AN EXPERIMENTAL STUDY OF THE STRIO-NIGRAL RELATIONSHIP IN THE CAT BRAIN

By

Donald Truman Smith, B.S.

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TABLE OF CONTENTS

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INTRODUCTION

Anatomical interest in the connections of the corpus striatum was greatly stimulated near the beginning of the twentieth century by the development of the concept of the extrapyramidal motor system, and the implication of this system in various clinical syndromes. Much of the anatomical basis for these early clinical interpretations was provided by the studies of Edinger(1), Holmes(2), Dejerine(3), and others, comprising normal and pathological human and experimental animal material.

Wilson(4,5), in his classical study of the lentiform nucleus and its projection fibers, produced one of the first purely experimental investigations designed to elucidate the definitive connections of the corpus striatum. Extensive descriptions of the extrapyramidal motor system, including the corpus striatum, and particularly its diencephalic and mesencephalic relationships, have also been made by Winkler and Potter(6), Morgan(7), and Bioch(8) in carnivores (cat and dog), Papez(9), Ranson and Ranson(10), and Mettler(11) in the monkey and baboon, and Hunt(12), Jakob(13), Foix and Nicolesco(14), Papez and Stotler(15), and Papez(16) in the human.

It is an interesting observation that the earlier, and now more classical, authors have almost universally considered the relationship between the corpus striatum and substantia nigra to be a descending one, either directly strio-nigral, as described by Edinger(1), Riese(17), and especially Papez and Handles(18) and Papez(9,16,19), or indirectly strio-pallido-nigral as described by most others.

A notable exception is the experimental study of Ferraro[20], who observed that degeneration of the cells of the substantia nigra resulted from striatal extirpation, and concluded this to be a retrograde, or Gudden type, degeneration resulting from the destruction of axon terminals of the nigral cells. More recently, using Marchi and Nissl preparations of experimental material, ascending nigral projections to the corpus striatum have been described by Kimmel[21], Fox and Schmitz[22], and Rosegay[23] in the cat and by Ranson and Ranson[24] and Mettler[11] in the monkey and baboon.

These apparent contradictions clearly show that evidence has not yet been presented which conclusively demonstrates the relationship between the corpus striatum and the substantia nigra. The purpose of this investigation was to attempt to do so by the experimental method.

MATERIAL AND METHOD

Healthy young cats, weighing between 1.4 and 2.0 kg. were employed as the experimental animal. Using intraperitoneal Nembutal for anesthesia, unilateral manual lesions were produced by a wire loop curette, or unilateral lesions were made electrolytically with the Horsely-Clarke stereotaxic instrument. The following lesions were made: partial and total manual destruction of the head of the caudate nucleus, partial electrocoagulation of the head of the caudate nucleus, total electrocoagulation of the putamen and globus pallidus, electrocoagulation of the mesencephalic tegmentum, electrocoagulation of the substantia nigra, and extirpation of the cerebral cortex and underlying projection fibers anterior to the coronal sulcus.

An appropriate period, varying from ten to thirty days depending upon the type and amount of neuronal reaction desired, was allowed for degeneration. The animals were sacrificed by the administration of a lethal dosage of Nembutal. They were quickly perfused with a 15% solution of formalin to insure immediate and adequate fixation. The brain was then removed, and further fixed in 15% formalin for seven days. Following dehydration and paraffin imbedding, the blocks were sectioned at between twenty and thirty microns. A series of every tenth section was stained by the intensified Protargol method as described by Stotler[25], and wherever indicated, a parallel series was stained with Carbo-thionine to demonstrate cellular changes resulting from the above lesions.

Studies previously mentioned in the introduction have relied on the accepted Weigert, Marchi, and Nissl type preparations for analysis of their material. The use of silver staining techniques has been extensively applied by Cajal[26] in his investigations of the normal nervous system and by Glees and Le Gros Clark[27], Brodal[28], Stotler[29], and Nauta[30] in experimental studies of the optic, auditory, and other major fiber systems. The use of silver stained preparations in this study was prompted by the acknowledged superiority of this method for the demonstration of axonal, fine fiber, and terminal ending degeneration.

While many more animals were used during the course of the experiments, the histological analysis of only eleven lesions will be described to illustrate the results of this investigation.

OBSERVATIONS

In the histological study of all of the silver preparations, primary degeneration of efferents appeared as swollen, darkly staining, grossly fragmented fibers. Similarly, degenerated fine neuropil appeared as a marked clearing of the neuropil with the resultant deposition of a finely granular, argyrophilic debris. Depending upon the length of the survival period, degeneration of terminals appeared as black, swollen boutons or was represented by the complete absence of terminal endings.

Evaluation of cytological changes resulting from various lesions has followed the usual criteria; alterations of the staining characteristics of the cytoplasmic Nissl substance and nuclear chromatin material, eccentricity of nuclei, shrinkage of the cell mass, disruption and fragmentation of cytoplasmic and nuclear material, and loss of normal cell distribution and population.

Cat C1. Manual lesion; 21 day degeneration.

This lesion destroyed the entire head and more rostral portion of the body of the caudate nucleus. It also included by direct trauma and vascular extension the adjacent portion of the internal capsule, the corpus callosum, and the more anterior and lateral areas of the thalamus.

There was an extensive degeneration of fibers passing ventrolaterally through the internal capsule and into the dorso-lateral pole of the globus pallidus. The more medial portions of this nucleus were devoid of neuropil, being completely replaced by the granular

debris. Fiber degeneration then passed in a dorso-medial direction into the ventral internal capsule, traversed it for a short distance, and extensively involved the entire entopeduncular nucleus. A reduced, discrete bundle of degenerated fibers passed from the entopeduncular nucleus, having a caudal and ventro-medial course, and came to lie within the more medial portion of the rostral cerebral peduncule. Passing caudally in the comb system of the peduncule, degenerated fibers moved dorsally to involve both the pars reticulata and pars compacta of the substantia nigra. This nucleus showed very extensive degeneration of all but its most lateral extent. Neuropil and terminal endings could not be found within the area of degeneration. No degeneration was seen below the caudal limits of the substantia nigra.

There was also an extensive degeneration of the type previously described in the regions of the medial ventral, centrum medianum, parafascicular, reuniens, ventral, and lateral thalamic nuclei.

Analysis of the sections prepared with Carbo-thionine showed only moderate changes in the cells of the homolateral substantia nigra. These changes were not dramatic in either the extent or the degree of reaction. There was, however, in the homolateral globus pallidus, entopeduncular nucleus, and substantia nigra a very extensive glial proliferation within the areas of fiber degeneration.

Cat C2. Electrocoagulation lesion; 21 day degeneration.

This lesion destroyed approximately the dorsal two-thirds of the entire head of the left caudate nucleus. There was no lateral involvement of the internal capsule or posterior involvement of the

thalamus, but frontal radiation fibers were destroyed by the electro-coagulation.

On the side of the lesion a unilateral, relative, internal hydrocephalus was seen, due to a marked reduction in caudate mass. There was considerable clearing of neuropil and deposition of granular debris throughout the remaining ventral portion of the head of the caudate nucleus. Many discrete pencils of fine caudato-fugal fibers were entirely degenerated, leaving a fragmented, granular pattern of their former ventro-lateral course through the caudate nucleus and internal capsule.

Running along the lateral margin of the internal capsule, medial to the putamen, these degenerated fibers entered directly into the dorso-lateral border of the globus pallidus, but did not traverse the external lamina of this complex. The globus pallidus was diffusely and extensively involved, especially its more medial portion; being almost completely cleared of neuropil and having only a granular debris as a substratum for the remaining cells. Degenerated fibers could be followed through the capsule, passing directly into the entopeduncular nucleus. The afferent fibers of the entopeduncular nucleus were likewise almost entirely degenerated as were those of the medial globus pallidus.

Degenerated bundles of fibers then passed into the more medial portion of the rostral cerebral peduncule, and in the same manner as described for Cat C1, continued into the substantia nigra, distributing to both the pars reticulata and pars compacta of that nucleus.

Again the homolateral medial ventral, centrum medianum, para-

fascicular, reuniens, ventral, and lateral thalamic nuclei showed afferent, primary degeneration.

A parallel series of sections stained by the Nissl method showed only moderate degenerative changes in cells of the substantia nigra, which were located in the areas of fiber degeneration.

Marked gliosis involving the globus pallidus, entopeduncular nucleus, and substantia nigra was also present in this brain.

Cat C3. Electrocoagulation lesion; 21 day degeneration.

This lesion destroyed the dorsal one-third of the head of the left caudate nucleus. There was no lateral or posterior extension of the lesion outside of the limits of the caudate nucleus, but it did encroach upon, and destroy, some of the fibers of the frontal radiation and the corpus callosum.

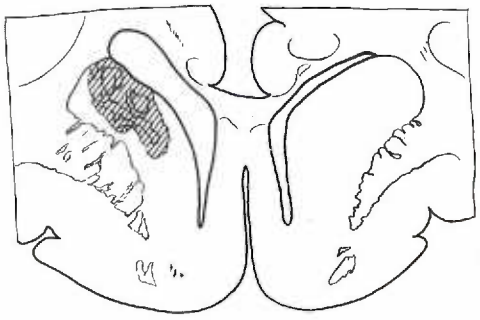
Although quantitatively not quite as extensive, the observed histologic effects of this lesion were identical to those described for Cat C2.

Cat C4. Electrocoagulation lesion; 10 day degeneration.

This lesion destroyed the dorsal one-half of the head of the left caudate nucleus. Again, there was extension of the lesion forward into fibers of the frontal radiation.

Sections stained with the Protargol technique showed clearly the same pattern of degeneration as described above for the twenty-one day survival animals. Degeneration of striatal efferents was marked, but the clearing of neuropil and its replacement by the argyrophilic debris was not as complete as that seen for the longer survival

Figure 1. A series of six drawings made from representative sections. Drawing (1) shows a typical area of a caudate nucleus lesion (slanting lines). The resulting degeneration (stipple) of the afferents to the (2) globus pallidus and the (3) entopeduncular nucleus, the (4) fibers in the medial cerebral peduncule, and (5,6) the afferents to the substantia nigra are shown to describe the descending strio-pallidal and strio-nigral pathways.



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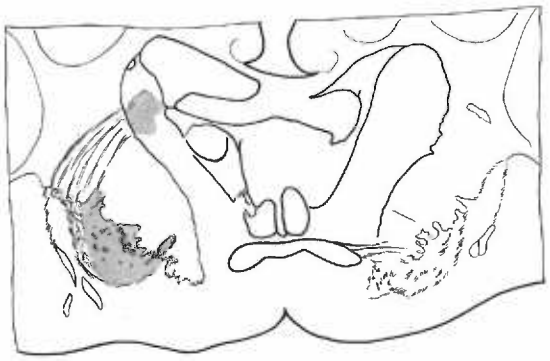

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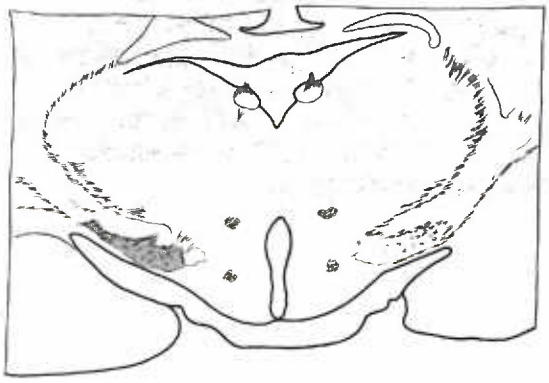

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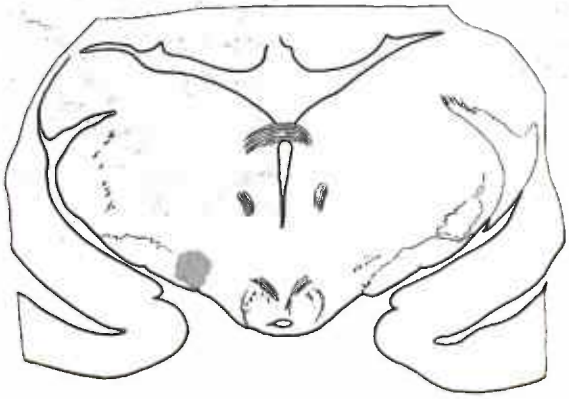

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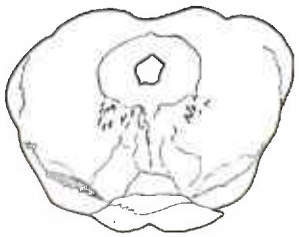

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period. Many swollen terminal boutons could be seen in relation to the nigral cells.

A study of the Carbo-thionine sections failed to show any degenerative changes in cells of the substantia nigra, and there was present only a slight increase of glial elements.

Cat C5. Electrocoagulation lesion; 30 day degeneration.

This lesion destroyed approximately one-half of the more posterior portion of the head of the left caudate nucleus. It was unique in that the entire lesion was confined within the limits of the nucleus. No other structures were involved. Histological analysis of the silver stained sections revealed the same descending striatal degeneration as seen in the first four preparations. The loss of afferents to the globus pallidus, entopeduncular nucleus, and substantia nigra fully corroborated the previously described observations.

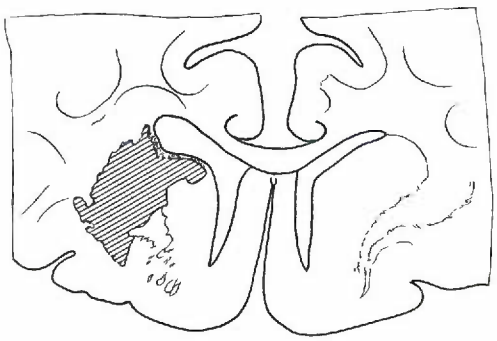
However, this brain failed to show any evidence of degeneration within the thalamus.

Carbo-thionine sections revealed only moderate cytologic changes in cells of the substantia nigra. There was again a marked gliosis of the nuclear areas containing degenerated afferent fibers.

Cat P1. Electrocoagulation lesion; 12 day degeneration.

In this animal the lesion was placed along the extent of the left putamen. The primary electrocoagulation destroyed not only the entire putamen, but also the lateral globus pallidus and the striofugal fibers lying near or within the destroyed nuclei. In addition,

Figure 2. A series of six drawings made from representative sections. Drawing (1) shows an anterior area of infarction (slanting lines) seen in Cat P1 and (2) shows the most posterior extent of lesion P1 (slanting lines) and the resulting degeneration (stipple) of afferents to the entopeduncular nucleus. Drawings (3-6) show the areas of destruction (slanting lines) seen in Cat T1 at various planes of the brain stem.



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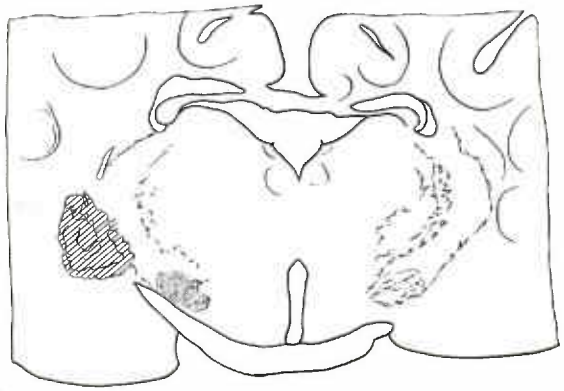

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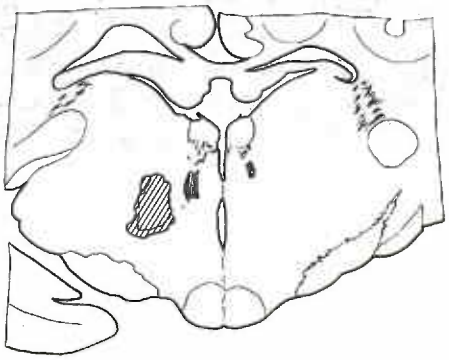

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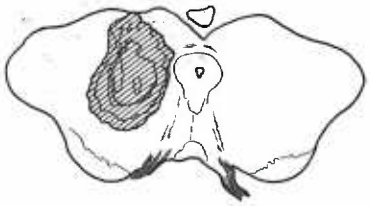

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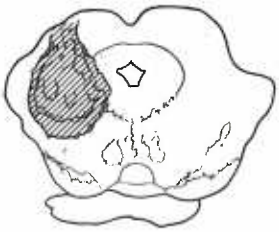

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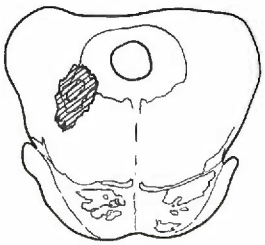

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there was seen both grossly and microscopically a typical vascular infarction involving the adjacent internal capsule and an extensive dorsal portion of the anterior head of the caudate nucleus.

Homolateral degeneration of entopeduncular and nigral afferents followed the same course as described for the previous caudate lesions. Degeneration within the substantia nigra was most marked at its middle and lateral portion, and many nigral cells could be seen to have numbers of swollen bouton terminals undergoing degeneration.

The subthalamic nucleus on the involved side had a very moderate loss of neuropil, and the entire lateral aspect of the thalamus contained degeneration granules.

Examination of the Nissl preparations showed no real evidence of cytologic changes of the nigral cells, although there was a moderate gliosis involving the entopeduncular nucleus and the substantia nigra.

Cat P2. Electrocoagulation lesion; 12 day degeneration.

This lesion represented an altered technique in an attempt to avoid the complication of infarction seen in lesion P1. Instead of the usual vertical insertion of the electrode along a series of frontal planes, a posterior, horizontal approach was used. However, the resulting lesion was identical to its fellow in that it destroyed the putamen and lateral globus pallidus and infarcted the anterior internal capsule and dorsal head of the caudate nucleus.

The degeneration pattern was likewise identical to that described for Cat P1.

Cat F1. Extirpation lesion; 12 day degeneration.

In this lesion the entire left sigmoid gyrus was removed and the left anterior sigmoid gyrus undercut by destroying the more dorsal fibers of the frontal radiation. As nearly as could be determined, the gyrus Proreus and its projections were not involved.

An extensive degeneration could be seen in the lateral one-third of the homolateral head of the caudate nucleus, and there was marked efferent degeneration into the entire ventral and lateral nuclear complex of the thalamus. Although the internal capsule showed diffuse involvement of its fibers and the left cerebral peduncule was seen to be diminished in size and number of fibers, no evidence could be seen of degeneration extending into the globus pallidus, the entopeduncular nucleus, or the substantia nigra.

Cat I1. Electrocoagulation lesion; 12 day degeneration.

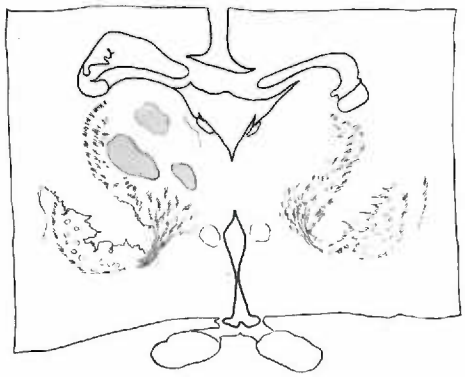
This was an extensive lesion placed in the rostral one-half of the left lateral mesencephalic tegmentum. A small portion of central grey and a considerable portion of the superior colliculus were involved, but the red nucleus, the substantia nigra, and the lemnisci were entirely spared. In linear extent the lesion involved an area projecting forward from the inferior colliculus to the posterior thalamus.

Nissl sections of the nigra failed to show cellular changes which could be interpreted as evidence of degeneration.

Cat S1. Electrocoagulation lesion; 21 day degeneration.

This lesion was also made by the posterior approach, as previously described, and directed through the dorsal medulla and

Figure 3. A series of six drawings made from representative sections. Drawings (1-3) show localized areas of afferent thalamic degeneration (stipple) seen at various frontal planes in Cats C1, C2, C3 and C4. Drawing (4) shows the area of destruction in Cat F1; the localization of afferent degeneration (stipple) seen within the (5) caudate nucleus and the (6) thalamus is shown in the last two drawings.



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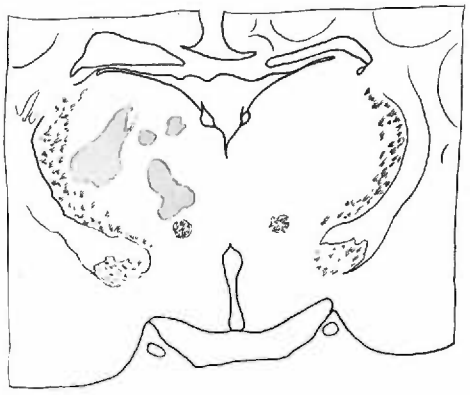

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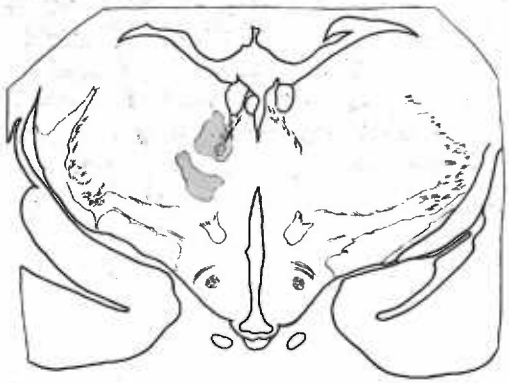

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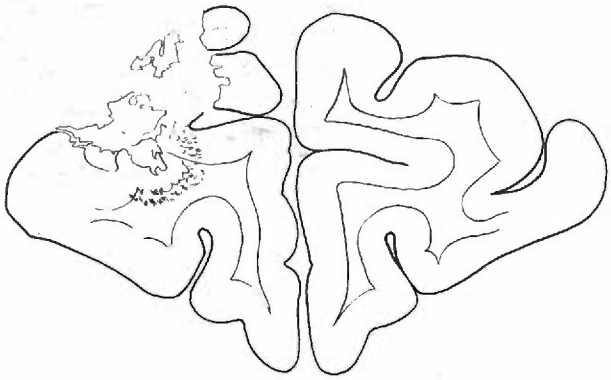

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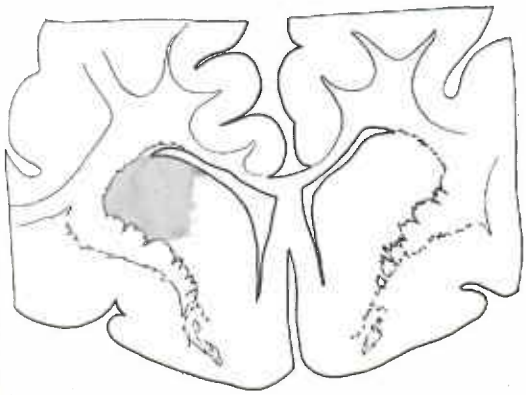

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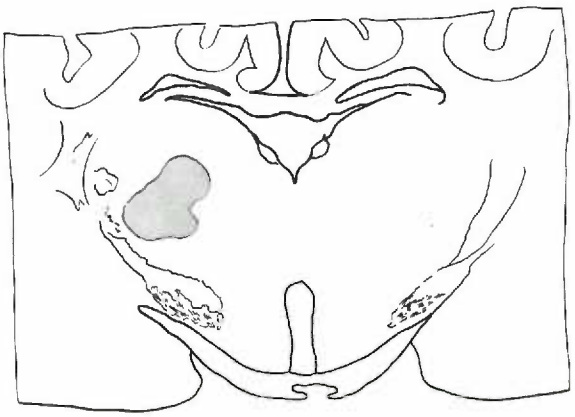

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caudal mesencephalic tegmentum to destroy the left substantia nigra. Although the nigra was extensively destroyed, the lesion was complicated in that the cerebral peduncule was grossly involved.

Analysis of the silver preparations did not show evidence of ascending degeneration into the entopeduncular nucleus, globus pallidus, or striatum. Some degeneration was observed in the peduncule and the internal capsule rostral to the lesion, and gross degeneration could be followed caudally within the pons, the medullary pyramid, and the crossed lateral cortico-spinal tract. This degeneration was interpreted as resulting from involvement of the cerebral peduncule rather than involvement of nigral efferents.

The passage of the electrodes had sufficiently damaged the caudal mesencephalic tegmentum so that histological analysis of that area could not be made.

Nissl studies revealed chromatolytic and other degenerative changes occuring in many diffusely scattered cells of the homolateral striatum, especially the caudate nucleus.

Cat 82. Electrocoagulation lesion; 21 day degeneration.

Again the posterior approach was used in placement of the lesion within the left substantia nigra. This lesion destroyed the medial two-thirds of the entire substantia nigra. However, the mammilary peduncule, small areas of the interpeduncular nucleus, the stratum intermedium, and the lemnisci were also involved.

No evidence of ascending degeneration could be found in the Protargol stained sections which was not referable to the extranigral involvement of the primary lesion. Particularly, the

entopeduncular nucleus, the globus pallidus, the putamen, and the caudate nucleus appeared normal and free of afferent fiber degeneration.

Possible connections of the substantia nigra with the caudal mesencephalic tegmentum again could not be verified due to the degeneration resulting from the passage of the electrodes through this area.

Carbo-thionine sections revealed retrograde changes in many cells of the caudate nucleus. The pallidum and putamen showed no such changes, and the diffuse cells of the rostral mesencephalic tegmentum were normal in appearance.

DISCUSSION

Cortico-Striatal Fibers.

The presence of direct cortical connections with the striatum has never been generally accepted. Wilson (5), Hunt(12), and Davison(31) have catagorically denied the existence of such a system, while Edinger(1), Papez(16), and Mettler(32,33) have all considered the subcallosal fasciculus of Muratoff to constitute a true cortico-striatal projection. Levin(34) and Verhaart and Kennard(35), using the Marchi technique, were unable to experimentally demonstrate such fibers entering the caudate or putamen, a finding not unexpected in view of the paucity of myelination these fibers possess. With a silver impregnation method, Glees(36) has described terminal cortico-striatal degeneration in the caudate nucleus resulting from ablations of the so-called cortical suppressor strip areas, though his demonstrations seem far from conclusive. This work has anatomically corroborated the findings of Dusser du Barenne, Garol, and McCulloch (37), who had earlier demonstrated cortico-striatal connections from these areas by recording evoked striatal potentials resulting from strychninazation of the cortex.

In Cat F1, destruction of frontal cortex resulted in a primary degeneration of the afferent fibers and a clearing of the neuropil within the head of the homolateral caudate nucleus. At its dorso-lateral extent, this appeared to totally deafferent the involved area, diminishing in degree toward the medio-ventral portion of the nucleus. Significantly, the subcallosal fasciculus was intact.

Although a cortico-pallidal projection has been described by Cajal(26) and Levin(34), in this brain no degeneration could be followed into the globus pallidus or entopeduncular nucleus, a finding in agreement with the observations of Verhaart and Kennard(35).

Cortico-Nigral Fibers.

Cortico-nigral fibers from the frontal lobe have been described by numerous investigators; Dejerine(3), Foix and Nicolesco(14), Jakob(13), Winkler(38), Levin(34), Verhaart and Kennard(35), Papez(16), and many others. They are usually considered to pass from the peduncule via the stratum intermedium into the pars compacta of the nigra. Papez(9,16,19) has considered the cortico-nigral fibers to terminate in the dorsal, compact portion of the nigra, in distinction to the ventral, reticular portion of the nigra receiving the striatal projection. Recently, Riemer and Jimenez-Castellanos(39), by the physiological neuronography method, have demonstrated a diffuse origin of cortical efferents to the substantia nigra arising from all accessible cortical areas excepting orbital cortex.

The one cortical lesion, Cat F1, failed to show terminal fiber degeneration within the substantia nigra. However, as this lesion was restricted to a rather small cortical area, it may be that a more extensive lesion in the cat brain is necessary to demonstrate degeneration of this pathway.

Strio-Pallidal Fibers.

Efferent fibers arising from cells of the caudate nucleus and putamen form the characteristic bundles of lightly myelinated axons

of fine caliber which impart to these nuclear masses their striated appearance, and hence their name. Their origin and course have been elaborately described by Wilson[5], Jakob[13], Foix and Nicolesco[14], Ranson, Ranson, and Ranson[40], Papez[16,19], Mettler[33], and others in the cat, the dog, the monkey, and the human. These strio-fugal bundles arising from the caudate stream through the internal capsule to enter the more dorsal and lateral extent of the globus pallidus. Wilson[5] and others have considered some of these fibers to constitute the dorsal portion of the external lamina of the pallidal complex. The efferent fibers of the putamen are described as radially converging on the lateral pallidum, some forming the ventral portion of the external lamina, and then passing into the pallidal complex.

In the series of caudate lesions, the degenerated fibers passing to the pallidum did not involve the external lamina, a finding not in keeping with observations of Wilson[5] and Mettler[33], nor was there evidence that fibers from the caudate pass to the putamen. In general, it appeared that the caudate especially projected to the more medial aspect of the globus pallidus, that is, the entopeduncular nucleus of the cat. That this nucleus in carnivores is the homologue of the medial segment of the globus pallidus in the primate is generally accepted; Smith[41], Kappers, Huber, and Crosby[42], Papez and Rundles[18], and many others. Although the lesions of the putamen destroyed the lateral globus pallidus, it is assumed from the previous observations that the projection of the putamen would principally be to the more lateral portion of that complex.

It appeared that destruction of the striatum resulted in almost total loss of afferents to the involved areas of the pallidum. It is inconceivable, in view of the degree and extent of degeneration seen in the series of striatal lesions, that any other major fiber system projects on the globus pallidus.

Strio-Nigral Fibers.

This system, since first being described by Edinger, has not been conclusively demonstrated by use of the Weigert and Marchi methods (Rosegay, 23). Although corroborated by the descriptions of Riese(17), Rundles and Papez(43), and Papez(9,16,19) in various species including man, it has been equally disputed by the studies of Ferraro(20), Stotler(44), Kimmel(21), Fox and Schmitz(22), Mettler(11), and Woodburne, Huber, and Crosby(45).

Verhaart(46) has pointed out the fine caliber and light myelination of the strio-fugal fibers, and has concluded that 99 per cent of these fibers are less than one micron in diameter, many perhaps devoid of myelin. The failure of the Marchi method to demonstrate degeneration of the strio-nigral system in continuity is perhaps thus explained.

It would seem from this study that massive, yet well localized, striatal lesions are necessary to involve sufficient numbers of strio-fugal fibers to make their degenerated course readily apparent. In the cat brain, the head of the caudate nucleus is easily accessible to the operator, and represents the far greater percentage of the total striatal mass. Large lesions of the caudate nucleus would therefore destroy proportionately more of the striatal complex than might

readily be done in certain other species of experimental animals, especially primates. This conception of total striatal mass has been emphasized by Harmon and Carpenter(47) in their study of striatal mass distribution in primates, and it would appear particularly applicable to the carnivore brain.

The description of strio-nigral fiber degeneration in continuity resulting from this study probably represents a fortunate combination of the above factors with the superior ability of silver staining techniques to demonstrate fine fiber and terminal degeneration.

The observations concerning the passage of strio-nigral fibers through the pallidum, their localization within the medial portion of the rostral peduncule, and their dorsal distribution into the substantia nigra is in general agreement with the descriptions of Papez and Randles(18), Papez(9,16,19), Ranson, Ranson, and Ranson(40), and others. Also, the relationship of the caudate to the medial nigra and the putamen to the lateral nigra is similar to that observed by Hassler(48), Stotler(44), and Papez(9,16).

That both the pars reticulata and pars compacta of the substantia nigra show terminal degeneration following striatal lesions is not in agreement with the descriptions of Spiller(49) and Papez(9,16,19). The extent of the degeneration seen in this series leaves little doubt as to the validity of this conclusion. Absence of descending strio-fugal degeneration caudal to the limits of the substantia nigra has also been reported by Randles and Papez(43), Papez and Randles(18), and Papez(19).

Nigro-Striatal Fibers.

Projection of nigral axons to the pallidum on the basis of Marchi degeneration studies has been reported by Kimmel(21) in the cat and by Glees and Hall(50) and Ranson and Ranson(24) in the monkey. Fox and Schmitz(22) inferred the same system after observing cellular changes in the substantia nigra following lesions of the entopeduncular nucleus. Using the method of retrograde cellular degeneration, a nigro-striatal projection has been described by Ferraro(20) and Rosegay(23) in the cat, and Mettler(11) in the monkey. Also with this technique, Stotler(44) has described this system in the human. On the basis of normal material studied in modified Weigert preparations, Woodburne, Huber, and Crosby(45) have also described a nigro-pallidal projection.

In this study, there was little evidence of change in the cells of the substantia nigra following massive striatal lesions. It was observed that no retrograde degenerative changes could be seen in the ten to twelve day survival animals, and that a marked gliosis accompanied the changes seen in the twenty-one to thirty day survival animals. Apparently this phenomenon, occuring in long term survival material, accounts for the extensive cellular degeneration within the substantia nigra so often reported following striatal and pallidal lesions.

Large lesions of the substantia nigra have also failed to show efferent degeneration passing in a rostral direction, either to the pallidum or striatum as previously indicated, or to the centrum medianum nucleus of the thalamus, as described by Glees and Hall(50).

Nigro-Tegmental Fibers.

Projection of nigral axons to the mesencephalic tegmentum has been described by Foix and Nicolesco[14], Morgan[7], Rioch[8], Papez[16], and Stotler[44]. Cat T1, a large lesion involving the entire dorso-lateral tegmentum rostral to the inferior colliculus, failed to show retrograde degeneration of cells of the nigra. In Cats S1 and S2, the posterior passage of the electrode and consequent mechanical destruction of the caudal portion of the mesencephalic tegmentum prevented an analysis of this critical area. It may in fact represent the area of projection of the substantia nigra, a consideration definitely suggested by a study of the normal morphology of the mesencephalon.

Thalamo-Striatal and Strio-Thalamic Fibers.

At the present time, considerable interest is being aroused concerning the anatomical relationships of the thalamus to the striatum, prompted by recent neuro-physiological studies of these areas.

Thalamo-striatal connections have been described by Le Gros Clark and Russell[51] passing from the centrum medianum nucleus to the putamen, and thalamo-pallidal fibers have been described by Papez[16] passing via the inferior thalamic peduncule from their origin in the medial and medial ventral thalamic nuclei. Quite recently, Whitlock and Schreiner[52] have reported degeneration of fibers projecting from the more medial thalamic nuclei to both the putamen and the caudate nucleus.

Although described by Edinger[1] and admitted by Wilson[5] as probably existing, no convincing evidence of strio-thalamic fibers

has been presented. The patterns of thalamic afferent degeneration seen in Cats C1, C2, C3 and C4 as compared to Cat F1 was suggestive of a direct strio-thalamic connection between the caudate nucleus and the medial and intralaminar thalamic nuclei. Complete absence of thalamic degeneration in Cat C5, a lesion restricted solely to the caudate nucleus, throws doubt on the existence of such a projection, but this interesting possibility warrants further experimental investigation.

SUMMARY AND CONCLUSIONS

The fiber connections of the corpus striatum and the substantia nigra have been investigated in the cat brain by selective destruction of the various nuclear components, and a histological study has been made of the resulting degeneration. In a series of cats, unilateral lesions were made in the caudate nucleus, putamen, globus pallidus, frontal cortex, mesencephalic tegmentum, and substantia nigra. After a survival period of ten to thirty days, the animals were sacrificed and histological sections prepared by the intensified Protargol and the Carbo-thionine techniques.

Analysis of this experimental material has yielded the following information:

1. Lesions of the caudate nucleus produce a degeneration of the strio-pallidal and strio-nigral fibers, and their course has been followed in continuity. This degeneration passes ventrolaterally through the internal capsule, into the globus pallidus and entopeduncular nucleus, and shows an almost complete destruction of afferents to these nuclei. The degeneration then passes to the medial portion of the rostral cerebral peduncle, and at successive levels extends dorsally into the pars reticulata and pars compacta of the middle and medial substantia nigra. No degeneration extends caudal to the limits of the substantia nigra.

2. Lesions of the putamen result in a degeneration of afferents to the globus pallidus, particularly its lateral portion, and the lateral substantia nigra.

3. Lesions of the pallidum produce a degeneration of nigral afferents comparable to striatal lesions, presumably by interruption of the striatal outflow.

4. Retrograde degeneration studies of the substantia nigra show negligible cellular changes resulting directly from either striatal or lateral tegmental lesions.

5. In animals having a survival period longer than two weeks, degeneration of afferents of the globus pallidus, entopeduncular nucleus, and substantia nigra is accompanied by an extensive gliosis and subsequent degenerative changes in the cells of those nuclei.

6. Lesions of the substantia nigra produce no ascending fiber degeneration to the entopeduncular nucleus, the globus pallidus, the striatum, or the thalamus.

7. Extirpation of the frontal cortex results in a degeneration of cortico-striatal fibers to the head of the caudate nucleus.

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TABLE OF ABBREVIATIONS

D	Degeneration	T	Thalamus
N	Normal	P	Putamen
CN	Caudate Nucleus	SN	Substantia Nigra
IC	Internal Capsule	CP	Cerebral Peduncule
CC	Corpus Callosum	IP	Interpeduncular Nucleus
LV	Lateral Ventricle	OT	Optic Tract

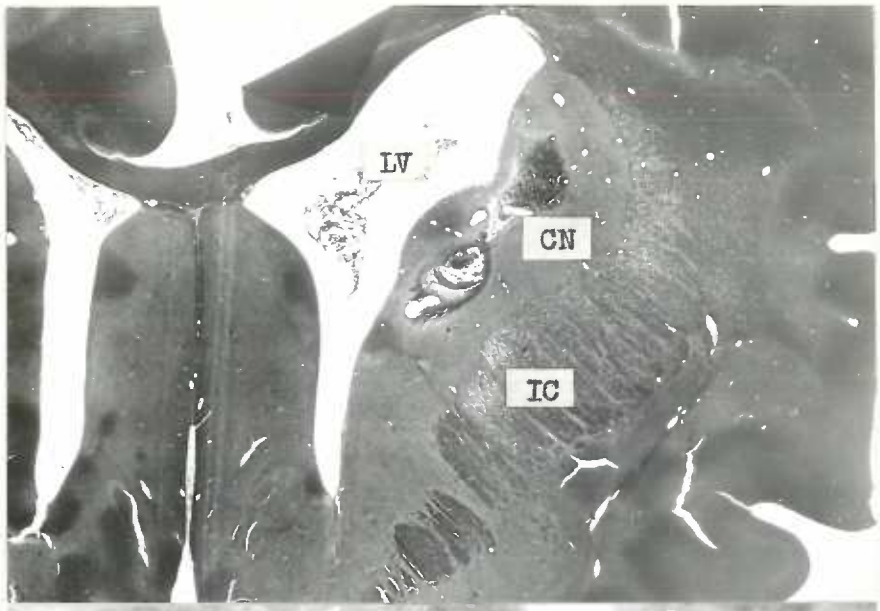
III	Third Ventricle
CFD	Caudato-fugal fiber degeneration
GPD	Globus Pallidus afferent degeneration
EPD	Entopeduncular Nucleus afferent degeneration
SND	Substantia Nigra afferent degeneration
CND	Caudate Nucleus afferent degeneration
SCB	Sub Callosal Bundle
STN	Strio-Nigral fibers
STND	Degenerated Strio-Nigral fibers

PLATE I.

Figure 4. Cat C2. Electrocoagulation lesion of the caudate nucleus (CN). Note the marked reduction of caudate mass as shown by a relative internal hydrocephalus of the lateral ventricle (LV); compare with Figure 5. Intensified Protargol stain.

Figure 5. Cat C3. Electrocoagulation lesion of the caudate nucleus (CN). Intensified Protargol stain.

Figure 6. Cat P1. Electrocoagulation lesion of the putamen and globus pallidus (P). Note the pale entopedunoular nucleus (EPD), outlined by the degeneration of its afferents. Intensified Protargol stain.



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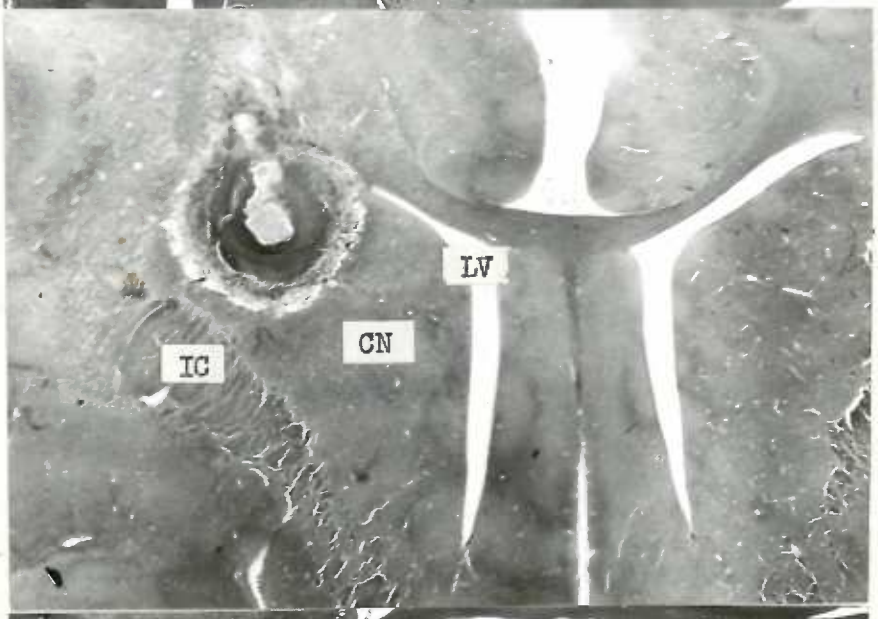

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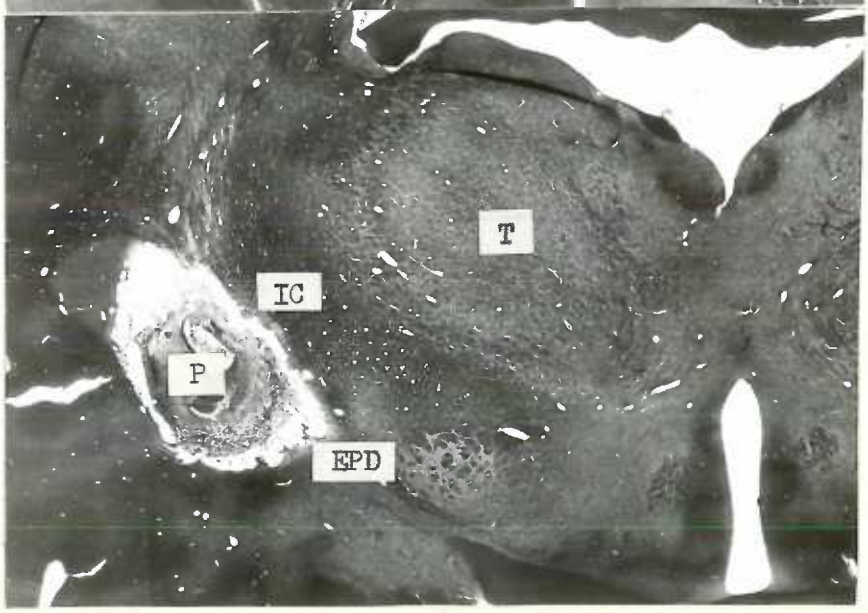

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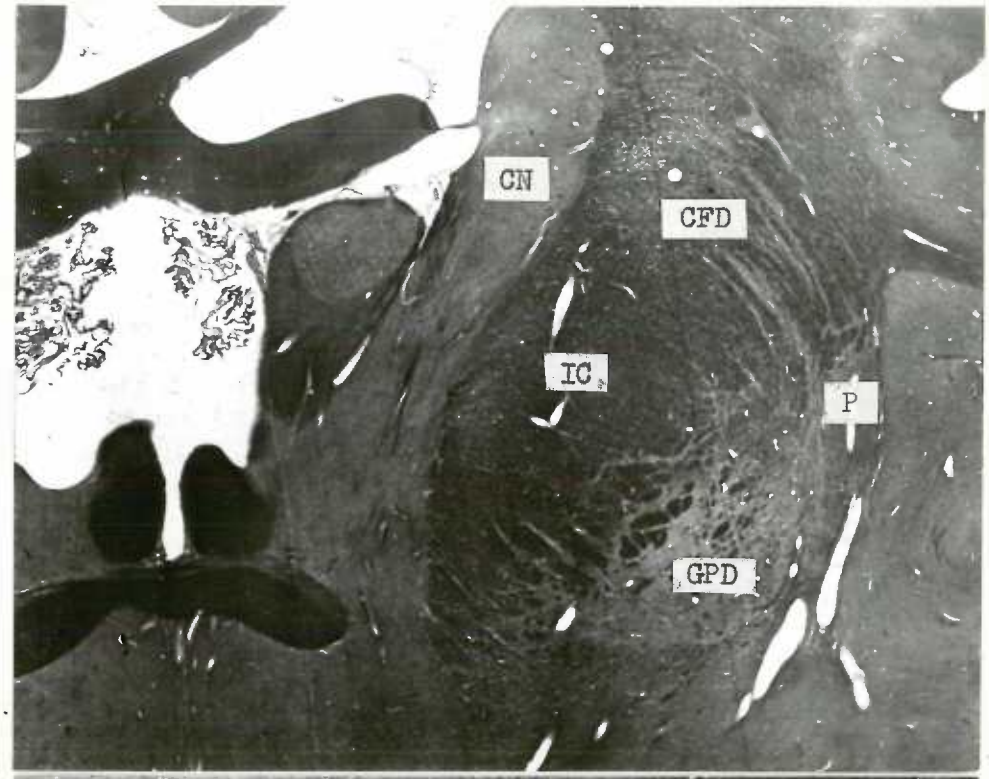
PLATE II.

Figure 7. A frontal section through the corpus striatum of Cat C2, on the same side and just posterior to the lesion. Note the pale, degenerated caudatofugal fibers (CFD) streaming through the internal capsule (IC) and passing into the dorsal pole of the globus pallidus (GPD). The nucleus is outlined by the extensive degeneration of its afferent fibers, passing particularly to the more medial portion. Intensified Protargol stain.

Figure 8. A frontal section through the entopedunoular nucleus (EPD) of Cat C2. Note how the entire nucleus is outlined by the degeneration of its afferent fibers. Intensified Protargol stain.



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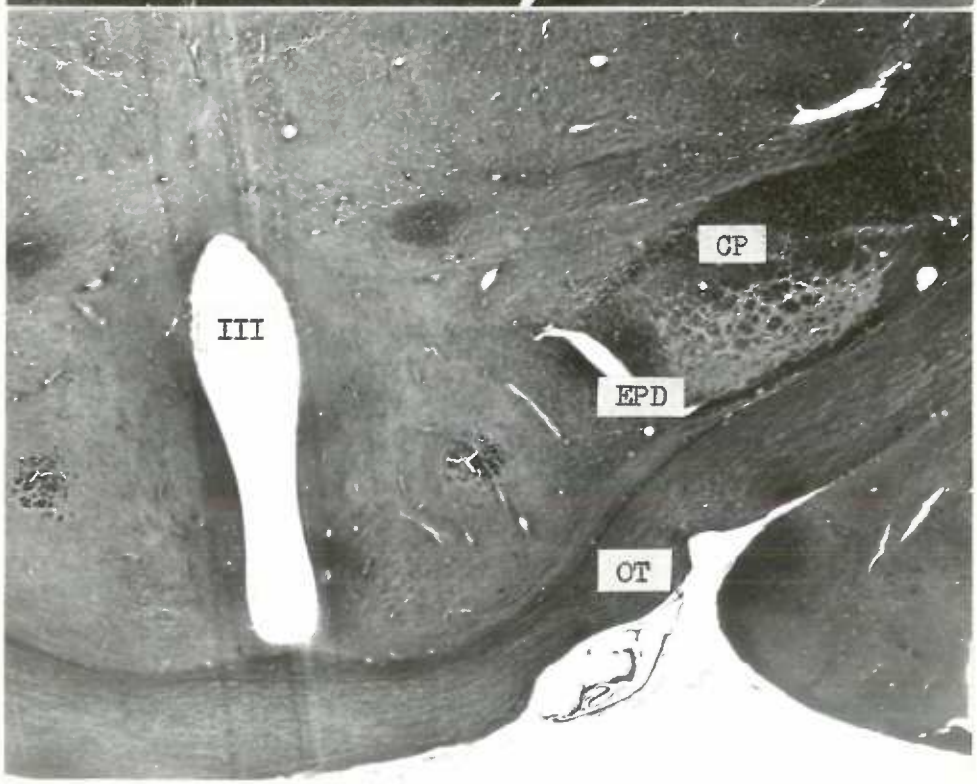

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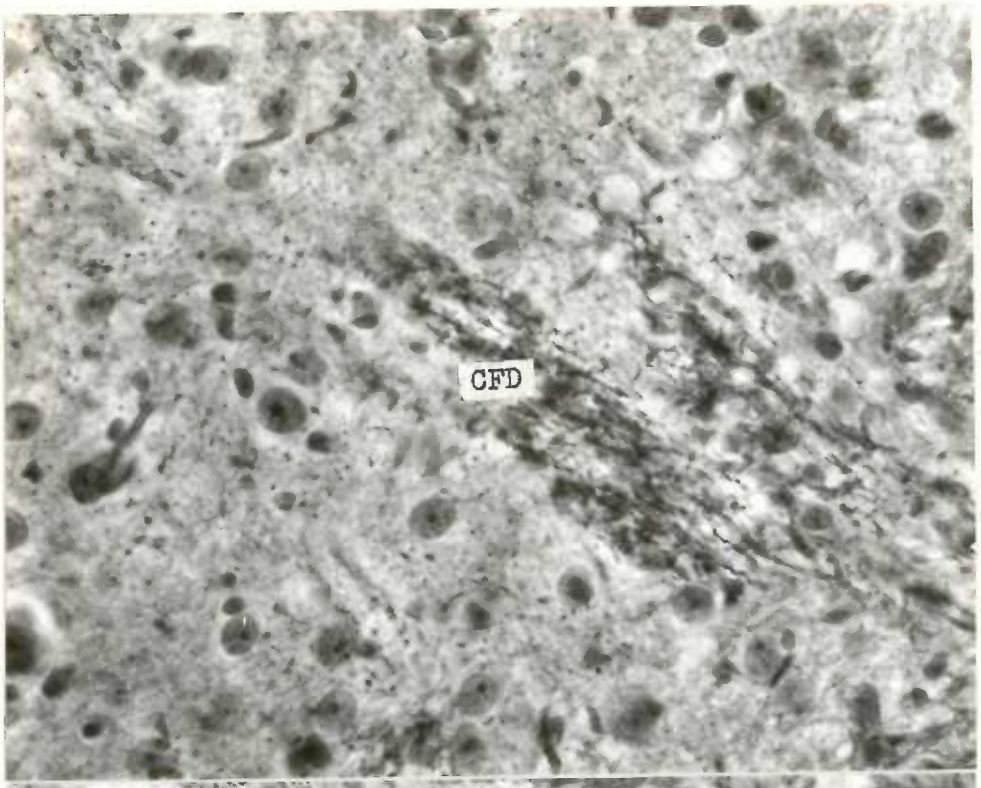
PLATE XIX.

Figure 9. Photomicrograph of the involved caudate nucleus, Cat C2, near the bordering internal capsule. Note the finely fragmented bundle of degenerated strio-fugal fibers (CFD) and the diffusely scattered degeneration which has resulted from the lesion. Intensified Protargol stain.

Figure 10. Photomicrograph of the homolateral internal capsule, Cat C2. Note the finely fragmented strio-fugal bundles (CFD) in passage through the internal capsule (IC). Intensified Protargol stain.



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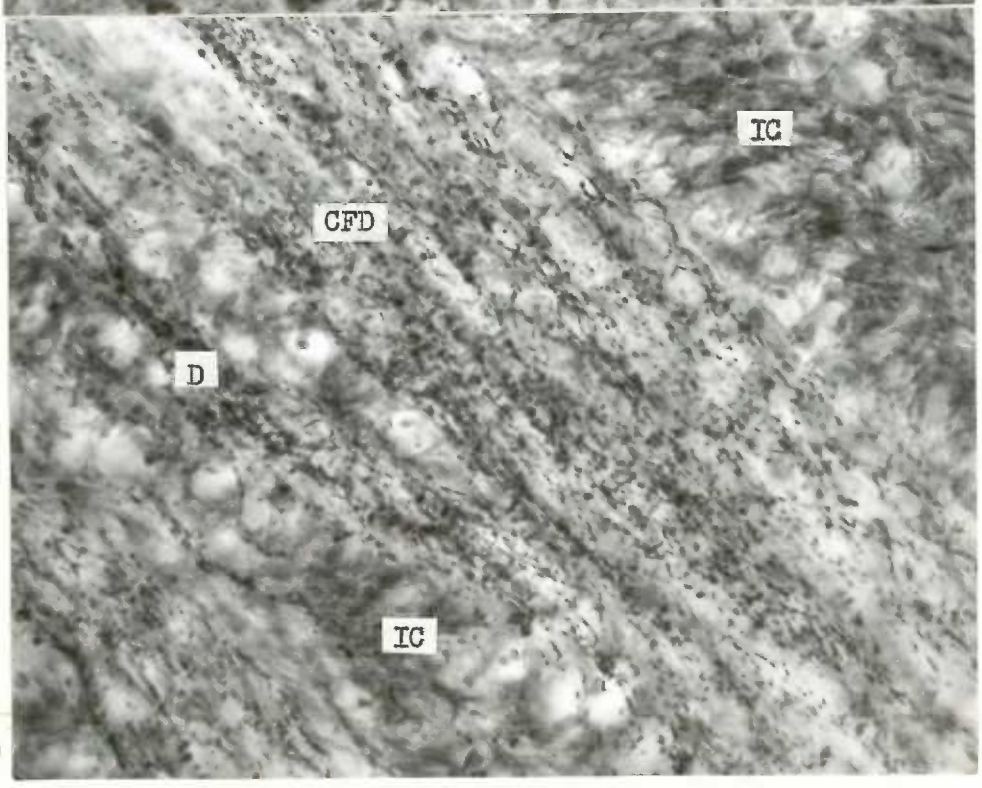

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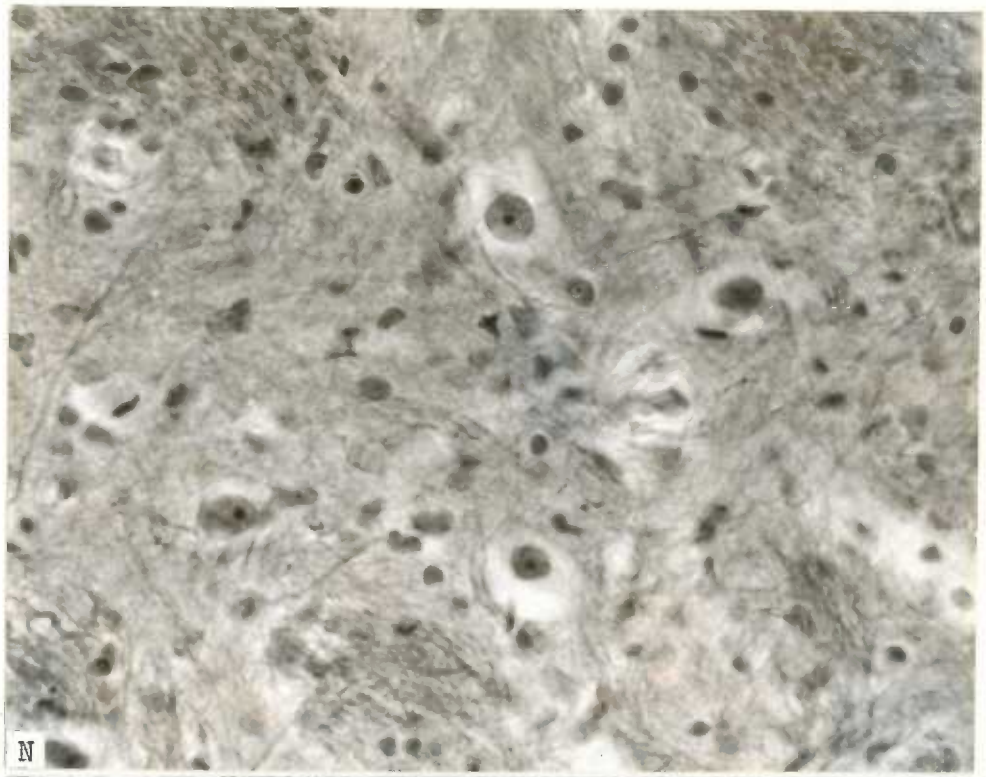
PLATE IV.

Figure 11. Photomicrograph of the histological pattern of the normal globus pallidus, Cat C2. Intensified Protargol stain.

Figure 12. Photomicrograph of the contralateral globus pallidus, Cat C2. The lesion of the caudate nucleus has resulted in marked degeneration of afferent fibers to this nucleus, as denoted by the clearing of neuropil and the deposition of a fine, granular debris. Intensified Protargol stain.



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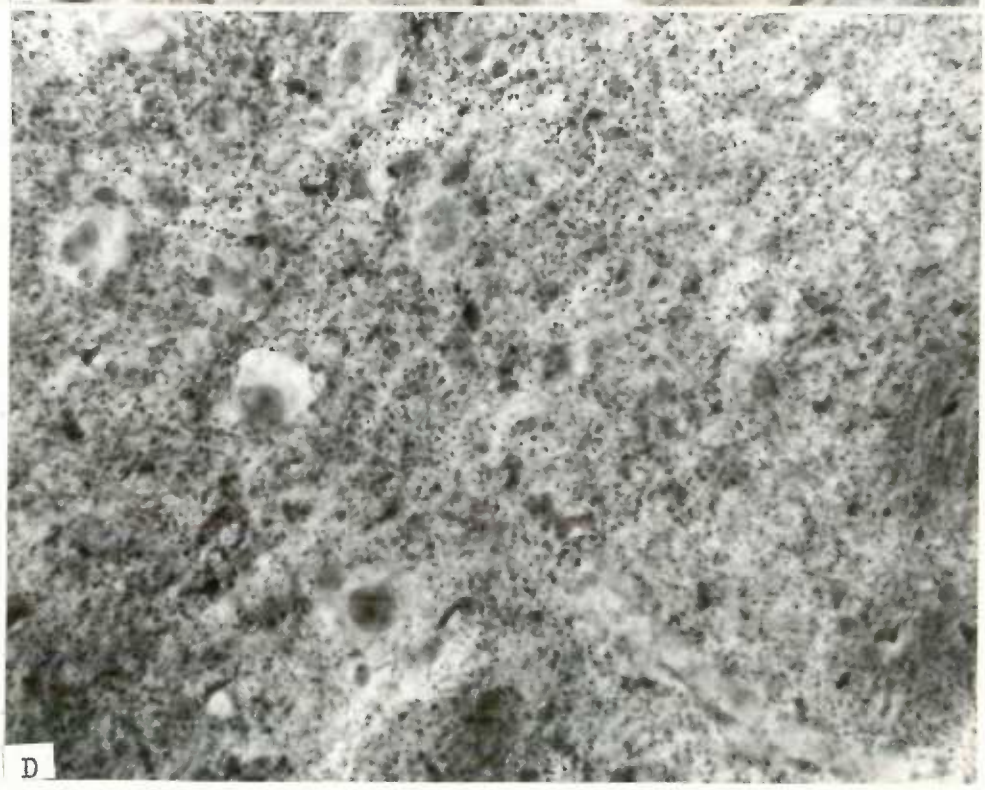

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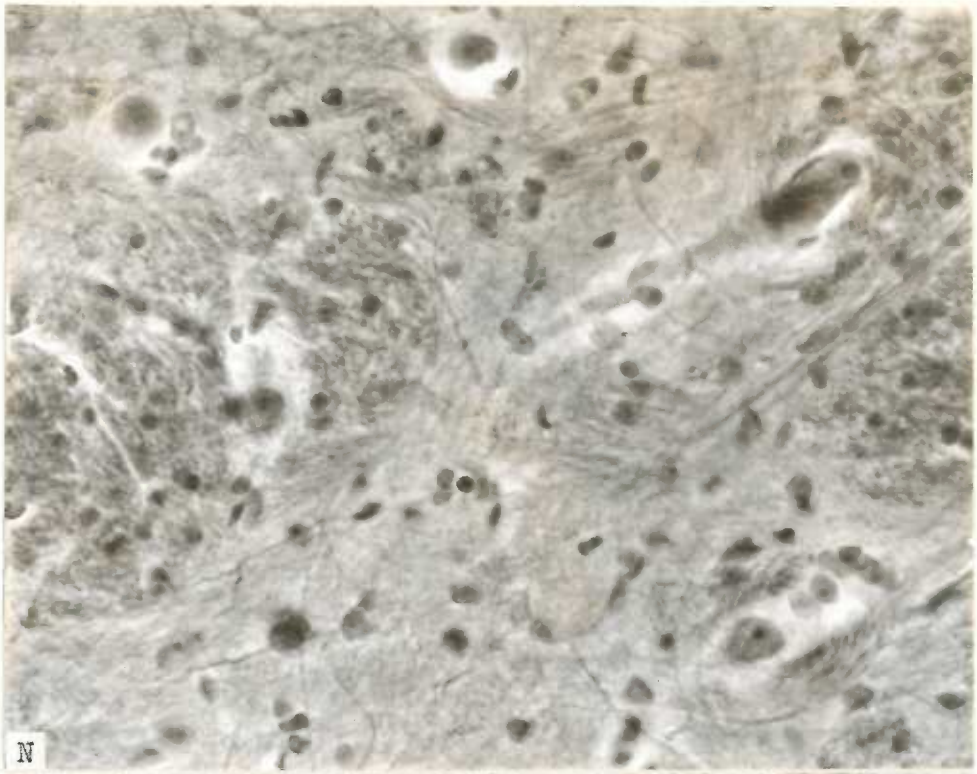
PLATE V.

Figure 13. Photomicrograph of the histological pattern of the normal entopeduncular nucleus, Cat C2. Intensified Protargol stain.

Figure 14. Photomicrograph of the contralateral entopeduncular nucleus, Cat C2. The lesion of the caudate nucleus has similarly resulted in a marked degeneration of afferent fibers to this nucleus as described for Figure 12. Intensified Protargol stain.



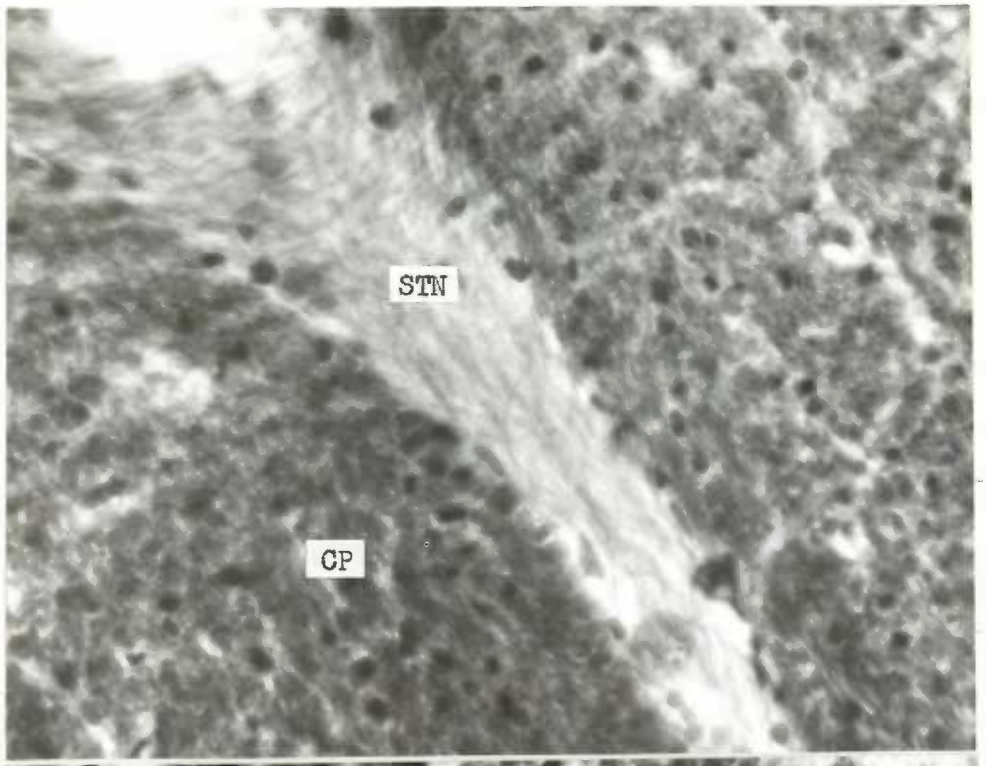
13 N

14 D

PLATE VI.

Figure 15. Photomicrograph of the normal rostral cerebral peduncule (CP) of Cat C3. A bundle of fine strio-nigral fibers (STN) is shown passing into the peduncule as part of the "comb" system. Intensified Protargol stain.

Figure 16. Photomicrograph of the contralateral rostral cerebral peduncule (CP) of Cat C3. The granular degeneration of a bundle of strio-nigral fibers (STND) within the "comb" system has resulted from a lesion of the caudate nucleus. Intensified Protargol stain.



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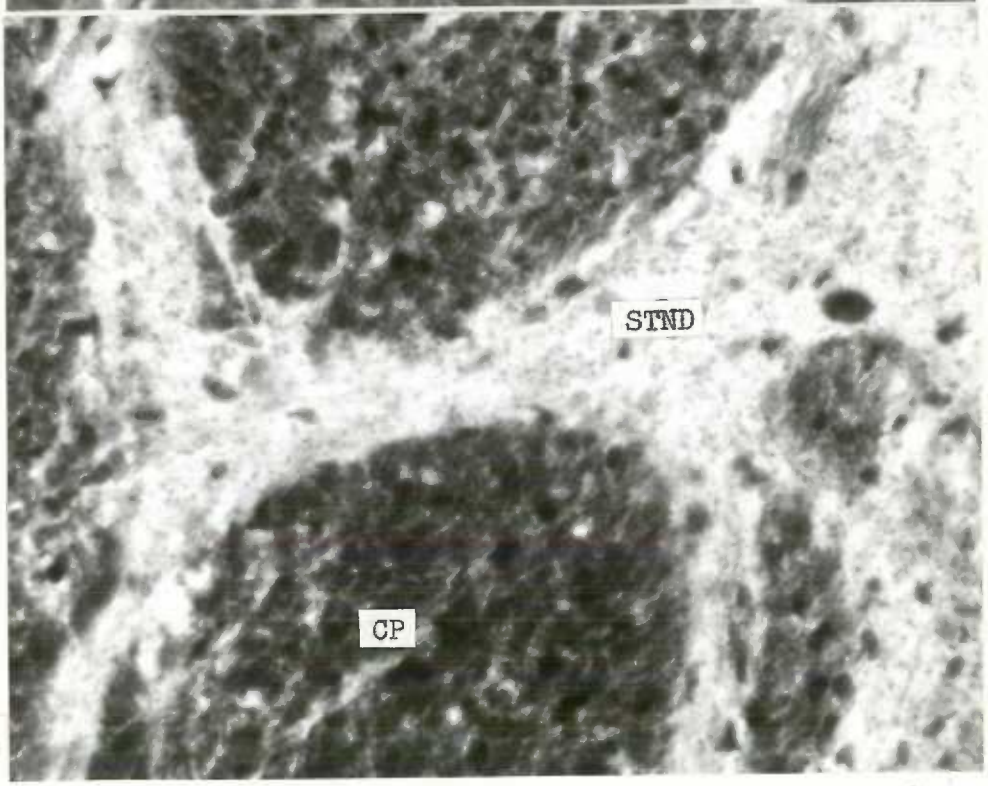

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PLATE VII.

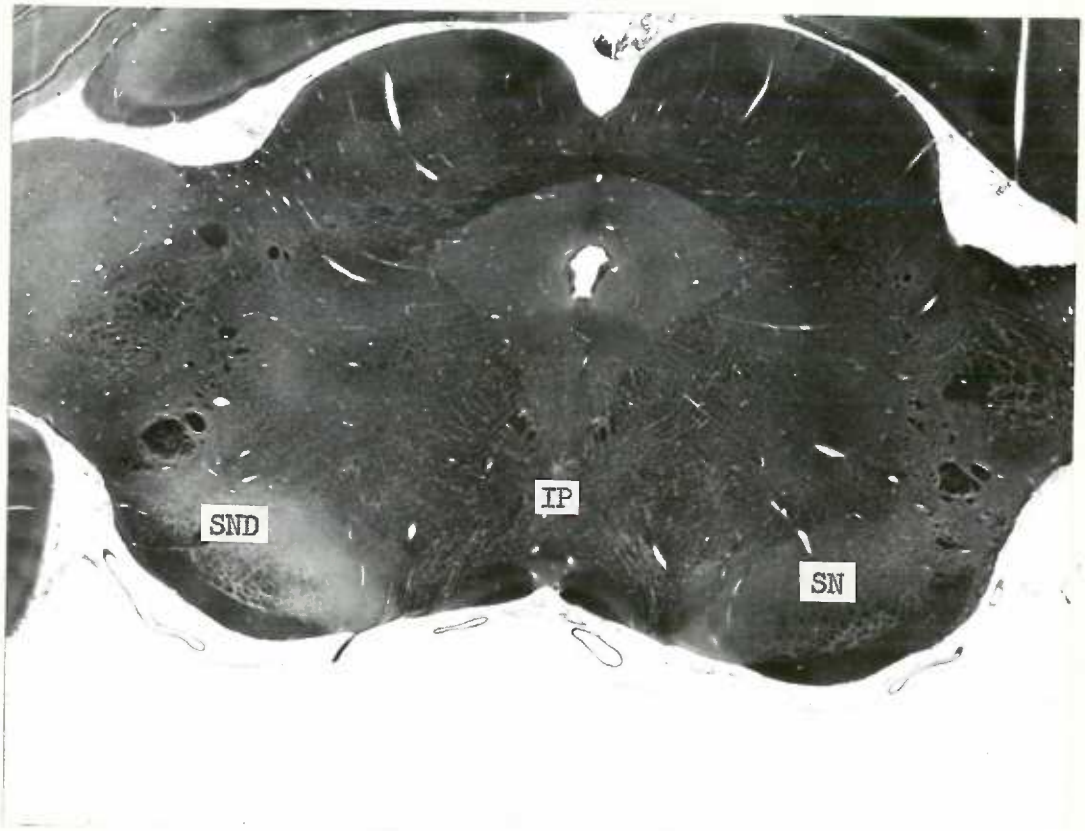


Figure 17. Cat C2. A cross section of the mesencephalon, demonstrating the extensive degeneration of afferent fibers to the substantia nigra (SN) which is seen following large striatal lesions. Intensified Protargol stain.

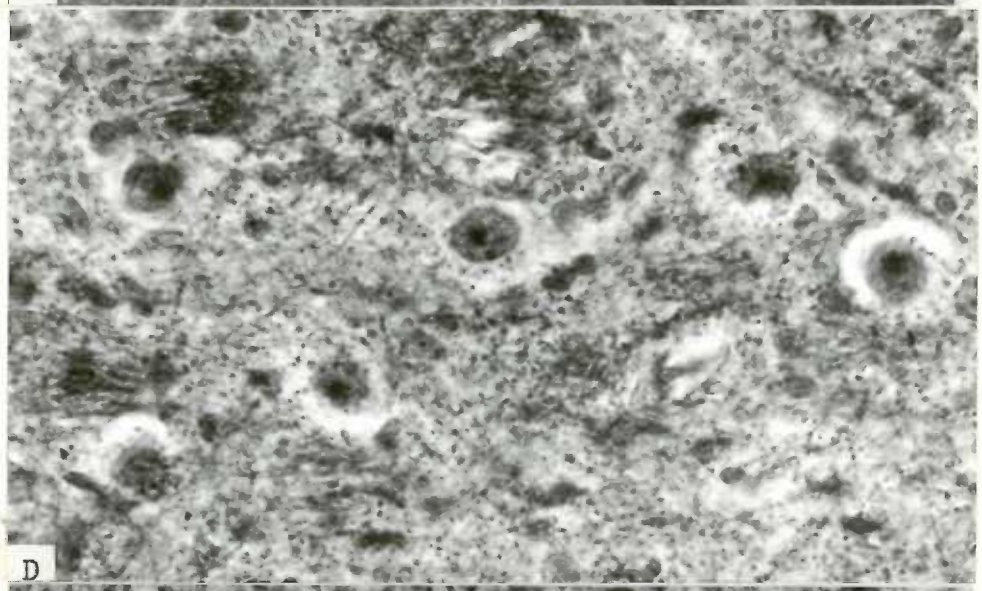
PLATE VIII.

Figure 18. Photomicrograph of the histological pattern of the normal substantia nigra, Cat C2. Note the rich neuropil of this nucleus. Intensified Protargol stain.

Figure 19. Photomicrograph of the partial degeneration of afferents to the substantia nigra, Cat P1, twelve day degeneration. Note the persistence of some neuropil, although there has been considerable degenerative change. Intensified Protargol stain.

Figure 20. Photomicrograph of the degenerated afferents to the substantia nigra, Cat C2, twenty-one day degeneration. Note the granular degeneration products and particularly the extensive glial reaction seen in the longer degeneration period. Intensified Protargol stain.

18 N



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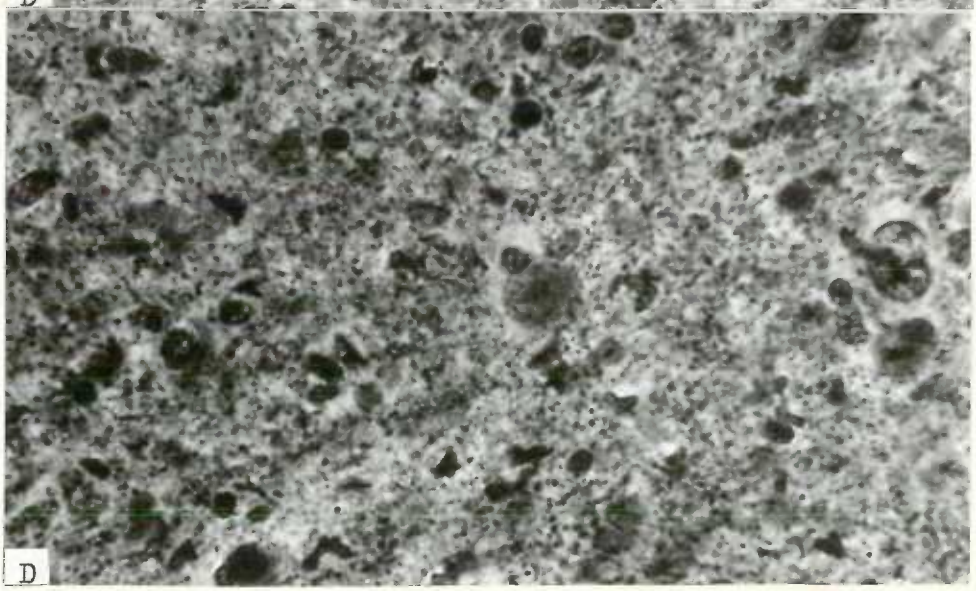

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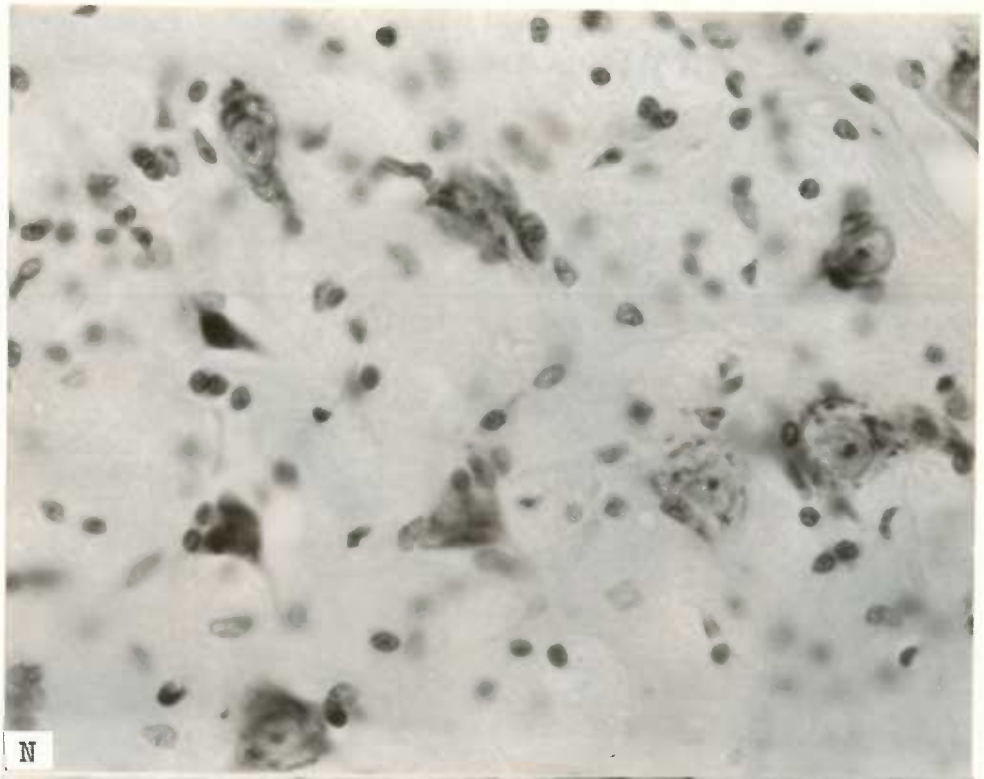
PLATE IX.

Figure 21. Photomicrograph of the histological pattern of the normal substantia nigra, Cat C2. Carbo-thionine stain.

Figure 22. Photomicrograph of the contralateral substantia nigra, Cat C2. Although suggestive of cytological alteration, the cells of the substantia nigra have a near normal appearance and population. A very marked gliosis dominates the histological changes which are seen following striatal lesions. Carbo-thionine stain.



21 N

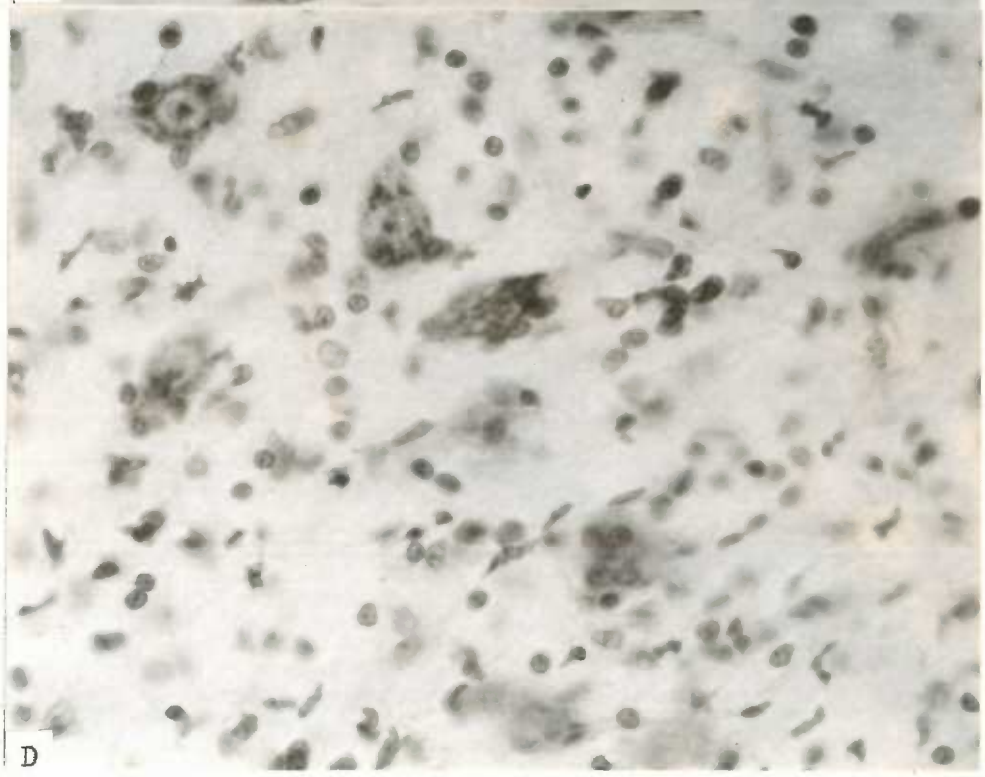


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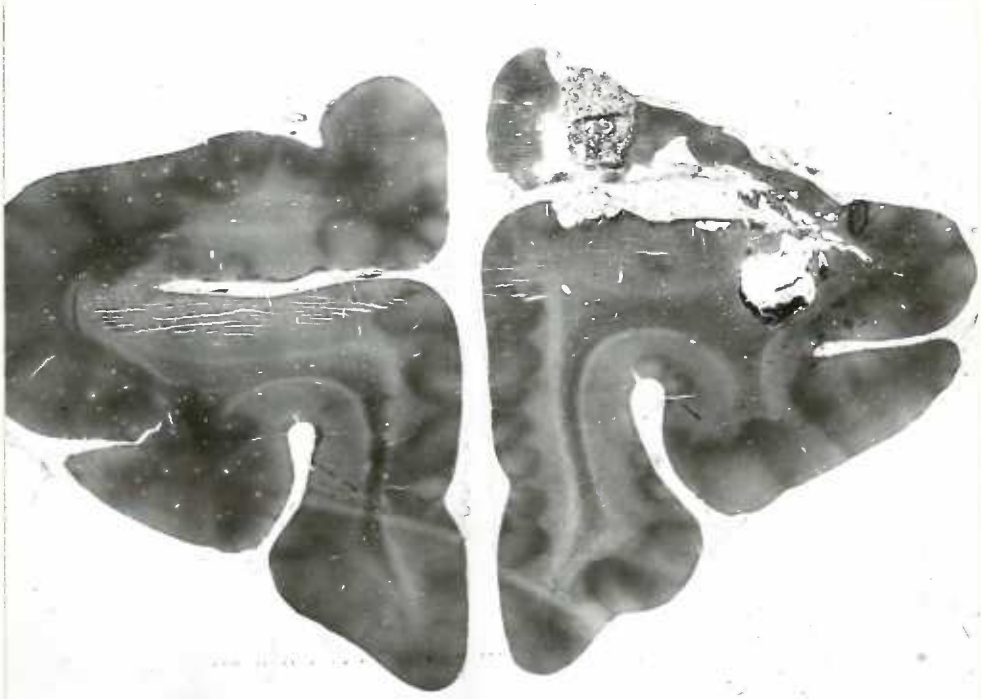
PLATE X.

Figure 23. A rostral section through the brain of Cat F1, showing the extent of the extirpation lesion at this level. Intensified Protargol stain.

Figure 24. A frontal section through the head of the caudate nucleus on the homolateral side of lesion F1. Note the complete clearing of the dorso-lateral head of the caudate nucleus (CHD) resulting from the degeneration of afferent fibers passing from the cortex to this nucleus. The intact sub-callosal fasciculus (SCB) may be seen forming the "capsule" of the caudate nucleus. Intensified Protargol stain.



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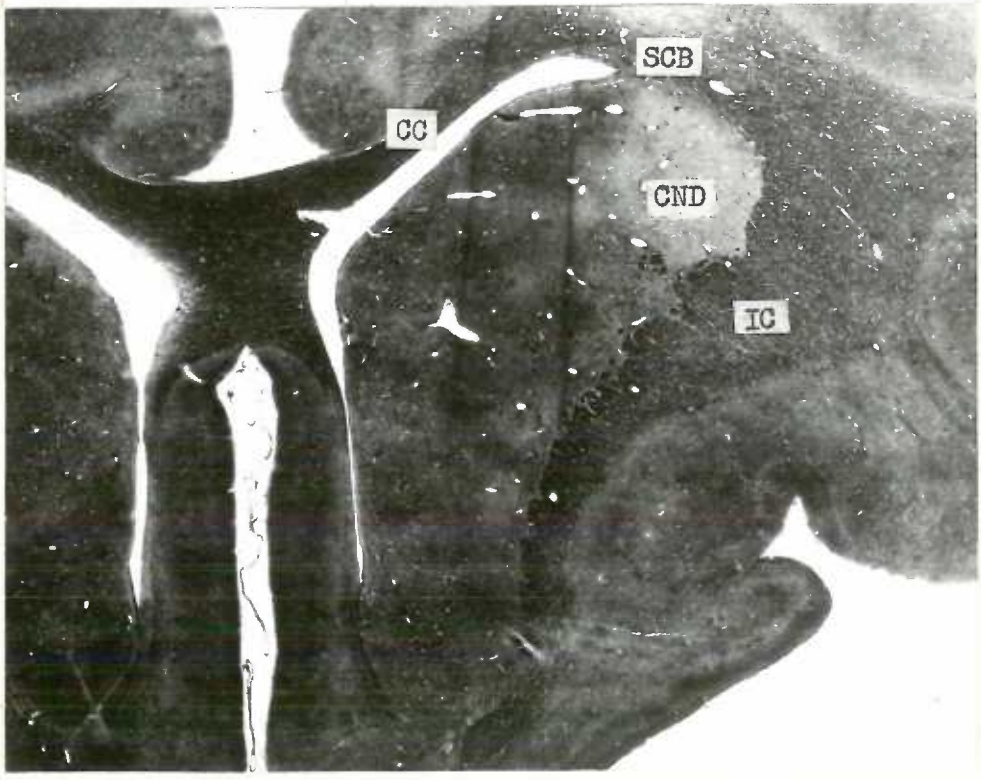
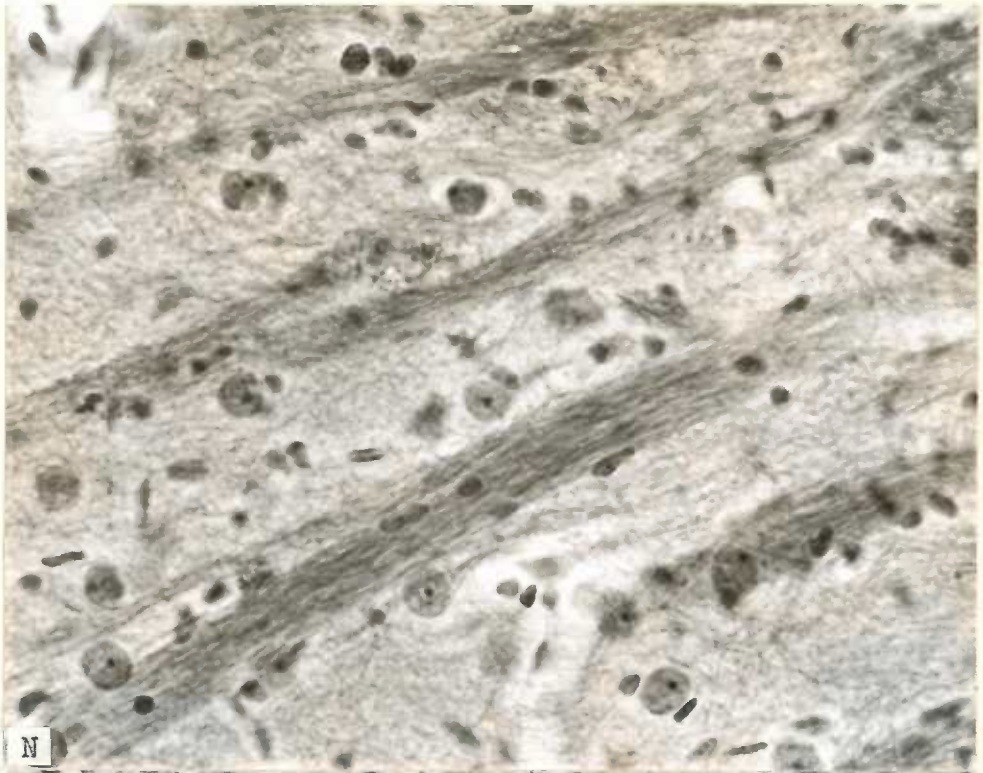


24

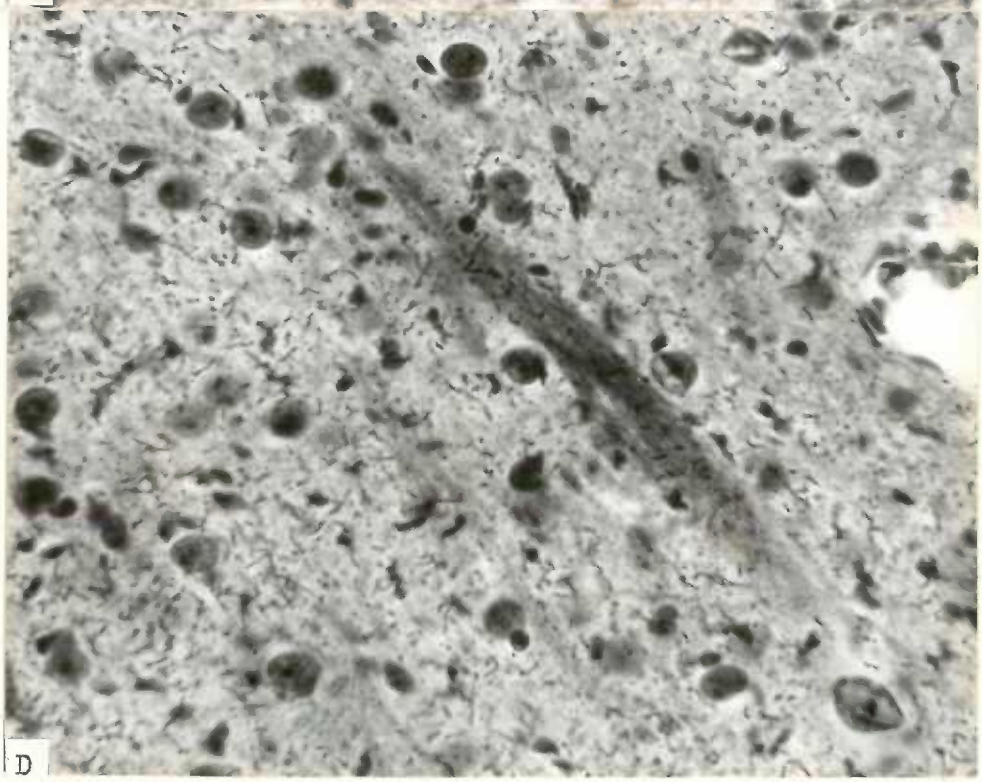
PLATE XI.

Figure 25. Photomicrograph of the histological pattern of the normal caudate nucleus, Cat #1. This area shows several "pencils" of strio-fugal fibers passing within the nucleus. Intensified Protargol stain.

Figure 26. Photomicrograph of the contralateral dorsal head of the caudate nucleus, Cat #1. There is a marked fragmentation of afferent fibers within the nucleus, but the efferent bundle is significantly not degenerated. Intensified Protargol stain.



25 N



26 D