablation of the strip areas gave degeneration to the caudate nucleus(15).

Dusser de Barenne and McCulloch had previously reported strychnine spikes in the caudate nucleus upon strychninization of area 4-s (1938) (9).

Dusser de Barenne, Carol, and McCulloch found that destruction of the caudate nucleus prevented cortical inhibition by stimulation of area 4-s (1942), suggesting that a reverberating circuit (cortico-caudato-thalamo-cortical) mediated inhibition. The cortical connections with the basal ganglia are diagrammed on the following page (taken from De Barenne, Carol, and McCulloch-1942. 8). The results pictured on this diagram were obtained by physiological neuronography, a technic which was introduced by Dusser de Barenne.
CORTICO-STRIATAL CONNECTIONS
(by physiological neuronography)

Figure 10

(from Dusser de Barenne, Carol, and McCulloch-1942, The Basal Ganglia)

Key:
E-external pallidal segment
I-internal pallidal segment
2- Thalamo-striate fibers have been described for lower animals (see section on comparative anatomy) and for man. They probably arise from the medial nucleus, the central medial nucleus (Kappens, 1936, Mettler, 1945, Crouch and Thompson, 1938), and from other medial and laminar thalamic nuclei. According to Papez (52) they go through the globus pallidus by way of the inferior thalamic peduncle. There is no strong evidence, as yet, for any of these thalamo-striate fibers; such connections, if proved, would argue strongly for a cortex-like relationship between striatum and thalamus. It may be, as Doctor Waller has suggested to me, that the corpus striatum furnishes a constant drive to motion in response to direct or secondary (nigric and subthalamic) sensory impulses; so that olfactory impulses in such creatures as fish or reptiles would stimulate a constant progression of movement through the subthalamus and the corpus striatum. Verhaart has expressed much the same opinion with regard to the primate striatum.

3- Nigro-striatal connections appear too be well established, although it had been thought that all the connections were in the other direction. One of the first to mention the possibility of nigro-striatal connections was Ferrare(11) who envisioned these as the efferent limb of a reflex arc from the cortex to the substantia nigra and thence to the caudate (1928). Ranson and Rabson found no degeneration with lesions of the caudate which might indicate nigro-striatals, but lesions of the substantia nigra did
give degeneration in the caudate and pallidum. They believe, however, that the connections are in both directions. Keller and Harris (1941) reported that the cells of the nigra disappeared when the midbrain was transected at an oral level, which they take to mean that ascending nigral fibers predominate[26] (57).

Kimmel (1942) found rostral degeneration in the internal capsule with lesions of the substantia nigra, medially placed lesions giving greater degeneration than lateral lesions.(29).

Rosegay (1944) studied these connections in the cat, using chromatolysis as the criterion for degeneration rather than the Marchi technique, which had given obscure results. His caudate lesions gave strong retrograde degeneration to the substantia nigra(62).

Fox and Schmits (1944) also described heavy nigral degeneration and degeneration in the entopeduncular nucleus as well, with lesions of the cerebral peduncles and the and parts of the globus pallidus[13).

From the preceding discussion it is obvious that a clear conception of the afferent striatal connections is still lacking. Attention might be called to a group of papers by Muskens (1913, 1922) which have some bearing on the subject at hand. Muskens made an intensive anatomical study of the dorsal longitudinal bundle of Schmitz, which he found to carry six different fiber
tracts, including ascending vestibulospinals from the nucleus of Deiter's. He also found that lesions of Cajal's interstitial nucleus caused pallidal degeneration and that lesions of the oral pallidum or of the dorsal longitudinal bundle caused circus movements in his animals (cats). According to Strong and Elwyn the dorsal longitudinal bundle contains fibers from the periventricular gray matter of the hypothalamus and from the dorsal reticular tegmental nucleus of the mesencephalon, which, in turn, is associated with olfactory and visceral impulses through the interpeduncular nucleus and the mammillary bodies (41, 50).

**Interstriatal connections** are well known and include striopallidals from the head and tail of the caudate nucleus (Papez-52).

**Efferent striatal connections**

1. Striopallidals have already been mentioned above.

2. Strionigral fibers have been described by numerous authors and have been confirmed by Mettler-1935-, Papez-1938-, and many others.

3. Pallidorubral connections are uncertain. Mettler (1942) and others claim to have found them, but Verhaart's thorough search for the same fibers in monkeys failed (see discussion of red nucleus).

4. Pallidoreticular fibers are as yet unproved, but Verhaart (1938) and Mettler (1942) strongly suspect their existence, as does Papez (1938).
5. Pallido-subthalamic fibers have also been well established and have been fully described under the account of Foix and Nicolesco-1927.

6. Pallido-hypothalamic tracts are well known, having been reported and confirmed by Foix and Nicolesco (above), Vidal (73), and Woodburne, Crosby, and McCotter (80). The last named authors also showed pallidal fibers ending in Forel's field and in the lateral tegmental nucleus. Guillain and Bertrand (1933) quote Fleschig as having mentioned lenticulo-olivary connections, and these same authors found such fibers in the central tegmental tract of cases with athetosis. Morgan (1927) described a strio-bulbar tract in carnivores, but no confirmation has been made, despite several attempts (45).

PHYSIOLOGY OF THE CORPUS STRIATUM

General opinion concerning the function of the striate bodies has been necessarily speculative, for the anatomical connections, as we have seen, are unsettled. The terminology has been very loose, especially regarding the so-called associated movements, which are never defined. On the whole, no clear explanations have been brought forth; but a considerable amount of "hemming" and hawing has been done by way of theory.
A brief review of pathological and physiological information is given here, with the reminder that the methods used are quite indirect, variable, and difficult to interpret with a great deal of supplementary data.

Dana (1908) discussed what he thought to be the cardinal signs of striatal injury and concluded that the corpus striatum is functional in lower animals, but of minor importance in man. He ascribed the so-called associated movements to this gray mass, which attitude persists today.

Wilson (1914) envisioned the striatal impulses as joining the final common pathway to effect striped muscle tone. His work was on monkeys as well as in the clinic.

Mella (1924) produced changes in the liver and in the basal ganglia by intraperitoneal injection of magnesium chloride and observed choreoathetoid movements as a result (monkeys used).

Jacob's article gives one of the important reviews of the extrapyramidal syndromes, although no new ideas are forwarded. The classification (1925) followed that of Wilson very closely, and may be summarized as follows:

1- mild pareses of voluntary movement, with a greater loss of synergic than of isolated movements (Wilson questioned the value of the term "voluntary", but it is as well entrenched in the neurological jargon as any other term one can think of)

2- muscular incoordination.

3- poverty of movement (as Wilson called it-1925), that is, the patients level of motor activity is low and more conscious effort is required to execute movements,
4—tremors and other involuntary movements (parakinesias).
5—rigidity, in cases in which the pathology is slow in onset.
6—flaccidity, in cases of acute (apoplectiform) lesions.
7—signs of autonomic nervous imbalance.
8—changes in emotionalism.

Lesions of the globus pallidus, according to Jacob's schema (1925), cause athetosis and torsion spasms, with contralateral rigidity; no autonomic changes are seen. His explanation of adventitious movements is the same as Wilson's (1914); that is, the unmasking of the old motor system (122) (76).

Morgan (1927) placed lesions in the cat's caudate nucleus and observed hypertonus, circus movements, dysphagia, and restlessness (hyperkinesia). He suggested that the primitive, complex motor sequences, such as the child's nursing behavior, speech, or walking are all striatal and cortical in varying degrees of interdependence. Morgan also stated that some of the striatal symptoms might result from irritation (hyperfunction) rather than destruction (46).

Verhaart, in 1938, published one of the most instructive studies on the extrapyramidal pathways, in which numerous degeneration experiments in monkeys were correlated to clinical material. This worker considers the corpus striatum as a vegetative organ of motor function, independent of other motor centers (cortex). He lists the autonomic signs in striatal injury, including the interesting case of a young girl with post-encephalitic parkinsonism who showed a complete remission of her motor symptoms.
at night. The autonomic control of striped muscle tone has been
a question of considerable significance since Sherrington's
demonstration of muscle contraction in response to stimulation of
autonomic fibers (quoted by Verhaart-1938). Marinesco (also quoted
by Verhaart in 1938) considered vagotonus a constant feature of
extrapyramidal disease. Verhaart's interpretation, then, is that
the corpus striatum regulates the "mood of the muscles" or the
"zest for work": such a notion implies an indirect, but constant
extrapyramidal contingent in all movements of striped muscle(71).

Mettler(1939) also emphasized the affective quality of the
extrapyramidal syndromes. Mettler's stimulation and ablation
experiments form a substantial part of the literature on these
phases of the problem. Some of his results are given here:
1- Stimulation of the caudate always reduces cortically induced
movements. The same action, in a weaker form, obtained with the
putamen and the claustrum.
2- Stimulation of the globus pallidus alone gives no movement,
but it causes an arrest of cortically induced movements.

Davison (1942) noted that all of his cases with tremor or
rigidity showed lesions in the nigra compacta and in the globus
pallidus(5) He claimed that lesions of the substantia nigra alone
were the cause of tremor.

These several physiological and pathological observations
have been made repeatedly, but the mechanisms are still to be
clarified by anatomical information.
THE SUBSTANTIA NIGRA

The substantia nigra is a large gray mass lying dorsal to the cerebral peduncles. It extends orally to the junction of the mesencephalon and diencephalon, and caudally to the oral pontine level. In cross-section lateral, middle, and medial cell groups are seen (comprising the zona compacta). A zona reticularis lies embedded in the deeper fibers of the cerebral peduncle. The cupuliform is also included in the substantia nigra by certain authors (Rosegay 62), because of cell similarities and of similar connections.

In addition, Ferraro (1928) finds a nucleus linearis oculomotorius in the cat and possibly in man, which he thinks is a mesial extension the the substantia nigra(11).

Malone (1913) distinguished sensory and motor type cells in the substantia nigra, the latter being termed the intrapeduncular nucleus. The cells of the zona reticularis are definitely of the motor series according to Malone, who has emphasized the importance of cell structure in identifying the functions of nuclei in the nervous system. The cells of the substantia nigra, for example, are sensory and motor. Not only are the cells of the intrapeduncular nucleus of the motor type, but they are also continuous, anatomically, with pallidal and pontine reticular cells of the same kind(33).

Morgan (1928 1928) classified the nigral cells into the lateral motor cells, the middle group (sensory according to Malone), and a medial group receiving subthalamic fibers.
The neurones of the substantia nigra are large multipolar, elongate cells with numerous branching dendrites (Foix and Nicolesco 1927);

The embryology of this area was clarified by Cooper in 1946 (1), before which time it had been attributed to the mesencephalon, the diencephalon, and to both of these areas. Kappers, Huber and Crosby (1936) classify nigra and pallidum as "vegetative" because of their supposed origin near the sulcus limitans.

Cooper found that cells from the mid-ventral proliferation migrate towards the cerebral peduncles during the seventh to eleventh foetal weeks, at the end of which time a dorsal corpus and a ventral cauda are differentiated. At mid-term a new stratum develops, between corpus and cauda, called the caput (1).

THE CONNECTIONS OF THE SUBSTANTIA NIGRA

Corticonigral and pallidonigral fibers have been considered to be the afferent fibers to the substantia nigra, while nigrosegmentals and nigropedunculars are said to be the main efferent connections.

Ferraro (1928) attributes the description of corticonigral to von Monakow, who evidently overlooked the striatal lesions in his motor ablations. Ferraro (1928) is one of the first to suggest that nigrostriatal fibers existed, forming an efferent arc in a cortico-nigro-striatal system (11). Nigrosegmental fibers were described by Foix and Nicolesco (1927).
Papez's schema of the extrapyramidal pathways (1942) places the substantia nigra as a link in the descending system of pallidals, as Jacob had diagrammed (55) (22).

Regarding the polarity of nigrostriatal connections, Ranson and Ranson (1941) found no nigral degeneration with lesions of the caudate, putamen, or pallidum; but lesions of the substantia nigra did give ascending degeneration to the pallidum through the internal capsule. These authors suspect that ascending degeneration had been masked in their materials and that nigrostriatals may exist (57).

Keller and Harris (1941) reported that the cells of the substantia nigra disappear when the mid-brain is transected at an oral level, indicating the predominance of ascending fibers (26).

Kimmel (1942) found rostral degeneration in the internal capsule with lesions of the substantia nigra, the degeneration being greater for medially placed lesions (29).

Rosegay (1944) used cellular chromatolysis as a criterion for retrograde degeneration and confirmed the nigrostriatal connections (62) (5).

It seems justifiable, then, to assume ascending and descending nigrostriatal connections.

Cooper found nigroretinal, nigropeduncular, and subthalamo-nigral fibers in his foetal preparations (1).

As to the function of the substantia nigra, I have not found any attempted explanations in the literature. The idea that the connections may be mainly ascending is rather recent and will certainly alter any theories of function (5).

Stimulation of the substantia nigra causes increased extensor tonus (Wettler-1939).
THE SUBTHALAMIC NUCLEUS OF LUYS

This gray mass lies oral to the substantia nigra and dorsal to the cerebral peduncles, which separate it from the globus pallidus. The neurons are medium sized multipolar cells, densely packed in a myelinated neuropil (Papez, 1942). Cakal (1909) described the cells as spindly shaped, with a fine, unevenly arranged chromatrin.

The connections - Morgan (1927) described the subthalamic fiber connections for the dog as follows (47):

Afferents - 1. Collaterals from the internal capsule (Mirto 1896).
2. Pallidal fibers from the subthalamic fasiculus.
3. Medial leminiscal fibers.

Efferents - 1. A descending subthalamic tract dorsomedial to the subthalamic nucleus.
2. Commisural fibers.

Papez (1938) described the course of the subthalamo-tegmental tract, which descends along the ventral aspect of the medial leminiscus, to end in the lateral tegmental nucleus of the midbrain (52).

Glees and Wall (1946) studied subthalamic connections in monkeys and found afferents from nigra to the pallidum. Efferents were mainly to the pallidum, ventral thalamic and centromedian thalamic nuclei. Commisural connections occur through the ventral tegmental decussation, and the supramammillary commissure. These same authors suggest that the subthalamus is an oral extension of the substantia nigra, closely related to the pallidum—perhaps reinforcing the pallidal suppressor circuit.
Physiology of the subthalamic nucleus—Mella (1923) had noted that walking movements persisted in his cats in all transections which left the subthalamus in tact (37).

Morgan (1927) injected magnesium chloride intraperitoneally in monkeys with resulting liver and basal ganglia damage which was accompanied by hypertonia. He considered this nucleus a center for automatic walking movements, working with the corpus striatum (47).

Waller (1940) found that stimulation of a very localized area in the subthalamus (not in the corpus Luys, but near it) caused smooth walking movements in the cat, indicating that the subthalamus may regulate the order of limb movement in progression by way of a descending, nonpyramidal pathway (75).

..............................
THE CORTEX

Since the time of Ferrier and Hitzig (1898), investigations of the cortex have greatly overshadowed interest in the more deeply placed basal ganglia; but our subject has fallen heir to certain information secondarily, through the discovery of extrapyramidal cortical effects.

Essentially, the extrapyramidal system has been conceived as the pre-cortical motor mechanism or mechanisms; so that cortical extrapyramidal effects reflect the motor domination of all cortical activity according to this interpretation.

The present idea of the extrapyramidal cortex stems largely from Tower's paper (1936) in which the extrapyramidal system was defined simply as the cortico-bulbospinal pathways as opposed to the direct corticospinal.

Tower mapped out various cortical inhibitory and motor areas which were active when the pyramidal tracts had been cut. The lateral pre-cruciate areas of the cat's cortex were found to inhibit muscle tone, while the frontal and sylvian areas inhibited movement. In general, the extrapyramidal movements were slower in onset and more massive in distribution as compared to the quick, isolated pyramidal stimulated movements. Tower theorizes that the cortex integrates these two types of activity into synergic movements (67).
Mettler described the cortical connections in the macaque (1935). His materials showed corticorubrals and cortico-olivaries from the frontal cortex; cortico rubrals, corticopontines, and corticonigral from the parietal cortex; and corticorubrals, corticopontines, and cortico nigral from the temporal cortex; these were demonstrated by tracing degenerating fibers in cortically ablated animals (39).

In another paper (1947), Mettler plotted the extra-cortical projections according to cortical areas as follows (42):

Area 8 - a few fibers enter the subcallosal fasciculus, the medial thalamic nucleus, and the medial pallidal segment.

Area 6 - sends fibers to the septal nuclei, the putamen, the pallidum, the reticular thalamic nuclei, the medial thalamic nuclei, the anteroventral part of the lateral thalamic group, the posterior hypothalamic area, Forel's field H, the substantia nigra, the oculomotor complex, the mesencephalic, pontine, and medullary tegmentum, and to the inferior olives.

Area 4 - The rostral part of area 4 may send fibers to the red nucleus, and to the medullary tegmentum; the caudal part fires into the cord, lateral thalamic nuclei, the substantia nigra, pontine nuclei, reticular nuclei, and to the motor nuclei of the brain stem.

Area 4-s fires into the red nucleus and the centromedian area of the thalamus.

In 1948 Mettler confirmed the above results in a series of stimulation and ablation experiments on the frontal cortex of the monkey. He suggested that the extrapyramidal action was to create postural background for more exact (pyramidal) movement, much the same way as Tower had intended.
Denny-Brown (1950) has written an extremely careful analysis of the status of our knowledge concerning the cortex and motor functions, in which certain terms (voluntary movement, cortical "area," and functional centers) are submitted to critical discussion and shown to be inadequate (Lashley had made many of the same points in his 1924 article—6). Denny-Brown's conception of motor action is that area 4 serves to maintain a background of motor excitability (also Lashley 1924). His article (1950) is an invaluable chronicle of present day trends in motor physiology and of some of the important methodological fallacies which have grown out of contemporary thinking.

Finally, the cortico-ponto-cerebellar pathways must be mentioned, for they are well established fibers which may have important motor functions, as Papez has suggested (1942). Their theoretical significance will be discussed in the concluding section, which follows.

CONCLUSIONS AND SUMMARY

Several different conclusions have been quoted in the course of this thesis on the extrapyramidal pathways and motor function. It has been evident at every turn that the absence of sufficient evidence greatly hampers speculation and that many of the details of structure are not agreed upon. There are certain themes in many of the theories discussed which have been repeated often enough to emphasize here.
Wilson's analysis (1914) of the extrapyramidal diseases has had a lasting effect upon the neuropathological classification of these diseases. Disturbances of tone and movements are still the prime considerations in the clinical approach today.

Hunt (1920) elaborated the idea of old and new motor systems, as Sherrington and Wilson had done. Hunt was interested in the dual innervation of muscle and the duality of muscle structure, itself, which might reveal an overall system of tone central and regulation of movement (18). He hypothesizes a paleostatic system in the form of the cerebellum, and a paleokinetic system in the corpus striatum. The neokinetic system is represented by the cortex and the corticospinal pathways.

Lashley (1924) and Denny-Brown (1950) have emphasized the Jacksonian view of the brain as an essentially "integrative" mechanism, rather than a composite of separate systems. Although they do not disagree with the idea of dual motor function, they object to the artificial separation of static and kinetic actions.

von Bonin envisions the extrapyramidal system somewhat as an electrical circuit:

"The extrapyramidal system appears to be essentially a complicated servomechanism, supporting the steering of the final common pathway by the pyramidal system."

An idea which is of considerable interest is one which interprets the striatum as an energizing force contributing to the energy level of motor activity in the central nervous system. Verhaart (1938) has emphasized this view.
The linking of the corpus striatum and the reticular system, which has also been referred to as an energizing mechanism is another facet to this kind of theory. The intention seems to be to ascribe the drive to movement, in the sense of forward progression (as a fish or salamander progresses) to the extrapyramidal system, perhaps piloted by the corpus striatum.

As for the connections of the extrapyramidal systems, these appear to be the immediate problem which deserves the attention of experimentalists. If such details are made sufficiently clear, it may be possible to make a more meaningful generalization concerning extrapyramidal function. Perhaps the reticular outflow will be an answer to the question of pathways.

For the present, little can be said with certainty of the nature of the extrapyramidal pathways and their contribution to motor function.
BIBLIOGRAPHY


57. Ranson, S. W. and Ranson, S. W., Jr., 1941: Strionigral or Nigrostriatal Fibers? Tr. Amer. Neurol. Assoc. 67: 167.


78. Wilson, S., 1925: Disorders of Motility and of Muscle Tone, with Special Reference to the Corpus Striatum. Lancet, 2: 209.


Supplement


84. Lloyd 1941 Reticulo-spinal tracts in the spinal cord. J. of Neurophysiology, 20: 115.