POSTERIOR CUTS IN PREFRONTAL LEUCOTOMY: A CLINICO-PATHOLOGICAL STUDY.

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THE usual leucotomy cut in this country, made through burr holes orientated by means of skull measurements, in the majority of cases enters the brain at about the middle of pars triangularis of the inferior frontal gyrus (Brodmann's Area 45), and if performed in a strictly coronal plane remains entirely within the prefrontal region. Intentionally or unintentionally cuts are not infrequently placed either anterior or posterior to this plane. That cuts made posterior to strictly prefrontal levels are often followed by an unfavourable post-operative course distinguished by particularly severe personality change, persisting incontinence, vasomotor, trophic and neurological disturbances has been demonstrated by Knight (1943), Meyer and Beck (1945), Ziegler and Osgood (1945), Reitman (1946) and others.

Such posterior cuts usually involve the posterior orbital region, the striatum, the external capsule or the premotor region. Of these, the posterior orbital region has recently received special attention, particularly in American experimental work. It had long been known that after bilateral frontal lobectomy hypermotility might develop in monkeys, but it was left to Ruch and Shenkin (1943) to show that this occurred only when Area 13 of the posterior orbital region (delineated in the monkey's brain by Walker in 1940) was included in the lesions. This was confirmed by Fulton (1947) in monkeys, but not in a chimpanzee.* Richter and Hines (1938) and Mettler (1945), on the other hand, concluded that to produce spontaneous hyperactivity in monkeys the striatum in addition must be damaged.

Smith (1938) and Bailey and Sweet (1940) observed inhibition of respiration and gastric peristalsis after stimulation of a region roughly comparable to Area 13 in various species of animals, and Bailey and Bremer (1938) obtained abnormal electroencephalographic potentials from the same region in the cat upon stimulating the central end of the cut vagus nerve. Some of these findings have been confirmed, and amplified, by Delgado, Fulton and Livingstone (1947).

In view of these experimental results we have paid special attention to the posterior orbital region in the following analysis of the clinical and pathological data from our leucotomy material. It should be borne in mind, however,

* Fulton, in lectures in this country, recently described further interesting findings after electrical stimulation of the posterior orbital region in chimpanzees and man, but they have not yet been published and will not therefore be quoted in this paper.

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that in leucotomy the lesions are much less precise in their location than in cortical stimulation or ablation. For instance, a leucotomy cut which involves the head of the caudate nucleus is very likely at the same time to damage the premotor region or the posterior orbital region, either directly, or more remotely by severing their afferent and efferent fibres where they course out of and into the internal capsule. This imposes the need for particular care in the evaluation of our findings, and deters us from any too strict a statistical treatment of our tabulated data. Another limiting factor in our data is that in none of our cases had a scientific attempt been made to record the relevant symptoms before or after the operation. We are, thus, not in a position to make any statement on important indications of autonomic function, such as blood pressure, respiration, heat regulation, pupillary reaction, gastric motility, sweating, salivation, pilo-motor reaction, electrical skin resistance and psychogalvanic reflex. We have had to confine ourselves to some gross autonomic and other signs which we could be reasonably certain would not have been overlooked in the usual routine investigation. This, again, necessitates the greatest reserve in analysis and conclusions.

Out of a total of 60 leucotomy cases 40 were suitable for clinico-pathological study. Twenty-two were found to have in both hemispheres what in this paper will be called " posterior " cuts, i.e. they had involvement of the posterior half of the orbital region, the striatum, the premotor region (Areas 6 and 44 of Brodmann), the region of the external capsule (insular cortex, claustrum, capsula externa or extrema), or any combination of these. These 22 cases have been collected together in Table I. The regions involved in each case are indicated by plus signs within the appropriate columns, except in the case of the posterior orbital region, where further subdivision has been carried out into terms of involvement of medial, central and lateral thirds—this because Area 13 has not yet been defined in the human brain. In addition to columns for these four posterior regions we have included one for indication of involvement of the anterior half of the orbital region, for reasons to be mentioned. Other segments of the prefrontal region have been omitted, since they are not very relevant to our main theme.

The remaining 18 cases, that is to say the more truly prefrontal leucotomies, are collected together in Table II, and analysed in terms of involvement of the same regions.

On the right hand-sides of the Tables have been recorded the clinical sequelae reported in each case to have followed the operation. They have been distributed under five headings :

Personality change has been graded according to severity in terms of three degrees of plus, irrespective of whether the change was of the euphoric type or of the akinetic (torpid) type. Where the brevity of post-operative survival limited evaluation of the clinical observations the grading has been bracketed.

General restlessness is often included within the term "personality change," but we have given it separate mention, wherever reported, on account of the experimental evidence described above that its manifestation implies damage to a particular posterior region. It cannot, however, be compared directly with the restless pacing of experimental animals which Ruch and Shenkin

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regard as the characteristic result of bilateral damage to Area 13, for all our six patients displaying restlessness were confined to bed.

Vasomotor and trophic lesions.—These terms have been used to cover such symptoms as cyanosis of extremities, oedema and blisters of the skin.

Persisting incontinence of urine was taken to be positive when of over six weeks' duration.

Miscellaneous.—In this column "E" has been used to denote epilepsy developing for the first time after operation; "H" to mark the occurrence of hyperpyrexia as a prominent sequel; "N" to indicate the development of signs of nutritonal deficiency; "R" to denote marked respiratory disturbance; and "U" to indicate the appearance of uraemia. All purely neurological sequelae have been omitted.

The penultimate column shows the post-operative survival period; the last column those cases in which death can be attributed definitely to an intercurrent illness.

In spite of the shortcomings in the clinical data and the other limiting factors mentioned, not a few points of theoretical and practical interest can be derived from the tables.

In the first place, the contrast between the *general total of sequelae* in Tables I and II is most striking: 42 clinical items in the group of cases with posterior cuts, only 8 in the group with essentially prefrontal cuts.

A second striking point is that the *survival period* of the cases with posterior cuts is, on the average, much lower (6½ months) than the average of those in Table II (1½ years), especially if, as has been done in calculating the former average, one takes into account in Table I only the uppermost 17 cases, which had bilateral involvement of either the posterior orbital region or the striatum, or both. A third notable fact is that only one of the top 17 cases in Table I definitely died from an *intercurrent disease*, as against 10 of the 18 cases in Table II. Manifestly, therefore, posterior cuts, especially if they affect the striatum or posterior orbital region, tend to determine relatively early death, i.e. "*delayed post-operative death.*" Many of the "clinical sequelae" reported were undoubtedly either primary or precipitating lethal factors. In this connection it is interesting to recall that Heath, Freedman and Mettler (1947) found that after bilateral enucleation of striatal tissue in felines death always occurred within a few days, due, they thought, to upset of metabolic function.

The *personality change*, it can be seen, tends to be severest when the posterior lesions are most widespread. A mild degree of change was reported in three of the cases with the lesions confined to the prefrontal region, and it can safely be assumed that in other cases in Table II lesser degrees of change passed unrecorded. Hence personality change is not dependent upon, although amplified by, damage to posterior regions of the frontal lobes. This occurrence of personality change after lesions confined to the prefrontal regions proper is stressed (see also Meyer and McLardy, 1947), because it has recently been contended by Hebb (1945) that the personality is not affected by almost total removal of both prefrontal regions. That the personality change becomes more severe in posterior cuts may simply signify that the prefrontal connections have been more completely cut off.

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TABLE I.—*Bilateral "Posterior" Cuts.*

Case number.	Regions involved.												Clinical sequelae.					Survival.	Intercurrent cause of death.
	Posterior orbital.		Striatum.		Pre-motor.		Exteral capsule.		Anterior orbital.		Personality change.	General restlessness.	Vasomotor and trophic.	Persisting incontinence.	Miscellaneous.		
	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.							
3	Lat. Cent.	Lat.	+	+	..		..		..		+	..	..	+	N	2 mth.	..
4	..		+	+	+	+	+	+	..		+++	+	+	+	U/N	4 mth.	..
10	Lat. Cent.	Lat. Cent.	..		..		..		..		++	..	+	..	N	3 yr.	..
11	Lat. Cent. Med.	Lat. Cent.	+	+	..		..		+		++	..	..	+	..	5 mth.	..
16	Lat.	Lat.	+	+	..		..		..		+	..	..	..	..	7 wk.	..
20	..		+	+	..		..		..		++	..	+	+	..	2¼ yr.	+
22	Lat.		+	+	+	+	+	+	..		..	..	+	..	..	9 wk.	..
29	Lat. Cent. Med.	Lat. Cent. Med.	+	+	..		..		..		..	..	..	..	H	9 dy.	..
32	Lat. Cent.	Lat. Cent.	+	+	+	+	+	+	..		++	..	+	..	..	7 wk.	..
33	Lat. Cent.	Lat. Cent.	+		..		..		..		+++	+	+	+	..	10 wk.	..
38	Lat. Cent.	Lat. Cent.	..		..		..		+	+	+	+	+	+	..	..	1½ yr.
41	Lat. Cent.	Lat. Cent.	..		..		..		..		..	..	..	..	H	6 dy.	..
49	Lat.	Cent.	+		..		..			+	(++)	+	..	..	H	24 dy.	..
52	Lat.	Lat. Cent.	+	+	+	+	+		..		(+++)	+	..	..	..	20 dy.	..
56	Lat. Cent. Med.	Cent. Med.	+	+	+	+	+	+	..		+++	..	+	+	..	9 mth.	..
58	..		+	+	..		+		..		(++)	+	..	..	U	7 dy.	..
59	Lat. Cent.	Lat. Cent.	..		..		..		..		..	..	..	..	R	4 hr.	..
26	..		..		+	+	..		..		..	..	..	..	E	3¾ yr.	+
8	..		..		..		+	+	..		..	..	..	..	..	1¼ yr.	+
27	..		+		..		+	+	..		..	..	..	..	..	3¾ yr.	+
37	..			+	..		+	+	..		..	..	..	..	..	4¼ yr.	+
47	..		..		..		+	+	..		..	..	..	..	..	3½ yr.	+

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TABLE II.—*Essentially Pre-frontal Cuts.*

Case number.	Regions involved.												Clinical sequelae.						Survival.	Intercurrent cause of death.
	Posterior orbital.		Striatum.		Pre-motor.		External capsule.		Anterior orbital.		Personality change.	General restlessness.	Vasomotor and trophic.	Persisting incontinence.	Miscellaneous.					
	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.										
5									+	+	:	:	:	:	:				1½ yr.	:
18									+	+	+	:	:	:	:				1¼ yr.	+
19									+	+	+	:	:	:	:				6 mth.	+
34									+	+	:	:	:	:	:				2 yr.	:
44									+	+	:	:	:	:	:				3¾ yr.	:
57		Med.							+	+	+	:	:	:	:				2¼ yr.	+
9									:		+	:	:	:	:				1¾ yr.	+
12											:	:	:	+	:		E		2 yr.	:
13	Lat.			+					+		:	:	:	:	:		N		7 wk.	:
14									+		:	:	:	:	:		:		8 mth.	:
21							+				:	:	:	:	:		:		1¾ yr.	:
31									:	:	:	:	:	:	:		:		1¼ yr.	+
35											:	:	:	:	:		:		1 yr.	:
36						+		+			:	:	:	:	:		:		2 yr.	:
39											:	:	:	:	:		:		1 yr.	+
46											:	:	:	:	:		:		9 mth.	+
60				+					+		:	:	:	:	:		:		3 yr.	:
61	Lat.									+	:	:	:	:	:		:		1¼ yr.	+

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Another conspicuous fact is that all cases displaying *general restlessness*,* all displaying *vasomotor or trophic lesions* and all displaying any of the " miscellaneous " sequelae except epilepsy, fall within the upper 17 cases of Table I, i.e. possess bilateral damage to either the posterior orbital region or the striatum, or both, and often to the premotor region as well. A noteworthy corollary to this is that none of the six cases having bilateral involvement of only the anterior half of the orbital region shows any such sequel, beyond personality change. This would indicate that in man, as in animals, the mechanism concerned in the production of these clinical changes, so far as related to the orbital region, is confined to its posterior half. The central third is, by direct homology, the most likely to correspond to Area 13 of monkeys. Fulton, however, has suggested that perhaps in chimpanzees and man Area 13 is more widespread. Final settlement of the matter will depend upon exact delineation of the area in the human brain by architectonic studies.

It should be mentioned here in passing that although evidence is accumulating that the cingulate region may have important autonomic functions (McCulloch, 1944 ; Smith, 1945 ; Kremer, 1947), the involvement of the anterior cingulate region in our material was about equally distributed between cases falling into the top 17 of Table I and those of Table II. Hence damage to this area (Brodmann's Area 24) has apparently no causal connection with at least the rather gross types of clinical manifestations to which our report is limited.

That the four cases having bilateral posterior lesions confined to the external capsule (the bottom group of Table I) display no sequelae whatsoever indicates clearly that the anatomical substrate concerned in these undesirable clinical changes does not include the external capsule, claustrum, extreme capsule or insular cortex (or, it should be added, the uncinate fasciculus, which was bilaterally involved in at least three of these four cases). The other three posterior regions, however, cannot be dealt with in isolation, for lesions in the region of the head of the caudate nucleus are extremely liable to damage fibres there which are projecting to and from premotor or orbital cortex. The four cases of bilateral striatal damage without direct posterior orbital lesion show no significant difference in incidence of general restlessness and vasomotor or trophic lesions from the six with bilateral posterior orbital damage but no striatal involvement. Fulton, Livingstone and Davis (1947) have, in fact, suggested that fibres projecting to Area 13 pass through the caudate nucleus. This would, to some extent at least, reconcile the views of Richter and Hines and Mettler (who relate restlessness to striatal damage), and of Ruch and Shenkin (who relate it to posterior orbital damage).

With regard to vasomotor and trophic disturbances, it will be recalled that Kennard (1935) created vasomotor changes in monkeys by ablation of the premotor area, and that in Ziegler and Osgood's leucotomy cases displaying vasomotor and trophic phenomena there seemed to be some relationship with posterior cuts, as determined by contrast radiography.

Persisting incontinence of urine is a very general symptom which cannot

* In a previous communication (1948) based on a smaller number of cases a more reserved statement was made on this point.

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be expected to correlate closely with damage to any circumscribed region, for although it is well known to be brought about by lesions of the dorsal part of the premotor region, it may, on the other hand, be determined simply by the general deterioration in a patient's conduct—and, in fact, all but one (No. 38) of our nine cases exhibiting it either had lesions likely to affect fibres from the dorsal premotor region or showed post-operative mental deterioration.

The "*miscellaneous*" *sequelae* are too few to warrant full discussion at present. It is interesting, however, that of the three cases developing *epilepsy*, the two in which it commenced within a few months had the most anteriorly placed cuts in our series. The third case (No. 26) had posterior cuts, but here the epilepsy bore a somewhat doubtful relationship to the operation (since it did not commence until two years later, and two courses of E.C.T. had been given in the meantime). A fourth case, mentioned in a previous communication (1948), has been omitted from the present series because of the discovery of an independent organic disease of the brain which complicates the picture. A fifth case (not included in the present series) has only just been received which shows the combination again of post-operative epilepsy and an unusually anterior lesion on at least one side. The damaged anterior regions peculiar to these three cases lie definitely rostral to any of the sites which Russell (1947) has tentatively related to post-traumatic epilepsy. They remind one more of Pennybacker's (1945) series of cases of abscess of the anterior pole with epilepsy. Our cases, however, are still too few and incompletely investigated to warrant further discussion at present.

Nutritional deficiency took the form of pellagrous symptoms in two cases, Wernicke syndrome in one case and vitamin C-like deficiency symptoms in a fourth. It is difficult to determine what the causes, extrinsic or intrinsic, of this nutritional deficiency may be in these patients, and in view of the complexity of the whole problem of nutritonal deficiency it would be idle to speculate.

The three cases displaying *hyperpyrexia* revealed no histological evidence of infection of the brain or meninges. They had in common only bilateral damage of the posterior orbital region.

It is difficult to say whether the *uraemia* which developed after operation in Cases 4 and 58 had anything to do with the damage to the brain, but it has been recorded in view of Cumings' (1942) findings in cases of head injury.

The one case of marked *respiratory disturbance* (No. 59) merits special attention in view of the bearing which experimental findings may have in its interpretation. Because the patient was suffering from impetigo of the scalp 100,000 units of pure penicillin were run into each of the leucotomy wounds at the time of operation. The anaesthesia was without incident, but very shortly after recovery from it the patient showed left-sided twitching, and his respiration was noted to have become alarmingly slow and irregular. Artificial respiration and oxygen were administered repeatedly. Twitching continued at intervals. Two hours after the operation the respiratory rate became 30 per minute, and a quarter hour later the patient developed a first major epileptic fit. Fits recurred at 5-minute intervals and were not fully controlled by intramuscular gardenal, being reduced to one per half hour. Respiration

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again became irregular but deep, and in spite of further gardenal and coramine injections the patient died during his eleventh fit, four hours after return from the operating theatre. Diagrams 1 and 2 indicate the position and extent of the cuts. The interpretation of the symptoms is not simple, on account of the known epileptogenic effect of penicillin in contact with the C.N.S. (Johnson, Walker, Case and Kollross, 1946). The respiratory effects were so primary—long before major epileptic fits developed—that one is led to postulate a double aetiology for the symptoms, attributing the respiratory disturbance to the bilateral damage of the posterior orbital region, the site of the lesions which Bailey and Sweet and Delgado, Fulton and Livingstone found to produce respiratory inhibition in animals.

That other cases with bilateral involvement of the posterior orbital region did not display such respiratory disturbance—or, for that matter, the fact that all cases with similar lesions did not display identical sequelae—does not necessarily invalidate the positive correlations which have been pointed out. Quite apart from the possibility of constitutional variation in the homeostatic mechanism of different individuals, it may well be that grossly similar lesions differ in details which we have not yet distinguished, but which may determine differences in the nature of the upset of physiological balance. We have, actually, examined other variables than these discussed in this paper—e.g. involvement of the ventricles, damage to fasciculus subcallosus, affection of grey as well as merely white matter of Brodmann areas—but have found no correlation trend.

The anatomical pathways concerned in these post-operative autonomic and other changes remain obscure. Only one of the many postulated cortical connections of the hypothalamus has been definitely established—namely, the connection with the orbital cortex by way of unmyelinated periventricular fibres which relay in the magnocellular part of the dorsomedial nucleus of the thalamus. The present writers, together with E. Beck (1947), previously described some histological evidence that the medial part of the anterior half of the orbital region connects with the anterior part of pars magnocellularis of the dorsomedial nucleus. Further histological investigation is necessary, and is in progress in this laboratory, to determine the precise thalamic, or other, connections of the posterior orbital region.

Summary.

Clinico-pathological analysis is made of 40 cases of prefrontal leucotomy, with particular reference to the relation of restlessness and certain autonomic disturbances to the posterior orbital region. The results emphasize the potentialities of such studies and the importance of full clinical investigation of cases before and after operation and their eventual correlation with the pathological findings.

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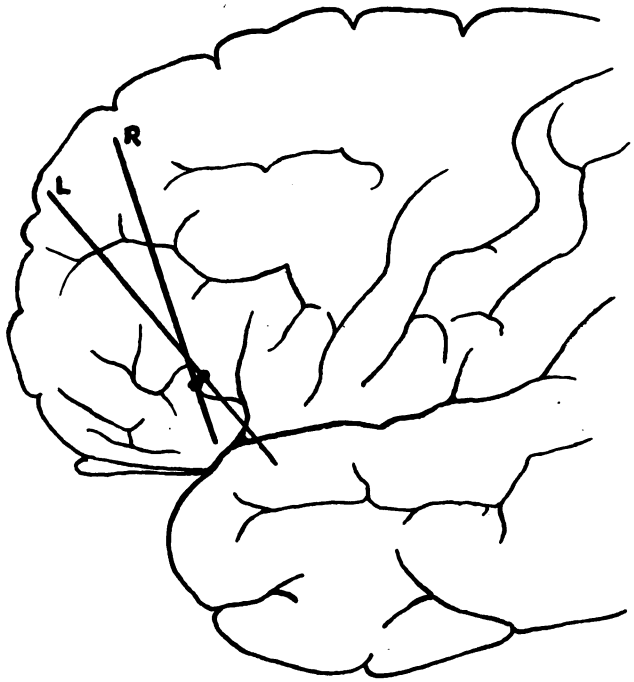


FIG. 1 (Case No. 59).—Showing the plane of the leucotomy cut in left and right hemispheres.

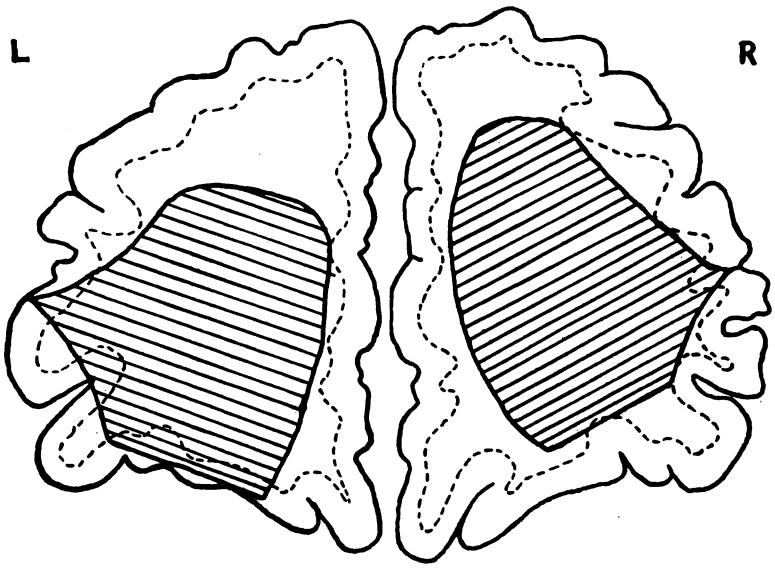


FIG. 2. (Case No. 59).—Showing the extent of involvement of the white matter and cortex in the two frontal lobes.

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thank the Superintendent and the Clinical Director of the Crichton Royal, Dumfries, for permission to mention the more fully described case of post-operative respiratory failure.

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