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Part I.—Original Articles.

NEUROPATHOLOGICAL PROBLEMS ARISING FROM PREFRONTAL LEUCOTOMY.*

By A. MEYER, M.D.Bonn, and E. BECK.

From the Neuropathological Department, Central Pathological Laboratory, London County Mental Health Services.

Outline of Problems.

THE neuropathological problems which arise from prefrontal leucotomy may be conveniently divided into three groups.

The first group is concerned with the analysis of the anatomical and possible other factors which may influence the prospect of recovery. This group is naturally of the greatest practical interest to the psychiatrist and, for this reason, will require our foremost attention.

Secondly, the operation constitutes, apart from the therapeutic aspect, a human experiment of first-class importance in neuro-anatomy. Since much of our knowledge of the neuro-anatomy of the regions involved is based upon experiments in animals, a most welcome opportunity has arisen to compare these with the conditions in the human brain. The neuro-anatomical harvest has been considerable; so much so that only a few of the results which have a direct or indirect bearing on the problem of leucotomy can be summarily included in this paper. It is our intention to publish a fuller account later in the *Journal of Anatomy*.

Thirdly, the operation enables us to study biopsies from the brain of mental patients. The customary surgical methods limit the scope of this investigation, as it is usually impossible to obtain a sufficiently large and undamaged piece of cortex, but with certain precautions it is not difficult to produce a cylinder of white matter. We are at present utilizing this material and studying the oligodendroglia, which was found by Elvidge and Reed (1938) to be affected by swelling in patients suffering from functional psychosis. This special investigation, however, is not yet sufficiently advanced to be included in this paper; it will be the subject of a separate publication (in conjunction with McKissock).

Material.

Our material consists of seven histologically investigated cases of prefrontal leucotomy, to which has been added an eighth case in which frontal lobectomy had been carried out in a mentally normal patient suffering from a basal meningioma. This last case has proved of great value as a test case for complete severance of fibre connections. In two further cases (9 and 10) macroscopic investigation only has been carried out so far. We wish to express our gratitude to Prof. Le Gros Clark, Col. McCowan, Drs. Cook, Dax, Harris, McCartan, Rees and Ström-Olsen and to Mr. McKissock for their generous permission to utilize the brains from their cases for the preparation of this paper.

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It is not proposed to give a full description of the clinical and pathological data, as it is likely that, in due time, the problem will have to be reviewed on a more comprehensive scale, with the addition of a number of new cases now under investigation. For the purposes of this paper it was thought, however, useful to give a survey of the most important data in tabulated form (Table I). This shows that the survival period varied from 3 days to 3 years. Some of the cases had received unsuccessful convulsion or insulin treatment prior to the operation. Death in the early stages resulted from meningitis or haemorrhage. Haemorrhages may be very considerable, as, for example, in Case 1 (Fig. 1), in which the whole white matter of the frontal lobes was converted into a haemorrhagic mass. This patient died after six days, but other cases complicated by haemorrhage have survived, the haemorrhage being slowly converted into cysts or softening. Figs. 2 and 3 show such sequelae of haemorrhages. In these the white matter has an appearance quite different from the slit-like, smooth-walled cyst which Freeman and Watts (1942) described as the normal result of the operation. Other adverse complications include uraemia and a fairly advanced senile atrophy in Case 3; pellagra in the same case (Fig. 4); hypertensive disease and a terminal Wernicke syndrome with the typical mesodermal proliferation in the mammillary bodies and other hypothalamic centres in Case 4 (Fig. 5), indicating vitamin B_1 deficiency; and lastly, post-operative epilepsy in Case 5. So far we have not found any anatomical changes that would account for the epileptic convulsions. It is interesting that in this case the lesion was further away from the motor cortex than in any of the other cases, and the prefrontal cortex was certainly not more damaged than usual. The patient died in *status epilepticus*.

Analysis of the Factors which may determine Recovery.

The rationale of the operation is generally considered to be isolation of the prefrontal cortex by cutting its fibre connections with other parts of the brain. This is not the place to discuss at length the function of the frontal lobe. Much pathological evidence has accumulated in the past, tending to show that bilateral lesions of the frontal lobes and particularly the orbital parts result in syndromes of euphoria (Witzelsucht) and general disinhibition, considered likely to neutralize depression, tension, inhibition, obsessional features, etc., of patients submitted to the operation. According to Rees (1943), whose views are in close agreement with those of Freeman and Watts (1942), the frontal lobe is concerned with imagination, the social sense, self-consciousness and the projection of the self into the future. He goes so far as to associate the Freudian "superego" with the function of the frontal lobe and the "id" with that of the thalamus. This is, of course, an oversimplification, and comes dangerously near to what Cobb (1943) has criticized as "neurologizing psychology." Cobb is much opposed to regarding the frontal lobes as centres for foresight, imagination or, indeed, any specific traits of man. The frontal lobes are important, as they allow "long circuiting" actions, and the operation has its effect by reducing the number of possible circuits for association. According to Cobb this concept explains better than any "centre" theory the fact that the initial symptoms of lesions of the frontal lobes may subside in the course of time in measure as unspecialized paths of association take over the function of the cut fibres.

The majority of fibres cut by the operation belong to the thalamo-frontal tract, which connects the nucleus medialis dorsalis of the thalamus with the prefrontal region. The nucleus medialis dorsalis is connected with other thalamic nuclei and —by way of the medial magnocellular portion—with hypothalamic centres. According to Walker (1938), its role is to serve as an "integrating centre for somatic sensory and visceral impulses, presenting them to the cortex of the pre-frontal region in a complex form . . . as sensory concepts." Freeman and Watts (1944*a*) think that in addition to the thalamo-frontal fibres a bundle running near the midline is of importance. They suspect it to be the fasciculus cinguli, and give a vivid description how, after sectioning this suspected bundle, the patient loses contact with reality and drifts into confusion and unresponsiveness. The fasciculus cinguli runs along the white matter of the gyrus cinguli, and it is interesting that the latter is, again, connected with the anterior nucleus of the thalamus. Evidence is accumulating that the prefrontal cortex, and particularly its orbital region, the

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TABLE I.

Case number.	Age at the time of death.	Duration of psychosis prior to operation.	Symptomatology and diagnosis.	Previous treatment.	Prefrontal leucotomy.	Post-operative course.	Interval between operation and death.	Special pathological findings.	Cause of death.
1	43	4–5 years	Agitated depression, with the usual melancholic delusions	Unsuccessful convulsion treatment	Watts' technique	—	6 days	—	Purulent meningitis, cerebral haemorrhage. Moderate cerebral arteriosclerosis as a contributing factor.
2	30	9 years	Schizophrenia (hallucinated, deluded, impulsive and violent)	Ditto	Ditto	—	3 ,,	—	Purulent meningitis.
3	72	About 4 years	Depression (acutely agitated, distressed, self-reproachful, no intellectual impairment)	,,	,,	No improvement	2 months	Slight diffuse loss of nerve cells in all cortical regions with corresponding degree of glial proliferation. Fair number of senile plaques. Retrograde degeneration of large nerve cells of precentral cortex, pons and medulla, suggesting pellagra.	Uraemia due to hypertrophy of the prostate. Pellagra.
4	50	2 years	Paraphrenia (deluded, hostile and impulsive. Suffers from hypertensive disease)	—	,,	Disappearance of hallucinations, but offset by severe frontal lobe deficit syndrome and restlessness	4 ,,	Mamillary body and nucleus paraventricularis contained gliomesodermal proliferation and petechial haemorrhages characteristic of the Wernicke syndrome.	Exhaustion due to restlessness. Thiamine deficiency. Hypertensive disease may have been a contributing factor.
5	44	About 20 years	Schizophrenia (hallucinated, deluded, violent and destructive)	—	,,	No improvement	17 ,,		*Status epilepticus.*
7	30	At least 3 years	Schizophrenia (deluded, excited, abusive and destructive, attempted suicide)	Unsuccessful convulsion treatment	Crombie's technique	Considerable improvement	8 ,,	—	Tuberculous abscess.
8	41	4–5 years	Paraphrenia (hallucinated, deluded, sometimes excited)	—	Ditto	Ditto	16 ,,	—	Carcinoma of oesophagus.
9	39	About 3 years	Schizophrenia (depressed, suicidal, hallucinated, deluded)	—	,,	,,	21 ,,	—	? Pulmonary tuberculosis.
10	28	Since early childhood	Psychopathic personality with violent hysterical outbursts	Unsuccessful insulin and convulsion treatment	,,	,,	3 years	—	Streptococcal stomatitis and dermatitis (? nutritional deficiency).

cingular cortex, thalamus, hypothalamus and possibly the hippocampal region in the temporal lobe are important in relation to emotion, emotional expression and personality organization (*cf.* Meyer, 1944).

We have not been able to procure, in time to be included in this paper, a full account of the technique employed by the various neuro-surgeons who have operated on our cases. We have, therefore, no adequate knowledge of the criteria used in order to determine the place of introducing the leucotome, nor are we informed about special intentions which guided the surgeons. Dax (1943) has commented on the " alarming discrepancies between the actual point of the insertion of the leucotome and the desired point," if the surgeon relies upon surface markings only. McKissock (1943) is of the opinion that there will always be—even with improved technique—some degree of variation in individual cases, not only as regards the plane of the cut, but also as regards differences of depth of the cut, completion of the circular movement of the leucotome (if the Watts technique is used), and different amounts of haemorrhage, softening or scarring on one or both sides.

This scepticism is borne out by our pathological experience. In Fig. 6 the plane of the cut in all our nine cases of leucotomy is indicated ; the striking variation in individual cases cannot be satisfactorily explained by deliberate surgical intentions. Fig. 1 (Case 1) shows a fairly well placed cut and an extensive all-round lesion of the white matter produced by the cut plus haemorrhage. The lesion extends well to the midline and has involved the cingular region, to which Freeman and Watts attached importance. The patient, however, died after six days from excessive haemorrhage and meningitis. In Case 3 (Fig. 7) the plane of the cut is fairly optimal, but only the lateral and dorsal aspects of the white matter have been severed, while the midline structures and the orbital areas have escaped. In the other hemisphere the cut has been placed in a slightly more rostral plane ; the lesion is smaller, but occupies a similar position. In Case 5 the cut was placed too anteriorly ; on the right side (Fig. 8) the whole white matter has been damaged, while on the left side the main lesion is situated in the orbital and midline parts, while the dorsal and lateral parts have been less involved (Fig. 9).

A cut in too posterior a level has been recognized as leading to unfavourable clinical results. The chance of cutting thalamo-frontal fibres is slender, as the fibres, in their backward course, soon converge to a small compact bundle which runs in the neighbourhood of the septum pellucidum to enter the ventromedial parts of the internal capsule. In order to cut the bundle in this place too many important structures would be involved, damage to which probably accounts for the unfavourable clinical result. Cases 2 and 4 are examples of a too posterior cut. Figs. 10*a* and 12 demonstrate that in both cases fairly symmetrical damage has been caused by the cut to the anterior horn and the antero-dorsal aspects of the striate body and internal capsule. The haemorrhage and its sequelae have involved, in both cases, the white matter of the posterior—granular and agranular —frontal lobe, and laterally extend even into the opercular and insular regions. But whereas in Case 2 the orbital region has been severely affected at the point near the septum likely to involve severance of the thalamo-frontal bundle (Fig. 10*b*), the orbital region is spared in Case 4 (Fig. 11).

Severance of thalamo-frontal fibres leads to retrograde cell degeneration in the nucleus medialis dorsalis of the thalamus (Figs. 13, 14), and this is the best method of assessing the damage done to this fibre system. Tracing of myelin degeneration is less reliable, as the thalamo-frontal system has only a poorly developed myelination (Walker, 1938). Investigations by Glees, A. Meyer and M. Meyer (so far unpublished*) have shown that it is possible to trace the degeneration of the terminal unmyelinated fibres of the thalamo-frontal and fronto-thalamic pathways, but a quantitative assessment will be difficult because of the use of silver impregnation methods. Freeman and Watts (1944*b*) briefly state that in their fatal cases about 75 per cent. of the nerve cells in the parvicellular portion of the nucleus medialis dorsalis had been destroyed, but they do not indicate whether and in what proportion their material includes recovered cases. In order to obtain a more accurate quantitative assessment we have counted the remaining cells in three coronal levels of the nucleus medialis dorsalis, and compared the results with those in a normal brain and in the one (Case 6) in which a complete severance

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of thalamo-frontal fibres had been accomplished by frontal lobectomy. Counting was done in each level throughout the whole extent of the nucleus medialis dorsalis (parvicellular part), the thickness of the section being 20μ, and the figures obtained were calculated for unit areas. The results have been compiled in Table II:

TABLE II.—*Dorso-medial Nucleus (cells per unit area).*

	Anterior portion.	Degeneration. %.	Middle portion.	Degeneration. %.	Posterior portion.	Degeneration. %.
Normal	22	—	19·8	—	14·8	—
Case 1, 6 days	11·5	48	21	0	13·6	8
,, 2, 3 days	13	41	11·1	44	11	26
,, 3, 2 months	12·7	43	9·6	52	10	33
,, 4, 4 months	16	27	8	60	12·7	14
,, 6, R., 17 months	14·3	35	11·8	41	15·7	0
,, 5, L., 17 months	11·7	47	15·9	20	15·8	0
,, 6, 6 weeks	4·6	79	6·3	68	11	25

It is seen that in the case of lobectomy the degeneration is not complete, either because during the survival period of six weeks not all the cells have been destroyed, or because a small proportion of the cells is not concerned with the projection to the prefrontal cortex. In the leucotomy cases the loss of cells is still less complete. It is surprising to find a considerable loss in Cases 1 and 2, both of which survived the operation for only a short time. Further analysis revealed, however, that the cells had not actually disappeared, but as a sign of early degeneration were only slightly stained and thus escaped being counted. The obvious difference in the degree of severity of cell loss in the antero-posterior axis of the nucleus will be discussed elsewhere.

Unfortunately a similar analysis is not available for the four recovered cases of our series. Two of the cases (7 and 8) were investigated by Prof. Le Gros Clark, who kindly communicated his observations to us; in the remaining two (9 and 10) only a macroscopic examination has so far been made.

The first (Case 7) was an excitable schizophrenic. Prior to the operation the mental illness had been apparent for at least three years. Throughout the survival period of eight months following the operation the patient was much quieter, less aggressive and easy to manage, although towards the end there was an occasional recurrence of violence. In this case the operation had resulted in an appreciable severance of thalamo-frontal fibres on only one side. The orbital and midline areas had almost entirely escaped, and there was only patchy damage in the nucleus medialis dorsalis of the affected side, while the contralateral nucleus was unaffected (Fig. 15).

The second recovered case (No. 8 of our series) was a typical paraphrenia with little personality deterioration after five years' duration of the attack. After leucotomy he was much better in every way, less excited, his hallucinations and delusions far less obvious. The following note was made seven months after the operation: "It is a great pleasure to see him, walking about on parole with other patients, laughing, happy and friendly. So far a great success." There was no relapse, but he died from carcinoma of the oesophagus sixteen months after the operation. In this case leucotomy was performed in a very posterior plane (Fig. 16), and merely resulted in cutting through the operculum, insula, external capsule and claustrum. The thalamo-frontal connections had not been severed, and the nucleus medialis dorsalis was preserved.

The third recovered case (No. 9 of our series) suffered from schizophrenia with symptoms of suicidal depression, hallucinations and delusions. He remained almost inaccessible until the leucotomy, which was performed in August, 1943, at least three years after the onset of the psychosis. The condition improved rapidly, he talked rationally and showed appropriate emotional response. He denied hallucinations, and there was no evidence of persistent delusions. He worked well in the stores, doing clerical work and weighing. He died in April, 1945, probably from pulmonary tuberculosis. Macroscopic examination (Fig. 17) of the brain revealed a fairly symmetrical lesion occupying the white matter of the inferior frontal gyrus at the level of the genu of the corpus callosum. The lesion is a slit-

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like, smooth-walled cyst and stops ½ cm. lateral of the dorsal angle of the anterior horn. In the antero-posterior direction its extent is not more than 1½ cm. The anterior horns have not been opened and the midline structures, including the fasciculus cinguli, have not been damaged. It may be expected that a large number, if not most, of the thalamo-frontal fibres have escaped, partly owing to the circumscribed nature of the lesion, partly to the rather dorsally placed cut.

The last recovered case (No. 10 of our series) was a woman, aged 28, who since her early childhood had been subject to very gross hysterical outbursts of shouting, screaming and violent impulses. Prefrontal leucotomy was performed in February, 1942. She made an uninterrupted recovery. She still had outbursts, but they were much less frequent and much milder. In December, 1943, she was able to go home to her parents, who were very pleased with her. She held a few light jobs. About six months before her death she developed a streptococcal stomatitis and dermatitis, and died from broncho-pneumonia on February 21, 1945. The anatomical effect of the prefrontal leucotomy is shown in Fig. 18. The lesion is situated at the level of the genu of the corpus callosum in front of the anterior horns, and occupies fairly symmetrically the deep white matter corresponding to the inferior frontal gyrus. Its antero-posterior extent is probably not more than ½–¾ cm. On the right side a few small cysts are seen, while on the left a slightly yellowish scar is all that remains. A greyish colour of the white matter of the orbital gyri might indicate a slight gliosis. A forecast as to the effect of the lesion upon the thalamo-frontal projection is more difficult in this case than in the previous one, but it is quite likely that a large number of these fibres have escaped, as has also the region of the gyrus cinguli and fasciculus cinguli.

A final analysis of the factors that are responsible for recovery or failure must wait until a sufficiently large material has been investigated. Some interesting points emerge, however, from the comparison of the three unrecovered cases with a sufficiently long survival period (Cases 3, 4 and 5), and Cases 7–10, in which a notable degree of recovery was observed. All the recovered cases were patients with little or only moderate deterioration. During the decisive period after the operation there were no clinical complications to interfere with recovery. The operation itself produced circumscribed lesions uncomplicated by severe haemorrhage and softening of any appreciable extent.

Among the three cases of the unrecovered group one (Case 5) was severely deteriorated. The two others (3 and 4) were little deteriorated and should have had a fair chance of recovery. However, in Case 3, uraemia, developing as a result of a hypertrophic prostate, nicotinic acid deficiency and a senile condition of the brain must be considered as adverse factors. In Case 4 the cut was placed too posteriorly, involving the agranular frontal cortex and the caudate nucleus. In addition, extensive haemorrhage had destroyed a considerable part of the white matter of the prefrontal lobe. One positive result of the operation was the complete disappearance of the delusions, but this was offset by the severity of the frontal lobe deficit syndrome (fatuous euphoria, drowsiness, incontinence), combined with symptoms arising from damage to other regions of the brain. Hypertensive disease may also have been an adverse factor. The patient died from a terminal Wernicke syndrome (thiamine deficiency), which was probably due to exhausting restlessness. In Case 5 (long-standing catatonia, severely deteriorated) the lesion was placed in too anterior a plane; one might speculate that in this type of patient the cutting off of a larger portion of the frontal lobe would have achieved a better result, despite the post-operative epilepsy.

As regards the recovered group, it is surprising how little damage was sufficient to produce a remarkable clinical improvement. The cut in these cases was, as far as we can judge at present, incomplete in regard to severance of the thalamo-frontal fibres, and in none of the cases had the midline structures, including the fasciculus cinguli, been cut. In one of these cases only a unilateral (incomplete) severance of thalamo-frontal fibres had been achieved, and in another the prefrontal lobe had been entirely spared, the cut involving merely the opercular region, insula and the claustrum.

From this it follows that in suitable (non-deteriorated) cases a good recovery may follow rather surprisingly incomplete and circumscribed cuts in the white matter of the prefrontal lobe. In a similar type of case recovery may be prevented by an excessive lesion, either by cutting in too posterior a plane, or by causing

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extensive haemorrhage. The avoidance of haemorrhage seems to be a major necessity, and it may well be wise tactics for the neuro-surgeon to sacrifice a measure of completeness in favour of safety. On the other hand, deteriorated cases with fixed and automatized symptoms seem to require a more substantial severance of fibres, as instanced by Case 5. This is in accordance with the views of Freeman and Watts (1944*a*), who found that "well integrated individuals with disabling tension states but with no schizoid distortion respond to minimal interruption, while schizophrenics, chronic obsessives, hypochondriacs and long-term involutionals require the placement of lesions far posterior in the prefrontal region." In practice it will not always be easy to strike the right balance, both for the clinician, who has to make a careful study not only of the psychotic syndrome but also of the premorbid personality, life history, adaptability, etc., and for the neuro-surgeon who, with the methods available at present, is never quite sure in what plane he is introducing the leucotome and what amount of damage he will cause.*

In our material, involvement of the midline structures including the fasciculus cinguli has not proved to be an essential condition for recovery. This is also of some practical importance, as Knight (1943, his fig. 3) has demonstrated that if the leucotome is introduced too near the cortex, a haemorrhage may be caused during the circular movement by opening one of the arteries in the depth of a sulcus.

Recovery may follow unilateral prefrontal leucotomy, although in Case 7 there was a short recurrence of symptoms during the terminal disease. And finally, a good recovery was achieved by a lesion entirely outside the prefrontal cortex. We do not believe that this discredits the rationale of the operation. Even if it should be proved that damage anywhere in the brain might have a beneficial effect in a number of cases, it would be difficult to conceive of a theoretically and practically more rational place for surgical intervention than has been suggested by Moniz. Experiences of this kind emphasize, however, that the severance of a particular fibre system is perhaps not the only factor, and that others (anatomical, physiological and psychological) may, to a varying degree, contribute to the success of the operation. In this connection observations made on depressive patients who, in suicidal attempts, had inflicted brain injuries upon themselves, are of great interest. In the course of a clinical investigation of such cases Guttmann (1943) has shown that recovery may take place without any damage to the frontal lobe: "General damage to the brain and effect of injury and sickness on the one side, and on the other the release of tension, the substitution of recognized physical illness for hidden mental incapacity, the experience of interrupted consciousness and amnesia, finally the change of the life situation brought about by the injury, combine in bringing about the mental change." Most of this is applicable to the conditions of leucotomy, with the reservation, perhaps, that often the operation is not considered serious by the patients (Frank, 1945). Frank explains this by the assumption that the frontal lobes do not appear in the body image.

The Orbital Cortex in Relation to Prefrontal Leucotomy.

The fact, first established by Le Gros Clark in 1932, that the nucleus medialis dorsalis projects to the prefrontal cortex, is now generally recognized, but the detail of this projection has for a long time been obscure and controversial. In 1940 (*a*, *b*) Walker made detailed experimental investigations in monkeys, and came to the conclusion that—roughly—fibres originating in the medial part of the nucleus medialis dorsalis project to the orbital area of the prefrontal cortex, while those from the lateral half go to areas nearer the convexity, viz. a dorso-ventral axis of the prefrontal lobe corresponds to a latero-medial axis of the nucleus medialis dorsalis. We have been able to show that a similar arrangement exists in the human brain. If, owing to the haphazard nature of the operation, the orbital regions were spared, retrograde degeneration was more or less confined to the lateral aspect of the nucleus medialis dorsalis (Figs. 7, 19). On the other hand, in Case 5, in which the convexity of the frontal lobe was less involved, the retrograde

* We deliberately abstain from discussing the relative value of the different techniques of prefrontal leucotomy. This is for the neuro-surgeon to decide, and our task is confined to providing pathological facts as a basis for his consideration.

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degeneration was situated in the medial half of the nucleus (Figs. 9, 20). Degeneration involving the whole of the nucleus medialis dorsalis was seen in Case 6 (Fig. 21), in which by frontal lobectomy all fibre connections were interrupted. It is interesting to note that the degeneration in the medial half is more intensive than in the lateral half. Possibly not all the cells in the lateral half project to the prefrontal cortex, and there is, thus, some suggestion that, as a whole, the projection to the orbital area is more massive than to the areas nearer the convexity.

The most medial part of the nucleus medialis dorsalis, the so-called pars magnocellularis, was originally considered not to participate in cortical projection (Le Gros Clark and Boggon, 1935; Freeman and Watts, 1942, 1944*b*). Recent observations,

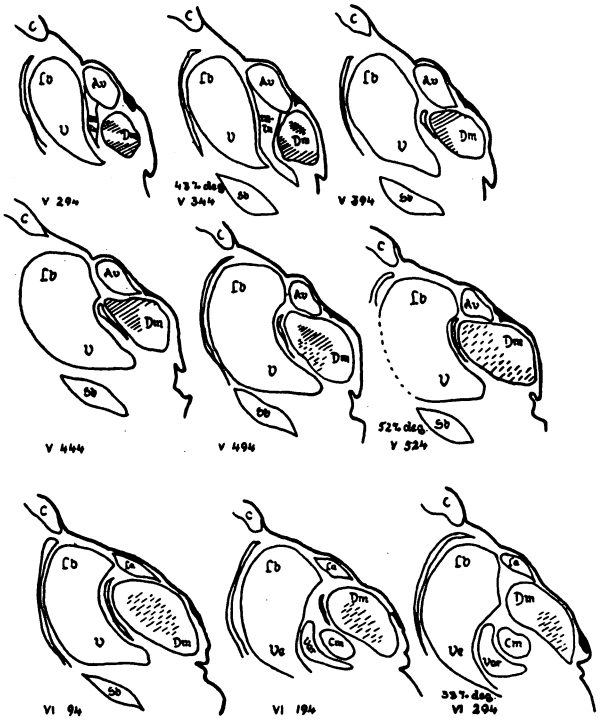


FIG. 19.—Case 3: L. hemisphere. Diagram of various coronal sections through the thalamus. The shaded areas indicate the extent of the degeneration in the nucleus dorsalis medialis.

however, made by Walker (1940*b*) in monkeys and by Le Gros Clark and Russell (1940) in a human case of complete cortical hemiatrophy have definitely established a cortical projection arising from this nucleus. Walker (1940*b*) assumes that it projects to the orbital region (area 11 of Brodmann). In our human material so far investigated a considerable degree of retrograde degeneration in the pars magnocellularis was seen in only Cases 5 and 6, and in these the damage to the orbital region was severe. This is of double significance as, in the first place, it increases the relative magnitude of the thalamo-orbital projection, and, secondly, owing to the recognized relation of the magnocellular nucleus to the hypothalamus, suggests the existence of a relatively direct hypothalamo-prefrontal connection, the only one which, so far, has been definitely established.

The relative strength of the projection to the orbital cortex is of some practical interest. It tends to lend additional weight to views expressed by Dax (1943), McKissock (quoted from Fleming, 1944) and others, that it might be desirable to ensure thorough cutting of fibre connections with the orbital areas. Hoffstatter,

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Smolik and Busch (1945) have recently sectioned the orbital quadrants only and, in contrast to earlier attempts (Freeman and Watts, 1942), claim satisfactory results in a series of 22 patients. It will be interesting to see whether these results can be confirmed in a larger series and by other investigators. From our point of view (as outlined in the previous paragraph) it would be a definite advantage to be able to section a large proportion of thalamo-frontal fibres by means of a fairly circumscribed operation.

Atrophy of the Prefrontal Cortex.

Freeman and Watts (1942, 1944*b*) did not find any appreciable loss of nerve cells in the portion of the prefrontal cortex which had been cut off by leucotomy,



FIG. 20.—Case 5: L. hemisphere. Diagram of various coronal sections through the thalamus. The shaded areas indicate the extent of the degeneration in the nucleus dorsalis medialis.

and they consequently assumed that the fronto-thalamic projection, though known to exist, must be fairly insignificant. They also failed to discover much Marchi degeneration of fibres going to the thalamus, but, as the myelination of these fibres is poor, this might not prove much. In all our leucotomy cases with a sufficiently long survival period, no significant degree of macroscopic atrophy was seen. Histological investigation, however, revealed a slight loss of cells, especially in the third layer, which looked emptier. This was particularly apparent when photo-micrographs of the affected cortex were compared with one taken from the same area of a normal control. Cell counts confirmed this visual impression (Table III). The table shows that there is a definite though not severe loss of cells, and that this loss is, again, most marked in the orbital region. The interpretation of these findings, which are not yet complete, is still under consideration. If confirmed on a large

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TABLE III.—*Frontal Lobe, Cell Count (3rd layer, 4 mm. length).*

	Vertex area 9.	Degeneration. %.	Lateral surface area 46.	Degeneration. %.	Lateral orbital surface area 11.	Degeneration. %.	Medial orbital surface area 11.	Degeneration. %.
Normal .	1,136	—	1,240	—	1,166	—	1,238	—
Case 1, 6 days .	1,500	0	1,404	0	1,286	0	1,324	0
Case 2, 3 days .	1,134	0	1,282	0	1,012	13	1,044	16
Case 3, 2 months .	964	16	922	25	758	35	660	47
Case 4, 4 months .	955	16	930	25	870	26	875	29
Case 5, L., 17 months .	1,312	0	1,536	0	1,130	3	1,100	11

scale, they might indicate that the fronto-thalamic pathway, though definitely inferior to the thalamo-frontal, is not quite insignificant, and that more fibres originate in the orbital areas than in the convexity.

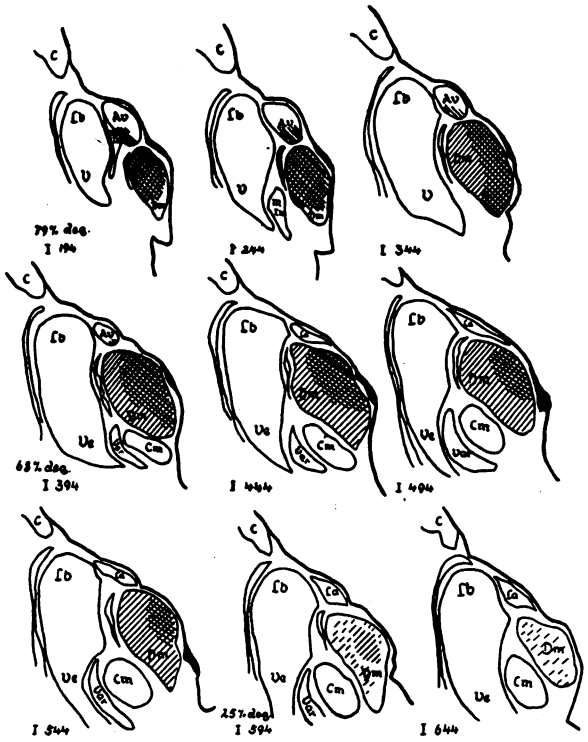


FIG. 21.—Case 6: L. hemisphere. Diagram of various coronal sections through the thalamus. The shaded areas indicate the extent of the degeneration in the nucleus dorsalis medialis.

Centre Median Nucleus of the Thalamus.

Whereas it has been established that almost all the thalamic nuclei project to the one or other region of the cerebral cortex, there is one notable exception—the centre medial nucleus. Nor is anything definite known about the connections of this nucleus with other centres of the brain. The consensus of opinion at present seems to be that the centre median nucleus is purely a thalamic association centre

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(Le Gros Clark, 1944). What appears to be a bilateral selective atrophy of this nucleus is, therefore, a surprising and unexplained finding. It has been recorded in a case of cortical deafness with lesions in the opercular and insular regions (Le Gros Clark and Russell, 1938). A similar "atrophy" was recently seen by Le Gros Clark (personal communication) in a psychotic patient after leucotomy. Independently we have made similar observations in brains from psychotic patients. For a moment it was tempting to consider a possible relationship of the pathology of this nucleus to functional psychosis. However, further observations made by both Le Gros Clark and the present writers have not substantiated a clear-cut relation to any form of psychosis. Figs. 22, *a* and *b*, demonstrate that in a fairly recent case of schizophrenia there may be almost complete "atrophy", while in another of twenty years' duration of the illness the nucleus appears to be normal. The centre was also normal in the case of frontal lobectomy in a mentally healthy patient. The only conclusion we can safely draw at present is that, under both normal and psychotic conditions, the centre median nucleus is liable to very considerable variations in cell density and spacing of cells, which apparently far exceed those seen in animal brains by Le Gros Clark and Boggon (1935). This variability is of remarkable interest if one regards the nucleus as an association centre within the thalamus, which itself appears to be one of the corner-stones of what one might call the anatomical substrate of personality organization. It is the more remarkable, as previous work on individual architectural differences within the cerebral cortex has demonstrated the relative constancy of the cortical pattern. Individual thalamic variation has not gone entirely unnoticed. Alexander (1942) has commented on individual differences of the myeloarchitectural pattern of the normal thalamus, and he has made the statement that " human thalami are almost as different in appearance as human faces." Here indeed seems to emerge a problem of the first magnitude which will require serious attention.

Summary.

A pathological investigation has been made in nine cases dying after prefrontal leucotomy, and in another case in which a frontal lobectomy was performed in order to remove a meningioma.

It has been shown that the place at which the leucotome was introduced into the brain and, also, the amount of haemorrhage and its sequelae varied considerably in the individual cases.

In the four recovered cases the lesion was surprisingly incomplete and circumscribed, and did not involve structures near the midline. In one case considerable improvement followed unilateral leucotomy; in another the prefrontal lobe was not involved at all.

There is some evidence that the projection of thalamic fibres to the orbital region is of considerable strength, and that the cortex in front of the surgical lesion is not wholly unaffected.

The centre median nucleus of the thalamus displays in the human brain a considerable variation of cell density. Its significance requires further investigation.

The results have been discussed with regard to both the clinical selection of cases for leucotomy, and the theory and practice of the operation, but final conclusions should be deferred until more material has been investigated.

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DISCUSSION.

The PRESIDENT said that Dr. Meyer had, as usual, been most instructive. This operation had always appealed to him as being the beginning of greater and newer techniques, and in the nature of things it had the element of crudity which in time would be smoothed out, and it would become more exact. Dr. Meyer had given some indication of the gradually increasing lesson of experience, and how the operation would have to be improved for it to be useful and to meet the requirements of cases. In fact it would be a development of neurosurgery.

Dr. Meyer lamented the small number of cases, but of course, the operation would die a natural death if he had a large amount of material. The material, if the operation was to go on and progress, would obviously be limited, and it was hoped that information would be gained from intercurrent cases rather than from direct action, because one of the effects of his investigations would obviously be to make the operation safer by improving the technique of the surgeons, both with regard to life-saving as well as performing the neuro-psychological functions which was the whole basis of the operation.

A number of the members had had cases of leucotomy, and he hoped the debate would be interesting and instructive. Those who had had good practical experience would add to the existing knowledge on this subject.

Dr. MCCARTAN said that one of his cases had been demonstrated by Dr. Meyer and he regretted that more neuro-surgeons were not present, because this was one of the most important papers read before the Association for some time. It was not often that one attempted such a faithful post-mortem investigation of one's patients, and he hoped when the paper was published that as many of the pictures shown during his reading of it would be published as possible, so that surgeons performing the operation could see what Dr. Meyer had demonstrated.

In his own case, the patient did not die of the operation, but because he had been allowed to go to operation with an enlarged prostate. In the actual operation, it was obvious from what Dr. Meyer had said that the surgeon had not been quite radical enough.

He congratulated Dr. Meyer on his very excellent and enjoyable paper.

Dr. CUNNINGHAM DAX said that he wished one could see more of these cases, so that one could see where the approach was made and the extent to which the brain was cut. He understood that an orbital section case had died quite recently on whom the operation was performed some time ago. The patient was an aged melancholic and did not show the improvement which was hoped for, and which it appeared might follow in the first period after the operation. When looking at the section in the first place and wondering how it could be done, both the vertical section, as one had hoped in front of the tip of the ventricle and also a horizontal section above the orbital cortex by the same incision, one found post-mortem investigation very useful. He had been informed, and indeed believed, that the position of the brain did shift in relation to the skull, and, of course, one had a proportion of older cases to investigate, and he had found the position at which the leucotome was inserted and cuts were made all over the brain. Having examined cases which died, one was also fairly shaken by the position of the incision, and that led to the adoption of a different approach through the temporal fossa where one could, on each occasion, see what was happening when the incision was made. It would be very interesting to see the distribution of the orbital fibres although, that being the older portion of the brain, he was told that one would have expected the results which had been described.

There was no doubt that some amazing results had been seen in cases of aged depressives with stereotyped speech. One was of an old lady who repeated that she "wanted to go to London," and got very upset about it, was constantly struggling and was difficult to nurse, but who settled down a little after the first vertical operation. Some months afterwards a horizontal section was done through another incision, and she had cleared up and had been at home for about 18 months. In another case of the same type the horizontal section was done in the first place, and she also cleared up and had been at home for roughly the same time.

With regard to the distribution of fibres and the path they took to the thalamus, he wondered whether a mistake was made by cutting two vertical sections and so missing a number of the fibres as they went from certain portions of the cortex back to the thalamus, and if something like a grape-fruit knife could be used in order to make a curved incision over the point of the

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lateral ventricle where one cut the greater number of fibres. An endeavour was being made to produce an instrument which might do this and he would report the results at a later date.

Dr. Dax hoped there would be an opportunity for seeing more and more of the results as time went on, mapped out in the very beautiful way in which Dr. Meyer had done it so that it would be possible to improve, correct and adjust, and make progress in this useful treatment.

Dr. MAYER-GROSS said that he had looked forward to this paper for some time, not only to see some old acquaintances on the screen, but also because it was of the greatest importance for the treatment that the pathologist should control the actions which produced the results.

He would like to ask a question on a point he had discussed with Dr. Meyer and which he deliberately left out of the paper—the question of how far the cortex itself, which, according to Freeman and Watts, showed no deterioration whatsoever and should be in a perfect condition, was, according to Dr. Meyer's findings, affected by the operation, and was responsible for the changes brought about by the operation. If the connection with the thalamus was of such importance it might depend not only on the nucleus of the thalamus, but also on the effect on the cortical layers.

Dr. F. A. PICKWORTH said that Dr. Meyer stated he was unable to follow the degeneration of the myelin sections. Did that mean that a large portion of the fibres which were cut were sympathetic fibres, and would that explain the peculiar visceral effects from prefrontal leucotomy?

Dr. R. B. TURNER said that it was difficult to exaggerate the importance of Dr. Meyer's contribution on this subject. The more one thought about it the more extraordinary it seemed that a mutilating operation on the brain could bring about mental improvement. What interested him most in Dr. Meyer's description was the case in which the patient—he thought it was Case 5—survived for 17 months or was very much improved although the operation was a failure from the point of view of its object, which was to sever the fibres connecting the dorso-medial nucleus and the prefrontal region. One wondered whether, as Dr. Meyer hinted, it mattered where the incision was made, and whether an incision in the occipital region would not have the same effect, whether the actual severance of the fibres was of such importance. Instead of dividing fibres rather blindly, could not one, through electrical means, destroy the dorso-medial nucleus of the thalamus? Neuro-surgeons seemed to be able to turn the brain inside out nowadays, and no part was inaccessible.

Another question which occurred to him was whether the surgeon had merely been content to do leucotomy on one-half of the brain, perhaps a right-handed individual on the left-hand side, and had the result been in any way satisfactory? The idiot was not troubled by projecting himself into the future or disturbance of his superego, as far as was known, but he was often very disturbed and disagreeable, and it occurred to the speaker that he would be a very satisfactory subject for this operation. At Leavesden leucotomy had been performed on many mental defectives; only two were high-grade, others being almost in the idiot class, and although there was not sufficient time to judge of the results, and one patient who was rather feeble-minded and whose voice could be heard through several blocks of the building before the operation, and who threw his utensils, his food and even his faeces about the ward, was now able to be put on parole. He was anaplegic, probably suffering from spina bifida, and he propelled himself about the grounds. One idiot diplegic, who spent all her waking hours destroying either the bedding or her clothing with her teeth to such an extent that she did £90 worth of damage in six months, had been remarkably improved and had ceased, except occasionally after an epileptic fit, to continue these acts of destruction. It must not be thought therefore that this was an operation suitable only for the psychotic or psycho-neurotic subject. It obviously had a field of usefulness in the mental deficiency institution. He believed that at the sister institution at Caterham equally disturbed patients made an even greater response.

Dr. BURROWS asked Dr. Meyer whether his investigations threw any light on vitamin deficiency in the immediate results of the operation. One of his cases, after weeks of post-operative confusion, cleared up to almost complete normality in three days with the administration of nicotinic acid, and he would be interested to know of other cases.

Mr. CLARK-MAXWELL (visitor) said that it had occurred to some neuro-surgeons that a direct approach to the dorso-medial nucleus would be a more rational thing to do than to attempt to section the frontal fibres with the great variation in results, both technically and mechanically. Brains varied very much; one did a sweep of 19° on one brain and a similar sweep in another and afterwards one found that the sweep was 30° in one and 70° in another owing to the different elasticity of the fibres.

It was very difficult to get at the dorso-medial nucleus, and he had been doing some experiments lately which were still in the early stages and still restricted to the cadaver. It was possible by an approach to introduce a small scoop into the ventricle, and one could see the degree of the outline of the thalamus and some of the landmarks therein. He had used a coloured dye to follow the track of the instrument, and found that that method was more variable than attempting to section the frontal fibres. The method was improved, but it was too early to say whether it was satisfactory. It should be the right thing to do, but so far skill was insufficient to hit the

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right spot with anything like certainty. If he could show some of the brains into which the dye had been put his hearers would be horrified.

One speaker mentioned getting a circular sweep round the hinder ventricle; he had done this in two or three cases but had found difficulty. With the ordinary ventricular cannula one could do a sweep, and it was possible to feel the wall of the ventricle before penetrating it.

Dr. BRODY said that he would like to hear a little more about the visceral and autonomic changes and what was the underlying neuro-pathology. It was very interesting; although one had seen recovery without very much in the way of visceral change he could not remember any case which had shown obesity which had not done well clinically.

The other point of interest was that one of the cases which Dr. Meyer had mentioned was one of two done at Runwell where the incision was made ½ in. posteriorly to the usual site. That did not mean that the actual brain was severed ½ in. posteriorly. One of the cases died. She showed very little in the way of outward visceral damage, whereas the other patient became extremely torpid, fat, very lazy, and had atrophic ulcers on her heels and atrophic changes to her hands which took about nine months to clear up. During the whole of that time she was excessively torpid, but as the atrophic changes cleared she got more animated. She remained like that for some months and then gradually relapsed and was much as she was previously, although she had left hospital in the meantime.

It would be very interesting to hear what Dr. Meyer had to say about the autonomic changes which occurred following leucotomy.

Dr. MEYER, in replying to the discussion, said that numerous questions had been asked, and he was glad that he had cut down his paper because he had already planned to discuss the questions which arose spontaneously.

He was sorry that he gave the impression that he expected a high mortality from leucotomy. Actually he did not think that the mortality was greater than that mentioned by Zeigler, but what he wanted to suggest was that it was of the greatest importance to remain in contact with the patients who recovered, and if they died later (and some would because many were elderly) their brains would be of the greatest value for this investigation.

Dr. Cunningham Dax mentioned the new methods of surgical approach, and he was very glad that the developments were making the cut more reliable. Dr. Mayer-Gross had asked about the cortex. There were few cases where there was atrophy in the frontal cortex. Freeman and Watts, in the eight cases which they reported, said that the frontal cortex was normal. He had made a special study of the frontal cortex, however, and had found that it was not quite normal. In all the cases with sufficiently long survival period the frontal cortex, particularly in the third layer, looked emptier than usual. It was interesting to see that the orbital region had suffered more than the region of the convexity. The damage was slighter than that of the dorso-medial nucleus, and this might reflect upon the relative strength of the thalamic pathways. Apparently the thalamo-frontal pathways which resulted in the degeneration of the dorso-medial nucleus were much stronger than the other fibres, and so if the route of the operation was correct this might be a tragic observation, because it showed that the human brain had made provision for the human race to present instinctual drives to the prefrontal structures, but not given adequate means for the prefrontal cortex to control them. He thought there was a definite lesion, but he had not mentioned it in his paper, not because of lack of time, but because the point needed further investigation before anything was published.

Dr. Cook asked whether the different cases had been operated on by the same surgeon. Different surgeons were concerned, and some of the operations belonged to an earlier experimental period. Technique as a whole had improved, but it was Mr. McKissock himself who said that even with improved technique there would always be vicissitudes of completeness of the operation and the placing of the cut.

Dr. Pickworth asked about the unmyelinated fibres. In fact, Freeman and Watts did not find a degeneration of thalamo-frontal fibres, and that it was slight in the thalamal fibres pointed to the fact that many of them were unmyelinated or had only a poor myelination. He did not think this of necessity involved visceral change. It was known from observations made in Professor Le Gros Clark's laboratory that the connections between the caudate nucleus and the premotor area, and the so-called suppressor band of area 4, were largely unmyelinated. Apparently many more fibres were unmyelinated, and a decision would have to be made as to the significance of their functions.

With regard to Dr. Brody's remarks, recovery might occur without damage anywhere in the brain, and this had been demonstrated in one of his cases and also by Freeman and Watts and Goodman in depressive patients who had tried to kill themselves and to inflict brain injuries to themselves. He thought one should not forget that the place where the cut was made was the soundest as far as a knowledge of personality, organization of emotion and emotional expression went.

With regard to the question of the electrical or other destruction of the dorso-medial nucleus, the answer had been given by Mr. Clark-Maxwell. He, personally, thought that the operation in this region would be major and larger in surgical intervention and less safe than the cutting of the thalamo-frontal fibres. He had put the dorso-medial nucleus into the foreground because he wished to take it as a test for the destruction of the thalamo-frontal fibres, but it must not be forgotten there might be other factors such as the cingulate cortex to which Freeman and

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Watts attributed so much significance. So far he had not seen any degeneration in the cingulate cortex, but these tracts were obscure in their pathology and physiology, and this applied to other tracts. So far it had been difficult, or even impossible, to find any degeneration, but these things had to be looked for, and a successful operation on the dorso-medial nucleus might mean that an important point was missed. Professor Golla had attempted to devise an electrical leucotomy which had not materialized beyond the experimental stage.

With regard to vitamin deficiency he mentioned that pellagra was the cause of death in one case, and thiamine deficiency was the cause of death in another. It was worth keeping in mind that in the post-operative phase the nutritional aspect was of some importance.

Dr. Brody asked about visceral change. The dorso-medial nucleus acted not only with the prefrontal cortex but with the hypothalamus particularly; its magno-cellular part was in direct communication with the hypothalamus. Recently Walker had pointed out that the magno-cellular part participated in the projection to the frontal cortex, and this would mean an almost direct pathway connecting the hypothalamus in a double way with the prefrontal cortex, which would, of course, explain the visceral change observed. Freeman and Watts found the magno-cellular portion intact in their cases; he found that all had suffered, though not to an equal degree to the parvicellular part of the dorso-medial nucleus. Whether this was of some significance to recovery or not he did not know. It was one of the points which he had in mind which would have to be ascertained in a larger material.

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