ANATOMICAL STUDIES
IN LOBOTOMY

by

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ABSTRACT

This thesis contains a report of an investigation that has been carried out over the last year and a half into the tracing of fibre tracts in the human brain by the method of terminal degeneration. Four brains have been used and the extent of the degeneration (where present) in each has been traced in detail. Particular attention has been paid to improving the method of terminal degeneration by setting up and using objective and quantitative criteria of degeneration in place of the subjective and qualitative criteria that have been used in the past. Descriptions of the different appearance of degeneration in different parts of the nervous system are also given.

Thus an accurate account can be given of the fibres cut in these cases of prefrontal lobotomy and of the efferent projections of that part of the frontal lobe undercut by the lesion. These accounts help in placing the operation on a rational basis and give information on the anatomy of the connexions in the human brain that cannot be obtained in any other manner.
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION AND SURVEY OF PREVIOUS LITERATURE</td>
<td>1</td>
</tr>
<tr>
<td>II. MATERIAL AND METHODS</td>
<td>13</td>
</tr>
<tr>
<td>III. RESULTS</td>
<td>19</td>
</tr>
<tr>
<td>IV. DISCUSSION</td>
<td>24</td>
</tr>
<tr>
<td>V. SUMMARY</td>
<td>27</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>28</td>
</tr>
</tbody>
</table>
DESCRIPTION OF FIGURES

MAPS

1 - 3  Maps of lobotomy wound: brain L-2 (R)
4 - 6  The same: brain L-2 (L)
7 - 9  The same: brain L-3 (R)
10 - 13 The same: brain L-4
14 - 19 Extent of the degeneration in the dorso-medial nucleus of the thalamus of brain L-2 (R)
20 - 23 The same: brain L-2 (L)
24 - 30 The same: brain L-3 (R) (Note figure 26 is from a section as shown in figure 25 in which the presence of any bouton or terminal was marked on the map with a dot.)
31 - 34 The same: brain L-4 (R)
35 - 41 Extent of degeneration in the prefronto-pontine tract and pons of brain L-3 (R)
42 - 46 The same: brain L-4 (R) In figures 42 - 43 one stroke stands for 2 fields.
47 - 49 Extent of the degeneration in the medial mamillary nucleus of brain L-4 (R)
50  Extent of 'degeneration' in the normal pons (NC2) mapped by 'dorso-medial' criteria. Mapped by 'pons' criteria this map would be blank.
51  The same for the nucleus parafascicularis

CAMERA LUCIDA DRAWINGS

52 - 55 Drawings of degenerating terminals in the dorso-medial nucleus. Units of degeneration are numbered.
REPRODUCTIONS

56  From Hoff ('32 a)
57  From Hoff ('35)
58  From Brodal ('49)
59  From Brodal, Walberg and Blackstad ('50)
60  From Getz ('52)
61  From Meyer ('49)

PHOTOMICROGRAPHS

62 - 63  Degeneration immediately around the lesion in brain L-2. 
          x 1,400
64  Degeneration in the dorso-medial nucleus in brain L-2. 
       x 1,700
65  The same in brain L-4.  x 900
66  Normal boutons termineaux in nucleus parafascicularis (NCl). 
       x 1,600
67  The same.  x 1,400
68  Degenerating fibres in the prefronto-pontine tract in brain 
       L-3.  x 1,800
69  The fibre plexus in the normal pons (NC2).  x 1,100
70  Degeneration in the pons in brain L-4.  x 1,000
71  70 enlarged.  x 1,800
72 - 73  The fibre plexus in the normal medial mamillary nucleus (NCl) 
          x 1,100
74  Degeneration in the medial mamillary nucleus of brain L-4. 
       x 1,100
ABBREVIATIONS USED IN FIGURES

FIGURE

1 - 13  a agranular  e eulaminate
d dysgranular  m mesocortex

14 - 49  A.C.  anterior commissure
A.D.  antero-dorsal nucleus
A.H.  anterior hypothalamus
A.L.  ansa lenticularis
A.M.  antero-medial nucleus
ATR.  anterior thalamic radiation
C.M.  nucleus centralis medialis
C.N.  caudate nucleus
CE.N.  nucleus centranum medianum
D.H.  dorsal hypothalamus
D.L.  dorso-lateral nucleus
D.M.  dorso-medial nucleus
F.  fornix
F.L.  fasciculus lenticularis
G.P.  globus pallidus
I.C.  internal capsule
I.T.P.  inferior thalamic peduncle
L.H.  lateral hypothalamus
L.M.  lateral mamillary nucleus
L.T.(Tu)  lateral tuberal nucleus
mc  large-celled portion
M.B.(M)  mamillary body
M.L.  medial leminiscus
FIGURE

M.T. mamillary-thalamic tract
N.A. anterior nucleus
N.S.M. supra-mamillary nucleus
N.V. ventral nucleus
pc small-celled portion
P. pyramidal tract
P.F. parafascicular nucleus
P.H. posterior hypothalamus
P.T. parataenial nucleus
PU. pulvinar
PUT. putamen
E.V. paraventricular nucleus
Pa.Cd. dorsal part of paracentral nucleus
Pa.Cv. ventral part of paracentral nucleus
R. red nucleus
R.E. nucleus reuniens
S.N. substantia nigra
S.T. subthalamus
SUM. nucleus submedius
Th. thalamus
V.A. anterior ventral nucleus
V.L. lateral ventral nucleus
V.P. posterior ventral nucleus
Z.I. zona incerta

52 - 55 glial cell
N. nerve cell
c. capillary
SIGNS USED IN FIGURES

THALAMUS

- 2 - 14 units of degeneration.

+ more than 14 units of degeneration.

HYPOTHALAMUS

- 2 or more units of degeneration plus obvious fragmentation of the fine plexus of unmyelinated fibres.

PONS (except 41, 50)

- more than 50 boutons and terminals plus obvious fragmentation of the fine plexus of myelinated fibres.

FIGURES 41, 50

- more than 15 boutons.

- 2 units of degeneration.

- both.

In all cases the sign \ shows the presence and approximate direction of degenerated fibres if more than 1 present.
CHAPTER I

INTRODUCTION AND SURVEY OF PREVIOUS LITERATURE

The method of terminal degeneration used to trace neuronal connexions in the nervous system depends on the fact that, following the cutting of an axon, the axon, its preterminal branches and the terminals themselves undergo a series of characteristic changes that can be detected by the use of silver stains. The first account of terminal degeneration in the axon was given by Nikolajew (1893). He used the methylene blue method to show the degenerating boutons on the ganglion cells of the frog's heart ten to fifteen days after cutting the vagus nerve. The normally delicate ring endings became fragmented and hypertrophied. Tuckett (1895) used the same technique to demonstrate degenerating pre-ganglionic fibres in the rabbit.

Cajal (111) makes the important point (in addition to others) that where an axon is interrupted in the white matter its central segment forms a late 'boute de retraction', having passed through a complex and slow hypertrophy with fusiform swellings, varicosities and 'boute en series'. The peripheral or severed part of the axon passes through active phases of neurofibrillar swelling, formation of isolated spheres, and complicated clusters of neurofibrils showing that local reaction is possible even in the isolated portion.

Ranson and Billingsley ('18) using a pyridine silver method were unable to demonstrate the normally dense plexus of fibres in the superior cervical ganglion following the section and subsequent degeneration of the pre-ganglionic trunk.
The History of the Method.

(a) The early years. De Castro ('30) carried out an intensive investigation into the degeneration in the superior cervical ganglion in over 100 cats (chiefly young). He used block silver impregnation methods with fixation in sommifene or chloral hydrate and showed that terminal degeneration appears at the end of seventeen hours although the axons to which they were attached were often intact. This work was confirmed by Lawrentjew ('34) who used the method of terminal degeneration to determine the method of ending of fibres in the superior sympathetic ganglion. At about the same time Levi ('32) studied degeneration in nerve processes separated from their cell bodies in tissue culture. Twelve hours following section the distal segment resembled a 'string of pearls', the swellings of which were in the process of fragmentary degeneration. Sereni and Young ('32) detected bouton changes in cephalopods fifteen hours after the mantle connective and stellar nerves had been sectioned and the process was complete in 7 days with gradual disappearance of fragments.

(b) Recent work. The recent use of the method dates from Hoff's series of investigations. In these he examined the degeneration produced in the cat spinal cord ('32a) after cutting the afferent roots of post-thoracic nerves. He then used the method ('32b, '35) to study the termination in the cord of fibres from the motor and premotor cortex in the cat and monkey. Gibson ('37) described the changes in the terminals in the spinal cord following its transection in the cat. Schimert ('38) used the method to trace the endings of the vestibulo-
spinal tract in the cat. This was followed by a number of communications from Glees and Le Gros Clark (*41) and Glees (*41, *42) in which the mode of termination of the optic nerve in the lateral geniculate body in various animals was studied. Glees (*44) studied cortico-striate connexions in cats. Glees, Meyer, and Meyer (*46) used the method to trace the terminal degeneration in the frontal cortex of the rabbit following interruption of afferent fibres, and Le Gros Clark and Meyer (*47) used it to trace the terminal connexions of the olfactory tract in the rabbit. Brodal (*49) and Brodal, Walberg and Blackstad (*50) investigated the termination of the spinal afferents in the lateral reticular nucleus of the cat and the termination of the spino-olivary fibres respectively. Adey (*51) and Getz (*52) used the method to trace the hippocampal connexions of the cingulate cortex of the rabbit, and the termination of spino-thalamic fibres in the cat respectively. It has been applied to human lobotomy material by Meyer (*49), Beck, Meyer and Le Beau (*51) and Martinez (*55).

We will now consider the question - How can this method be used so as to give as accurate and consistent results as possible? Three elements in the answer to this question can be isolated.

(1) A method of silver staining that will give reasonably consistent results must be used.

(2) The criteria which are used to decide if a given region contains degeneration should be made as objective as possible.

(3) The method of presenting the results should be as accurate as these criteria allow.
To take these in turn:

(1) We have found that Gibson's modification of Rio-Hortega's double-impregnation technique gives the consistent results providing that certain precautions are taken. We have described the method in detail elsewhere (1'55). The main points are that the material must be properly fixed and that the pH and temperature of the silver solutions must be kept within narrow limits.

(2) In all previous investigations the criteria of degeneration have been qualitative and subjective. Decisions as to whether degeneration is, or is not, present have been made on the basis of subjective comparisons with sections taken from the same region of a normal brain. These subjective criteria of degeneration are similar for most workers. The field must contain large argentophile masses, either solid or thick-ringed, usually of irregular shape and (in later cases) fragmenting. The more regular of these are regarded as being degenerating boutons termineaux and the more irregular, particularly if in visible continuity with a degenerating fibre, are regarded as being degenerating pre-terminal fibres. The two are subsumed under one term - degenerating 'terminals'. The presence of degenerating fibres in the field has been regarded as more reliable evidence that degeneration has taken place in that field.

As degeneration proceeds a progression from normal looped boutons to thickened, solid, and lastly fragmented boutons has been described (Hoff '32 a and b, Gibson '37, and others). Hoff ('32a) recognized a thickening (or filling in) of the ring form of the bouton, swelling, granularity, irregularity of shape (often pear-shaped or
great elongation) and a darkness of staining as evidence of degeneration. Hoff ('35) mentions only 'Progressive swelling and granulation' followed by 'an early disintegration' as signs of degenerating bouton termineaux. Gibson ('37) summarised the process of degeneration as follows: '... an average degenerating bouton passes through the processes of hypertrophy, elongation, fragmentation and granulation, and from the circular to the ellipsoid and back to the circular again.'

Fedorow and Matwejewa ('35) described the following succession of changes in the degeneration of terminals in the frog:

Stage 1. Increased argentophilia of fibres and boutons.
Stage 2. Swelling of fibres and boutons.
Stage 4. Vacuolation appears in the boutons. This stage is reached in the autumn in 11-12 days and in the winter not until 25-30 days.
Stage 5. Disintegration.

Glees and Le Gros Clark ('41) recognised swelling, thickening or a filling in of the ring (often with a dense, opaque mass composed of a very fine neurofibrillar network) and increased argentophilia as evidence of degeneration. They noted that there was considerable variation in the extent of degeneration, some terminal remaining quite small. Swollen, argentophilic fibres (particularly at their sites of branching into the terminal divisions) with 'cylindrical' swellings in their course were regarded as being degenerating. Glees ('41) noted that the normal terminal rings (present in great numbers in the lateral geniculate body of the cat) had mostly been transformed into thicker
rings or into solid black bulbs which later disintegrated into small granules. 'In addition there are also to be seen oval or elongated end-formations in the substance of which a strongly staining neurofibrillar network is visible.' Glees ('42) described similar changes in the rabbit and in the caudate nucleus of the cat ('44) the degenerating fine terminal fibres were swollen (particularly where the main fibre broke up into its terminal branches) and fragmented. Terminal arborisations had a fine beaded appearance. Glees, Meyer and Meyer ('46) noted the following signs of degeneration at the termination of injured axons; a thickening (or filling in) of the rings and the presence of fibrillated ring structures and a beading and granular disintegration of fine fibres followed by a distinct rarefaction of fine fibre plexus in the cortex. In the course of the fibres they recognised a progressive swelling, ballooning and fragmentation of thicker fibres. Le Gros Clark and Meyer ('47) used rigorous but still subjective criteria of degeneration. They compared the region under examination first with the unoperated side of the same animal and also with the same region of an entirely normal rabbit's brain 'which had been fixed and stained under exactly the same conditions as the operated cases'. Their criteria of significant degeneration were 'a massive degeneration of terminals, preterminals or unmyelinated fibres' followed in other experiments after a longer time interval by an actual loss of fibres in the same region. They considered that the massive degeneration, when found, provided conclusive evidence of terminal connexions but that its absence did not mean that no interrupted fibres terminated in the region.
Brodal ('49) described degenerating boutons as 'more or less spherical, ovoid or more irregular, sometimes almost triangular' "enlarged and argentophilic, sometimes with a lighter center. The degenerating fine fibres appeared as 'threads varying extremely in caliber along their course, swollen globular, spindle-shaped or ovoid parts being interconnected with attenuated fragments of the original fiber'. These showed vacuolisation and later fragmentation. Brodal notes that Phalen and Davenport ('37), Barnard ('40), Minckler ('40) and others had claimed that the appearance of normal terminal boutons may vary considerably and that 'pictures closely resembling degenerated boutons may quite frequently be seen'. He therefore took no account of 'Scattered structures with the morphological characteristics of degenerating boutons,' but only of 'larger quantities' of them. He laid more emphasis on 'the occurrence of fine degenerated terminal and preterminal fibers than on degenerated boutons' and (as 'additional evidence') the 'very clear cut loss of the fine fibers which can be seen after 7 days or more ...'. Blackstad, Brodal and Walberg ('51) make a further analysis of the method pointing out that 'The vagaries of the silver techniques are well-known' and that 'All authors studying normal terminal boutons agree that they are frequently difficult to identify.' They also note that there is not general agreement as to what is, and what is not, a degenerating bouton. They bring to notice one very important fact, namely that the picture of terminal degeneration is not the same everywhere. A particular feature of their findings was, in some areas of the olive, a great increase in the number of stained boutons (from an average of 3 to as many as 25 per field) and an increase in the
proportion of large and solid boutons and those of irregular shape. Whereas in other regions of the olive 'where pronounced alterations of fine nerve fibres are evidence of marked terminal degeneration the number of boutons appears not to be raised.' They conclude 'Only when the increase of boutons is exceptionally high in experimental animals can an area of degeneration be determined on this basis exclusively. [This is the first time that we have come across the suggestion that the mere increase in the number of boutons visible may be used as an exclusive criterion of degeneration.] In most instances the concomitant degeneration of the finest fibres is a more reliable sign. An increased number of solid, degenerating boutons is, however, significant enough of terminal degeneration to be of practical value.' The difficulties here are (i) how large must the increase in numbers be before it can be considered significant, and (ii) even within one nucleus there may be great differences of bouton concentration and morphology and so it is not sufficient to compare the degenerated with the normal unless both the extent of the variation of the boutons in different parts of one nucleus and in the same parts of the same nucleus in different brains is known in much more detail than it is at present. However, it must be noted that these same authors (150) had previously only accepted the presence of degenerated fine fibers as criteria of degeneration.

Wall, Glees and Fulton (151) stated that in view of 'the difficulties involved in the fine-fibre staining technique, we have recognised degeneration as occurring only in the following circumstances: first, when there was clear contrast between the operated and control sides stained simultaneously; second, when the section showed a clear
agranular background with discrete parallel-sided fibres; third, only
gross distortions of fibre shape and termination were accepted as
evidence of degeneration."

Adey ('51) does not give his criteria of degeneration except
to say that degenerating terminals are 'swollen'.

Getz ('52) states that 'provided that a comparison with
normal material is carefully carried out and that also degenerated
terminal fibres are found - the differences between the normal and the
degenerating structures are sufficiently clearcut to allow an exact
mapping out of the termination of transected fibre tracts.' His
criteria for the degeneration of boutons are - an increase in number
of all types, especially of solid black boutons, 'the shape of several
boutons being oval and irregular.' He states, however, that the finding
of degenerated boutons alone is not sufficient to allow the diagnosis
of terminal degeneration '... this diagnosis can only be made when
degenerating terminal fibres are also present'. His criteria of the
degeneration of terminal fibres are a 'drop-like appearance ... "beading",
vacuolisation and an increased affinity for silver.' He would not
include fibres distinguished only by 'irregular contours and diameters'.
Notice that Getz would only recognise degenerating fibres as providing
certain evidence of degeneration whereas Brodal, Walberg and Blackstad
would also recognise an 'exceptional' increase in the number of boutons
or 'an increased number of solid, degenerating boutons' as well. Glees
and Le Gros Clark ('41) quote Schimert ('38): 'He considers that the
appearance of the end-bulb itself is not always a safe criterion of
degeneration, unless it is accompanied by degenerative changes affecting
the terminal fibre which carries it.' However, it is not always obvious whether a given structure is a degenerating bouton or terminal fibre.

Meyer ('49), using human lobotomy material, followed these criteria of degeneration 'gross changes of axons and terminals'; in the case of boutons the ring form had to be completely filled in and replaced by 'large homogeneous or disintegrating swellings'; in the case of preterminal fibres these had to be 'broken up into fine droplets'; fibres had to show 'fragmentation and vacuolisation together with a marked swelling ... in their course.' Beck, Meyer and LeBeau ('51) recognised only 'an accumulation of grossly degenerated fibres and/or terminals as significant of degeneration. They stated furthermore that 'Negative findings in a given area could safely be regarded as proof of the absence of any fibre connexion with the ablated or isolated region.' (our italics; see also Le Gros Clark and Meyer ('47) on this point). Martinez ('55) recognises 'hyperargyrophilic' fibres and 'hypertrophic' boutons or 'club-shaped' terminals as being degenerated. (Note however that in our opinion the boutons shown in his figures 6 and 8 could well be normal for the globus pallidus and the pons.)

It will be noticed that in all the accounts given above the criteria of degeneration have been qualitative and subjective and moreover have differed somewhat from worker to worker (owing, probably to some extent, to the different regions and different species examined and to the different stains used). It will be clear that consistent and comparable results may not be obtained if different criteria are used by different people.

(3) The method of presentation of the results. In the case of nearly
all workers the evaluation of the extent of the degeneration has been presented (i) by written reports; (ii) by means of freehand drawings, or drawings made by some kind of projection apparatus, on which the extent of the degeneration is marked by dots, cross-hatching, etc. inserted by freehand (for examples see figures 58-61); and (iii) by photomicrographs. In Hoff's first presentation ('32a), however, dots were used on a camera lucida drawing of the cord to show the location of a cell supporting degenerating boutons (fig. 56). In his next presentation ('32b) round black dots were used to show the position of each cell supporting degenerating boutons, and black triangles showed the position of dendrites supporting degenerating boutons. Crosses were used to show the position of peridendritic degenerated boutons occurring very close to the cell body. In his 1935 paper the method was the same but no crosses were used (fig. 57).

It therefore seemed to us that, in order to make this method more rigorous, more objective criteria of degeneration should be attempted and more precise methods of presenting the extent of degeneration have evolved. The subjective and qualitative evaluation of degeneration has given reasonably accurate results in the hands of experienced workers but there is always the danger that not all the potentially available information will be gained from the investigation. That is to say that finer details of distribution of severed fibres may be lost that might have been revealed by objective and quantitative scanning methods. Furthermore, using the latter methods, the results of different workers could be compared with more precision than could be attained when the criteria that each worker uses differ from those
used by other workers to a greater or lesser extent. However, to be of much use, these criteria would have to obtain general acceptance as it would be of little advantage if every worker set up his own objective criteria of degeneration.
CHAPTER II

MATERIAL AND METHODS

Four lobotomised human brains were available for this study.

L-1. This brain came from a case with a survival time of only five days and no signs of degeneration were found (except immediately around the wound) in spite of intensive search.

L-2. This brain was obtained from a case of bronchogenic carcinoma who died aged 49 at the time of death. A bilateral prefrontal lobotomy was performed for intractable pain on April 11th, 1950. The day following the operation the patient was alert but had nausea and was incontinent. Four days after the operation he became dyspneic and irrational and he died on the seventh post-operative day. On examining the right side of the brain a leucotome entry mark could be seen on the extreme lateral edge of the orbital surface of the frontal lobe at the posterior end of the inferior frontal gyrus. Coronal sections of the frontal lobe are shown in figures 1-3. The lesion extended upwards and forwards undercutting the eulaminate cortex of the lateral surface of the frontal lobe. Nissl stained sections showed that the region of entry lay just anterior and lateral to dysgranular cortex. On the left the leucotome had entered a little farther forward in the posterio-intermediate part of the middle frontal gyrus. Nissl stained sections showed that this was anterior to dysgranular cortex. The lesion extended forwards and upwards as on the right side (figs. 4-6).

L-3. This brain was obtained from a case of schizophrenia (paranoid type) 25 years old at the time of death. On November 6th, 1947
bilateral prefrontal lobotomy was performed. Four days later he developed a temperature and a wound infection was noticed. Meningitis developed. Seven days after the operation the patient died following four generalised epileptiform convulsions. On examination of the right side of the brain the entry of the leucotome was visible in the middle of the middle frontal gyrus in Brodmann's area 9. Nissl sections showed this to be anterior to dysgranular cortex. The lesion extended downward and backwards to enter the anterior pole of the corpus striatum (figs. 7-9). The lesion on the left side was essentially similar.

L-4. This brain was obtained from a case of schizophrenia (hebephrenic type) aged 43 at the time of death. Bilateral prefrontal lobotomy was performed on August 17th, 1948 described as 'cortical undercutting of areas 9 and 10.' Twelve days after the operation the patient suddenly collapsed and a spinal puncture revealed a pressure of 500 mm. of water. An exploratory operation revealed extreme oedema of the brain. On each side of the brain the entry mark of the leucotome was visible in the middle of the superior frontal gyrus on the dorsal convexity in front of the dysgranular cortex (confirmed by Nissl staining). The lesion extended downward and forward to the extreme frontal pole. On the right side the leucotome had penetrated the cortex again to emerge from the brain through the frontal pole. On both sides the upper half of the prefrontal region had been undercut including some damage to the cortex of the cingulate region. There were also signs of recent haemorrhage in the anterior part of the corpus callosum. Although the leucotome entered eulaminate cortex and its path had extended forwards,
there was also brain damage (haemorrhage, softening and discolouration) extending backwards so as to cut into the rostral tip of agranular cortex (figs. 10-13).

Each brain arrived fixed in formalin and sectioned by the pathologist conducting the post-mortem examination. Drawings of each brain and each slice of brain were made from different aspects. Sections from the frontal lobe cortex were cut on a freezing microtome at 20 μ followed by sections taken to include the thalamus, hypothalamus and related structures; the red nucleus, substantia nigra and related structures; the basal ganglia and internal capsule; the hippocampus and amygdala; and the pons. These sections were stained by Gibson's modification of Rio-Hortega's double impregnation method. At a pH of 10.6 this stain also provides a good method of determining cytoarchitectonic features since, at this pH, the cell bodies are stained differentially with respect to the background. We have used this as a 'Nissl' stain as well as Cresyl violet. In the locations where degeneration was found accurate maps were prepared by plotting the outline of the nuclei on graph paper from readings taken from the micrometer scale of the moving stage of the microscope. The presence and extent of degeneration were inserted as follows:

(1) Objective criteria of degeneration were set up. These criteria were chosen after studying a large number of sections from these brains (not L-4 which we did not receive until much later than the other three) together with sections of the same part taken from each of our three normal control brains (NC1, NC2, and NC3; see Smythies, Gibson and Purkis '55). In the case of the dorsomedial nucleus of the thalamus
the following criteria were decided upon:

(i) One unit of degeneration was defined as a dark purple\textsuperscript{1} object in the field larger than 2.5\,\mu in average diameter; either solid or, if perforated, the diameter of the hole (or holes) was not to exceed $1/3$ of the total diameter of the object; and possessing an homogeneous internal structure (studies of brains with longer survival times than ours would presumably have to allow for the final stage of fragmentation). If there were two units of degeneration in a field (using a x 100 objective and a x 8 ocular) that field was marked on the map as a black dot in its position obtained from the co-ordinates given by the micrometer scale on the moving stage of the microscope. Traverses were taken across the section at intervals that varied depending on the size of the section. Every consecutive field on each traverse was examined. In most cases the fact that the degenerated terminal was larger than 2.5\,\mu could be judged by eye; in case of doubt it was measured by means of a micrometer eye-piece. Typical units of degeneration are shown in figures 52-55 and 64-65. We examined a total of approximately 6,000 fields in the dorso-medial nucleus in our three control brains without finding 2 units of degeneration in a single field. Maps of the control brains would therefore merely be blank.

(ii) In the pontine nuclei these same criteria proved to be quite unsuitable as this region normally contains a large number of bouton

\textsuperscript{1} Dark purple using this stain: this criterion excludes particles of metallic precipitate which are jet black and colloid globules which are light purple and have moreover a less clearcut outline than have terminals.
termineaux per field with a fair number fulfilling the criteria given above. Figure 50 shows a section from a normal pons mapped according to these criteria. After examining sections from L-4, which alone of our brains appeared to show some degeneration in the pontine nuclei, the following criteria were chosen. On the map a field was shown as containing degeneration if there were more than 50 boutons termineaux and 'degenerating terminals' of all kinds in the field together with an obvious thinning of the normal plexus of fine unmyelinated fibres (figs. 70-71). Although fields with more than 25 boutons per field are frequent in the normal pons as figure 50 shows we did not see any fields in the normal with as many as 50 boutons per field. But as we do not yet know the extent of individual variation in this respect we introduced the second criterion - the thinning of the fibre plexus - although this re-introduces a subjective element into the criteria. We were unable however to construct a workable objective criterion for the 'thinning' of a fibre plexus.

(iii) In the medial mammillary nucleus the criteria were fixed at two units of degeneration per field as in (i) together with an obvious thinning and fragmentation of the normal plexus of fine unmyelinated fibres as in (ii) (fig. 74). It was noticeable that the products of degeneration in this region were not as large, nor did they stain so darkly as those seen in (i) and (ii).

(iv) We were unable to reach satisfactory objective criteria for degenerating fibres. The mere size of the swellings along the course of the fibre would presumably depend to some extent on the initial size of the fibre. Fragmentation, vacuolisation and heightened argyrophilia
do not lend themselves readily to recordable quantitative treatment which would not at the same time be unworkably clumsy. In our figures the presence of degenerating fibres was shown where there was more than one fibre in the field which appeared to be grossly degenerated (showing increased argyrophilia, gross fusiform or more irregular swellings in their course, vacuolisation and fragmentation).

(2) A method of presenting the information was developed so as to show, as nearly as possible, the actual position of each area of degeneration in the part concerned. This was done by preparing accurate maps of the part by means of readings taken on the micrometer stage of the microscope transferred to graph paper and the exact position of each field showing degeneration could then be inserted on the map after taking similar readings.
CHAPTER III

RESULTS

L-1. As we mentioned above no degeneration was found anywhere in this brain except immediately around the wound where the appearance was the same as has been described previously in the literature. Meyer ('49) found no evidence of degeneration in a human case with a survival period of six days.

L-2 and L-3. In each side of both these brains the extent of the degeneration was very similar:

(i) Thalamus. On each side of L-2 twelve coronal sections at approximately equal spacing through the dorso-medial nucleus were examined and maps were prepared from nine of these on each side, six of which are shown in figures 14-19 (R) and four in figures 20-23 (L).

On the right side of L-3 twelve such sections were examined and maps prepared from eight of these, seven of which are shown in figures 24-30.

On the left side of L-3 and L-4 (extreme posterior part) two such sections were examined and were found to be essentially similar to those taken from the same position on the right side of these brains. In L-2 (R and L) and L-3 R two additional sections anterior to the rostral limit of the dorso-medial nucleus and one section posterior to its caudal limit were examined. Each of these sections included the full extent of the thalamus, all nuclei of which were included in the regular scanning. Maps were only prepared of regions showing degeneration.

Figures 14-30 show representative examples of these maps and these show that there was degeneration in the middle strip of the dorso-medial
nucleus along almost its whole length (fig. 64). This degeneration was more marked in the dorsal part of this strip than in the ventral part particularly rostrally. It extended a little farther forward in L-2 (R) than in the others. It was mostly in the small-celled part but was not confined to it. In any case the boundary between the two portions of the nucleus is not always clear cut and so we have described the region of degeneration relative to the extent of the whole nucleus. The most medial and the most lateral portions of the nucleus have escaped the degeneration. No degeneration was seen in the nucleus submedius. The apparent 'degeneration' marked in the nucleus parafascicularis is not true degeneration as a comparison with the normal nucleus shows (figs. 51 and 66-67). This merely demonstrates, as has been previously reported (Smythies, Gibson and Purkis '55), that the nucleus parafascicularis is unique amongst the thalamic nuclei in having a relatively large number of large dark boutons termineaux and is thus not a suitable location in which to apply criteria of degeneration appropriate to the other thalamic nuclei.

(ii) Prefronto-pontine tract. In L-2 a few fibres were seen degenerating in the course of the fronto-pontine tract (as described by Beck '50). In L-3 many such fibres were seen degenerating immediately below the inferior limit of the lesion (figs. 35 and 68). The number of degenerating fibres seen rapidly decreased the further caudal to the lesion the section was taken (figs. 35-40). No definite signs of degeneration were seen in the pons (compare fig. 41 with fig. 50).

(iii) Elsewhere. No degeneration was seen in six sections through the hypothalamus in each brain nor was there any to be seen in numerous
sections through the other nuclei listed above in either brain.

L-4.

(i) **Thalamus.** Twelve sections spaced through the dorso-medial nucleus were examined and maps were prepared from seven of these, four of which are shown in figures 31-34. The type of degeneration is shown in figure 65. It will be seen that the extent and type of degeneration is essentially similar to that seen in the other two brains. One point of interest is the heavy degeneration seen in the extreme posterior end of the nucleus in the region of the pulvinar. As no such heavy degeneration was seen in this region in brains L-2 and L-3 this provides some evidence that the medial aspect of the frontal eulaminate cortex (undercut only in L-4) projects particularly to the posterior end of the dorso-medial nucleus. On the other hand the place of origin of these fibres might be in the most posterior part of the eulaminate cortex in the dorsal convexity, also affected only in L-4. No degeneration was seen elsewhere in the thalamus.

(ii) **Prefronto-pontine tract.** Figures 42-46 and 69-71 show that the extent and nature of degeneration of the prefronto-pontine tract and in the pons is not significantly different from that reported by other workers. One possibly significant point is the heavier degeneration in the upper 1/3 of the pons than in the rest of the pons. It should be noted that the sections made by the pathologist in this brain were not true coronal sections but were very oblique being parallel to that part of the fornix that runs through the hypothalamus.

(iii) **Hypothalamus and elsewhere.** Four sections through the mamillary body were examined three of which are shown in figures 47-49. The type
and extent of the degeneration (figs. 72-74) was essentially similar to that reported by Meyer (149) except that there was a less clearcut antero-posterior difference. A small bundle of degenerating fibres was found running down beside the fornix in the inferior thalamic radiation (fig. 47) possibly on its way to the mamillary body. No degeneration was seen in four other sections examined through the hypothalamus and septal nuclei. There was no degeneration seen in the caudate nucleus, putamen, globus pallidus, substantia nigra, subthalamus, zona incerta or Forel's fields nor in four sections taken at equal intervals along the whole length of the hippocampus. In the red nucleus there were more (normal looking) boutons than we had seen in our normal controls but in the absence of any other signs of degeneration a mere increase in the number of boutons can not be regarded as evidence of degeneration until much more is known about the extent of normal variation between different parts of the same nucleus in one brain and the same parts of the same nucleus in different brains.

**Cortex:** An examination was also made of the extent of degeneration in the cortex. In L-1 and L-2, 68 sections (in each) from all parts of the cortex and in L-2 40 sections from the frontal cortex were examined. No signs of degeneration were found except immediately around the wound (figs. 62-63). It was noticed that the same general features of bouton distribution and morphology that we have reported previously were present in these brains. In L-4 20 sections of the frontal lobe and 7 sections of the occipital and adjoining portions of the parietal and temporal lobes were examined. In the former degenerating terminals were seen as has been described by previous
authors, progressively decreasing in number from layer 6 outwards. In
the latter no degeneration was seen.
CHAPTER IV

DISCUSSION

These results confirm previous reports that the eulaminate cortex of the prefrontal region projects to the dorso-medial nucleus of the thalamus. The extent of this degeneration is shown in our figures. The minor variations in the distribution of degeneration in these three brains may prove to have significance if compared with the results of many more such investigations. The most marked of the variations lies in the heavy degeneration in the extreme posterior part of the nucleus in the only case where the lesion undercut the cortex on the medial aspect of the hemisphere and extended to the most posterior part of the eulaminate cortex on the dorsal convexity. We were unable to confirm previous reports (Meyer'49, Martinez '55) that the nucleus submedius is also involved. The morphology of the boutons in the normal nucleus parafascicularis (figs. 65-66) should be taken into account in evaluating the presence of degeneration in this nucleus and in the rather ill-defined region between it and the nucleus submedius. Our results also confirm Meyer's observation ('49) that a lesion encroaching upon the granular cortex on the dorsal convexity of the frontal lobe projects to the medial mamillary body, particularly its ventral part. Our results also confirm that there are no significant hypothalamic connexions from purely eulaminate regions of the frontal lobe outside the orbital regions (which were not affected in any of our specimens). The prefronto-pontine tract is also involved in all our brains showing degeneration. The heavier involvement in L-4 may
merely be an indication of the noci-fugal spread of degeneration in
fibre tracts shown clearly in this tract in L-3 and described in the
rabbit by Glees, Meyer and Meyer (147).

We have also attempted to set up objective quantitative
criteria of degeneration and have utilised a mapping method of plotting
the location of degeneration. However, these criteria are not yet
completely objective as we could not find satisfactory quantitative
criteria for fibre degeneration nor for the disintegration of a fine
unmyelinated fibre plexus.

The local differences in the picture of degeneration seen
are also interesting. In the dorso-medial nucleus of the thalamus the
tendency was to produce large (often 3-5 μ) solid, or nearly solid,
masses without much sign of any fragmentation of the fine unmyelinated
plexus (figs. 52-55). It was also noteworthy that the picture seen at
12 days hardly differed from that seen at 7 days. In the medial
mamillary body the picture of degeneration was a marked disintegration
of the fine unmyelinated fibre plexus into a large number of
argentophil masses, mainly solid, but on the average considerably
smaller (and less argyrophilic) than those seen in the dorso-medial
nucleus and often not much more than beads (fig. 74). In the pons
there was an increase in the number of boutons seen (with a high
proportion of larger terminals) together with a fragmentation and
disappearance of the fine unmyelinated fibre plexus (figs. 70-71).
This account only describes what may be seen at certain periods after
the injury. Examinations at other post-operative periods might be
expected to give different microscopic pictures.
Finally, from our study of the normal distribution and morphology of boutons termineaux we can tentatively suggest that our 'dorso-medial' criteria are suitable for all parts of the forebrain except the nucleus parafascicularis of the thalamus, the mesocortex, substantia nigra and globus pallidus, and parts of the amygdaloid complex. Area 4 of the neocortex and the subiculum might give rise to some difficulties of interpretation. In the medial mamillary body the size and depth of staining of the products of degeneration were not so marked as to render the criteria of degeneration based solely on this feature as certain as one would wish thus necessitating the inclusion of fragmentation of the fine fibre plexus. This disadvantage might also be encountered in other nuclei in which we did not have the opportunity of examining degeneration. Specific criteria can only be set up for each nucleus and cortical area after a thorough study of the form of degeneration in each part and of the form of the normal synaptic morphology in each part.
CHAPTER V

SUMMARY

A study has been made of the extent of terminal degeneration in four lobotomised brains using a silver method. We have confirmed previous reports that the eulaminate cortex of the frontal lobe outside the orbital region projects exclusively to (i) the dorso-medial nucleus of the thalamus and we have localised this projection to a strip along the median part of the nucleus in the greater part of its length, and (ii) to the pontine nuclei. In one brain the lesion encroached upon agranular cortex and here degeneration was also found in the medial mamillary body but not elsewhere. Differences in the microscopic appearance of terminal degeneration in the various regions has also been described. We have also paid particular attention to the method of terminal degeneration itself and have endeavoured to place this on a more objective basis, using quantitative criteria of degeneration wherever possible.
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FIG. 4A.—An outline of the right half of the spinal cord at the seventh post-thoracic segment, from a cat completely de-afferented on the right side of the lumbar enlargement. The drawing was made from six sections, and each dot represents a cell upon which degenerating boutons were found. Cat 2, operation 2. (Camera lucida drawing.)

FIG. 4B.—A diagram showing the manner of termination of afferent nerves in the grey matter of the cord suggested by the location of degenerated boutons in the grey matter of de-afferented cords. The way in which cells in the mid-region connect with ventral horn cells is not suggested, as implied by the broken line.
Fig. 4 (experiment 2).—Sections of the spinal cord at the seventh cervical and sixth postthoracic segments, showing the distribution of bouton degeneration in the spinal gray matter of a macaque killed four days after ablation of the right premotor area. The black circles and triangles have the same significance as in figure 2. (The diagram was drawn with a projector.)
Fig. 7 To the left a composite diagram of the findings in this study. The terminal area of fibers from the cervical segments is indicated by rings, the area for fibers from below mid-thoracic by dots (for the sake of simplicity termed forelimb and hindlimb areas). To the right a series of transverse sections through the lateral reticular nucleus showing the distribution of retrograde cell changes following a paravermian incision of the cerebellum (43). Black denotes areas maximally changed, cross hatchings intermediate, and simple hatchings slightly changed areas. The figures 1-9 of the sections to the right refer to their order in the complete diagram in the previous paper, and the heavy horizontal lines indicate the level of each section with reference to the longitudinal sections to the left. Abbreviations as in figure 3.
Fig. 3. Diagram of findings in cat Sp. C.L. 12. Lesion of cord at C_2. Above, series of horizontal sections through inferior olive. Its different parts are indicated abbreviations as in Fig. 1. Dotted areas show parts in which terminal degeneration of fibers and boutons is present, density of dots giving an approximate impression of intensity of degeneration. Wavy vertical lines indicate coarse ascending degenerated fibers. Below, two sections through spinal cord; left, drawing of superimposed cell-stained sections from C_2; right, diagram of ascending degenerated fibers seen in Marchi sections from C_1. L: left, R: right, N.r.l.: Lateral reticular nucleus.
Fig. 2. Diagram of the findings in cat Sp. C. L. 21. Lesion of the cord at C_i. Above, series of frontal sections through the thalamus. The main nuclei are indicated as in figure 1. The dotted areas show where terminal degeneration is present, and the density of the dots give an approximate impression of the intensity of the degeneration. Below, a section through the spinal cord at C_i showing the lesion. The area totally damaged is indicated black, areas partly damaged are hatched.
Fig. 16 (Case 4).
Fig. 64.
Fig. 74