URÆMIC AND TROPHIC DEATHS FOLLOWING LEUCOTOMY : NEURO-ANATOMICAL FINDINGS

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Little has been published concerning the occurrence of delayed operative death after bilateral prefrontal leucotomy. The term "delayed operative death" in relation to leucotomy was introduced by Meyer and McLardy (1948; 1949) in analysing undesirable clinical sequelæ suffered by patients submitted to leucotomy who had survived the danger of fatal operative hæmorrhage, and whose brains had in due course come under systematic investigation at the Maudsley Research Laboratory. I have elsewhere (McLardy, 1948) described how I deduced from a study of the brains and clinical records of 101 leucotomy cases that probably as high a proportion of "the leucotomized population" dies a delayed operative death within five months of the operation as from hæmorrhage within two weeks of the operation.

In these three previous studies it was shown that delayed operative death was clearly related to the post-mortem finding of leucotomy lesions extending posterior to prefrontal domains in both hemispheres. It was not attempted, however, to decide whether the most responsible part of the lesions might be damage to the premotor regions, the putamen, the caudate nucleus, the posterior parts of the orbital region, or structures lying between any of these. Such a more precise anatomical analysis has now been carried out on a larger series of cases. The findings, which are tabulated and discussed in the present paper, seem to provide strong evidence that at least bilateral substantial damage to agranular orbital cortex, or to the region of the subcallosal fasciculus at certain levels, is fatal.

Material and Data

The brain material and clinical records of 122 leucotomy cases have been collected from some 40 British hospitals. Some of the records are extremely sketchy, due to war-time circumstances. Most of the patients had not shown sufficient clinical improvement to warrant discharge and had died in the hospital in which their leucotomy had

been performed. The shortest post-operative survival period in the series was five hours, the longest five and a half years. Thirty-one of the patients died from cerebral hæmorrhage due to the operation, all within 14 days (average 5 days). Four died from intracranial infection, all within 16 days (average 10 days). Of the remaining 87 cases, 27 survived for a period of less than six months. Of these 27 cases, two are discarded from the analysis because of undisputed death from organic brain disease, one on account of death by suicide, and two others because they are almost certainly examples of the liability of post-encephalitic patients to die after any surgical operation. This leaves 22 cases where the particular nature of the early death after operation might be causally related to the particular leucotomy lesions.

The 22 cases are listed and numbered serially in the Table in the order of length of post-operative survival. The only other clinical data tabulated are the age at death, the apparent cause of death, and, where relevant, the date of recorded onset of trophic phenomena. Sex and the nature and duration of illness showed no correlation trend whatever with the cause or time of death (nor, actually, did age at death). On the anatomical side, involvement of "dorsal non-granular region" implies extension of the lesion into cortex or digital white matter of the superior frontal gyrus at the topographical level of Brodmann's (dysgranular) area 8 or (agranular) area 6 (Fig. 1). The cytoarchitecture was not checked histologically in every case. Involvement of "orbital non-granular region" implies ventral extension of the lesion into those dysgranular and agranular zones of cortex, or related white matter, which Beck (1949) has delineated cytoarchitecturally within the posterior half of the orbital region in the human brain. The figures "3" and "4" plotted in the last column of the Table denote involvement of the third or fourth antero-posterior quarter respectively of the orbital region (Fig. 2): "c" indicates where cortex as well as white matter was affected. By

FIG. 1.—Brodmann's standard cytoarchitectural map of the frontal convexity and orbital region. The position of the head of the caudate nucleus is indicated in black. The relative position of the anterior horn and lateral angle of the lateral ventricle is represented by the full line. The position and extent of the leucotomy lesions (in each hemisphere) in cases Nos. 31, 56, and 86, are indicated by the interrupted lines.

"striatum" is meant caudate nucleus and putamen. For the purpose of this analysis the combined volume of these two nuclei which lie rostral to the anterior commissure was allotted the figure 100. The percentage fraction of this volume which was damaged in each hemisphere was then estimated and tabulated. The two nuclei are not distinguished in the Table because separate correlation with nature and time of death revealed no suggestive trend. The "subcallosal fasciculus" is a fairly distinctive structure visible even in fresh material at the lateral angle of the lateral ventricle (Fig. 3) lying between the corpus callosum and caudate nucleus. In most cases its involvement or non-involvement could be determined by inspection. When its damage by softening around the lesion was doubtful, it was studied in coronal sections stained for cells, myelin, and axis cylinders.

Other anatomical variables which were taken into account during the analysis but found to be irrelevant in relation to survival time and nature of death, were damage to the cingulate gyrus (area 24), the cingular belt (area 32), the superior

longitudinal bundle (Fig. 3), the external capsule, the uncinate fasciculus, the claustrum, the extreme capsule, and the insular cortex. Penetration of the ventricles *per se* likewise displayed no suggestive association with delayed operative death.

FIG. 2.—Beck's cytoarchitectural map showing the agranular (heavy stippling) and dysgranular (light stippling) zones of cortex in the human orbital region. The interrupted lines and marginal numerals indicate the portioning into quarters employed in the present analysis.

FIG. 3.—Coronal section at the level of the middle of the head of the caudate nucleus, showing the position of the subcallosal fasciculus (S.L.B.), the cingulate fasciculus (C), the superior longitudinal bundle (S.L.B.), the superior occipito-frontal fasciculus (O), and the uncinate fasciculus (U).

Discussion

The absence of any death between the twenty-ninth day and the seventh week after operation divides the cases in the Table into two groups. The eight cases ranging in survival period from 5 hours to 29 days will be called Group I, the remaining 14 cases Group II. That the gap between the groups is not due entirely to chance will become apparent.

Group I : Uræmia and Bilateral Damage to Cortex of Posterior Parts of Area 47

A striking feature of Group I is the occurrence of four consecutive cases, dying from 20–24 days after operation, all from uræmia. The concentration of urea in the blood was investigated only in Nos. 5 and 6, but Nos. 4 and 7 showed very similar clinical symptoms. The essentials of the protocols after operation are as follows :

Case No. 4.

Day after operation	1–9.	Very restless.
" "	"	9. Generalized jerky movements.
" "	"	16. Very drowsy; semicomatose; blood pressure 116/87 (pre-operative blood pressure, 124/90).
" "	"	17. Deep coma; temperature, 99° F.; pulse, 124; respiration, 30.
" "	"	19. Still in coma; slightly cyanosed.
" "	"	20. Died in coma. (No blood urea recordings. Kidneys not remarked upon at necropsy.)

Case No. 5.

Day after operation	3.	Blood pressure back to normal (160/100); no speech; blood urea rising.
" "	"	5. Drowsy; retention overflow of urine; blood pressure normal.
" "	"	6. Blood urea reached peak of 500 mg. %.
" "	"	9. Bladder function normal; blood urea falling; blood pressure, 140/85; still no speech.
" "	"	13. Very pale; temperature, 99° F.
" "	"	14. Blood urea down to 105 mg%.
" "	"	16. Pupils sluggish; hand-fed; urine normal; blood pressure, 120/60.
" "	"	17. Blood urea rising again; blood pressure, 130/90; very stuporose; continual twitching of lips; occasional hiccough; breath smells of urine; lumbar and ankle œdema; pulse, 120.
" "	"	18. Comatose; blood urea 305 mg%; blood pressure too low to measure.

Day after operation	20.	Died after generalized convulsion. (Bilateral, unsuspected, advanced pyelonephritis found at necropsy.)

Case No. 6.

Day after operation	3.	Drowsy; pyrexial with slight neck rigidity; temperature, 99–101° F.
" "	"	5. Drowsy; C.S.F. heavily blood-stained; temperature, 98.2° F.; pulse, 136; respiration, 23.
" "	"	6. Now no signs of meningeal irritation; blood urea 86.5 mg%.
" "	"	17. Very drowsy; doubly incontinent; blood urea 288 mg%; temperature, 96.4° F.; pulse, 88; respiration, 20.
" "	"	20. Comatose; blood urea 333 mg%; temperature, 100° F.; pulse, 130; respiration, 34.
" "	"	21. Died in coma. (No blood pressure recordings. Tuberculous left kidney removed six months before operation, but right normal at necropsy.)

Case No. 7.

Day after operation	6.	Sharp rise in temperature to 103° F.
" "	"	9. Sharp rise in temperature to 103° F. again.
" "	"	11. Looks very well now, but rather drowsy and not eating well.
" "	"	15. Temperature still down.
" "	"	16. Up from bed for two hours.
" "	"	20–23. Rather drowsy and unwell; twitches from time to time; sluggish pupillary light reaction.
" "	"	24. Died in coma. (No blood urea or blood pressure recordings. Kidneys not remarked upon at necropsy.)

A second notable feature is that these four cases all have bilateral damage to the cortex within the third or fourth quarter of the orbital region as their only common (bilateral) anatomical characteristic and as a characteristic which distinguishes them from practically all other cases in the Table. Case No. 9, in Group II, had bilateral involvement of the fourth quarter of the orbital region, but it was confined to slits in, and running parallel with, the fibres of the digital white matter. Case No. 12 was the only case in Group II having bilateral damage to the cortex within the posterior half of the orbital region and, significantly, the only case in Group II to die of uræmia. This case, it will be noted, had considerably less damage to other posterior structures than the cases in Group I. Among the 60 cases surviving over six months, there are only two (Nos. 56 and 86) which had bilateral damage to the cortex in the third or fourth

quarter. No. 56, dying nine months after operation without manifest evidence of uræmia, will be mentioned later. No. 86 had no other posterior structures involved: the patient, a woman, died from uræmia of unknown origin 11 months after operation, aged 65 years.

These facts would seem to point strongly to bilateral damage of the third or fourth quarter of the orbital cortex being a determinant of fatal uræmia, and to the probability that coincidental damage to other extra-prefrontal structures accelerates such an outcome. Scoville's (1949 a, b) experience of successful therapy by bilateral undercutting of the posterior orbital cortex, right up to the optic chiasma would seem at first sight to militate against such a conclusion; likewise Poppen's (1948) experience with the special posterior ventral extension of his cuts in treating intractable pain. It must be remembered, however, that these two surgeons confined their lesions essentially to the white matter, whereas it was by irritating the cortex of area 13 in the posterior orbital region, by electrical stimulation in cats, that Cort (quoted by Livingston, 1948 a), claimed

to reproduce Trueta's kidney shunt mechanism in his laboratory. It may be, therefore, that only direct interference with the cortex produces striking autonomic disturbances. Whether the uræmia was due to direct neural influence on kidney circulation, or was dependent on blood pressure changes (as suggested by Donovan, Galbraith, and Jackson, 1949) or on other factors, is impossible to judge from the information available in the present six cases. Certainly none of these cases gave any history of post-operative ileus or of ulceration in the gastro-intestinal tract (cf. Sweet and others, 1948). Only one had definite pre-operative renal insufficiency.

More minute analysis of the position of the orbital lesions in cases Nos. 4 to 7, 12 and 86 shows only the lateral half, i.e., posterior area 47 (Fig. 2), to be consistently bilaterally involved in all six. It is within this region that in all six cases there was substantial involvement, on at least one side, of cortex as well as of white matter. This would suggest that the whole of the orbital non-granular strip of cortex may well play as important a role in autonomic affairs in man as does area 13 in monkeys.

TABLE
RELEVANT CLINICAL AND ANATOMICAL DATA IN 22 CASES SURVIVING LEUCOTOMY BY LESS THAN SIX MONTHS

Serial Number	Clinical Data			Anatomical Structures Involved							
	Survival Period	Age at Death	Cause of Death	Dorsal Non-granular Region (Brodmann's Areas)		Sub-callosal Fasciculus		Striatum (per cent. damaged)		Orbital Non-granular Region (See Fig. 2)	
				L	R	L	R	L	R	L	R
1	5 hours	29	Respiratory inhibition ..	—	8	—	—	0	0	4, c	4, c
2	7 days	73	? Uræmia and hæmorrhage ..	8	8	+	—	20	20	4, c	—
3	13 days	66	? Uræmia and hæmorrhage ..	—	—	—	—	25	30	3	4, c
4	20 days	25	Uræmia	8	8	+	—	12	8	4, c	4, c
5	20 days	49	Uræmia	8	—	+	+	10	12	4, c	4, c
6	21 days	29	Uræmia	8	8	+	+	20	60	4, c	3, c
7	24 days	18	Uræmia	—	—	+	+	10	0	4, c	3, c
8	29 days	45	Gastric perforation ..	6	6, 8	+	—	12	50	4	—
9	7 weeks	37	? Over-sedation ..	8	—	+	+	5	0	4	4
10	7 weeks	44	? Trophic deterioration ..	—	8	+	+	20	30	—	4, c
11	8 weeks	48	Trophic deterioration (D. 32) ..	6	8, 6	+	+	0	0	—	—
12	8½ weeks	72	Uræmia	—	—	+	—	0	5	3, c	4, c
13	9 weeks	62	Trophic deterioration (D. 26) ..	—	8, 6, 4	+	+	10	5	—	3
14	9½ weeks	48	Trophic deterioration (D. 29) ..	8, 6	—	+	+	55	50	—	—
15	9½ weeks	71	Lobar pneumonia ..	—	—	+	—	0	20	—	—
16	10 weeks	64	Trophic deterioration (D. 31) ..	—	—	+	+	0	0	3	—
17	10½ weeks	31	Trophic deterioration (D. ?) ..	—	—	+	+	5	55	4	—
18	14 weeks	50	Trophic deterioration (D. 33) ..	—	—	+	+	20	15	3	—
19	15 weeks	42	Trophic deterioration (D. 42) ..	—	8	+	+	30	30	—	—
20	19 weeks	37	? Trophic deterioration ..	—	—	+	±	15	20	4, c	—
21	20½ weeks	60	Empyema	—	—	—	+	10	5	3	3
22	24½ weeks	35	Phthisis	6	—	—	—	0	0	—	—

"D" gives the day after operation of the first appearance of trophic symptoms.

Livingston and his associates (1948 a and b) have indeed already recorded an impression that the orbital autonomic "active focus in man is somewhat more laterally situated than in lower primates". Percival Bailey (personal communication, 1950) has found the most active focus to lie in the anterior insular cortex. The absence of manifest uræmia in case No. 56 might indicate that connexions between posterior area 47 and the head of the caudate nucleus must be cut to produce fatal uræmia.

Area 13 within the medial half of the posterior orbital region was in none of these uræmic cases substantially damaged. Case No. 1, where both lesions did extend into area 13, has been discussed elsewhere (Meyer and McLardy, 1948, Case 59). In No. 8, dying from acute perforation of the stomach, there was softening of the whole of the right putamen due to vascular damage.

Group II: Trophic Deterioration and Bilateral Damage to the Region of the Subcallosal Fasciculus

A most striking feature of Group II in the Table is the remarkable similarity of the nature of death in Cases 11, 13, 14, 16, 17, 18, and 19. They not only all became marasmic and died with multiple cutaneous septic sores within two to five months of operation (average survival, 11 weeks), but all first manifested such cutaneous "trophic" lesions in the fifth or sixth post-operative week. Typical protocols are as follows:

Case No. 11.

Day after operation	5.	Doubly incontinent; eating voraciously.
" "	"	6. Singing and talking cheerfully.
" "	"	32. Quieter; not well; still doubly incontinent; has developed blisters on left hand.
" "	"	34. Shows extreme inanition; early stage bedsores; tongue dehydrated; appears to be in pain if moved.
" "	"	41. Early gangrene in left hand and toes.
" "	"	48. Hand improving but toe gangrene progressing.
" "	"	50. Temperature, cough, low-grade bronchial pneumonia; slight albuminuria.
" "	"	54. Urine negative for sugar.
" "	"	55. Marked wasting.
" "	"	57. Died with bronchial pneumonia and chronic nephritis. (Given post-operative multiple vitamins.)

Case No. 14.

Day after operation	12.	Responding slowly to re-education; taking food himself.
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Day after operation	26.	Weight fallen to 6 st. from 7 st. 4 lb. at operation.
" "	"	29. Large bedsores; blisters on hands.
" "	"	40. Blisters now purulent.
" "	"	56. Temperature beginning to rise slowly; average pulse, 110; respiration, 24.
" "	"	68. Died with a temperature of 103° F. (Given post-operative multiple vitamins.)

These seven cases will therefore be spoken of as dying from "trophic deterioration".

On the anatomical side is the equally striking fact that these seven are the only cases in the whole series with a post-operative survival of over seven weeks and bilateral involvement of the subcallosal fasciculus at the level of the head of the caudate nucleus (Fig. 1), with the exception of No. 56. Five other cases in the total series had bilateral destruction of practically all white matter lateral and dorso-lateral to the subcallosal fasciculus at the level of the head of the caudate nucleus, but lived from 11 months to 5½ years (average, 2½ years) after the operation. There would thus seem to be strong evidence that severe bilateral damage to this region of the subcallosal fasciculus is a determinant of delayed operative death from marasmus accompanied by trophic skin lesions. It is difficult to exclude definitely the superior occipito-frontal bundle which lies just lateral and ventral to the subcallosal fasciculus. Detailed histological investigation of several crucial cases is in progress.

Post-leucotomy trophic lesions have been systematically studied only by Ziegler and Osgood (1945) and Meyer and McLardy (1948, 1949). From purely clinical and x-ray investigations Ziegler and Osgood concluded that (non-fatal) post-operative oedema and bullæ might be associated with more posteriorly placed lesions, especially those involving areas 8 and 6. Meyer and McLardy did not relate the clinical phenomena to any particular structure involved in posterior cuts.

There appear to be no experimental observations on the result of selective bilateral damage to the subcallosal fasciculus (Mettler, 1942). Whether this structure was damaged in the bilateral operations on the striatum performed in man (Meyers, 1942 a and b; Hamby, 1947) is not specifically stated in the descriptions published by the surgeons. It is, however, noteworthy that Hamby's operations proved fatal, even when done in two stages, whereas Meyers' patients survived. According to my measurements on numerous dissected brains, Meyers' sagittal cut through dorsal premotor cortex 2 cm. from the midline and parallel to the falx should enter the roof of the lateral ventricle through the corpus callosum, whilst Hamby's similar cut

(described by Browder, 1947, 1948) made 3 cm. from the midline, should enter the angle of the lateral ventricle by passing through the subcallosal fasciculus. Hamby's case No. 13, we are told, died three months after the second operation "in a state of inanition". Not enough is known of the blood supply of the subcallosal fasciculus to permit of more than speculation that Dandy's (1946) nine cases of death within 51 days after ligature of one or both anterior cerebral arteries may have been due to ischæmic softenings affecting both subcallosal fasciculi.

A subsidiary clinico-anatomical point illustrated in Group II, but not shown in the Table, is that in the cases dying from trophic deterioration the only two with complete sparing of the striatum (Nos. 11 and 16) were the only two in which the clinical records reported that the patient experienced acute pain when moved after the appearance of cutaneous

Histological Evidence of Nutritional Deficiency.—The brains of all 14 cases in Group II were specially investigated histologically for the characteristic pathological evidences of pellagra and Wernicke's disease. Nos. 10, 12, and 14 showed evidence of pellagra, No. 18 evidence of Wernicke's disease, and the remaining cases no evidence of either condition. In the whole group, No. 18 was the case with the greatest recorded restlessness throughout the post-operative survival period. The clinical records and anatomical findings in the other three positive cases showed no feature which distinguished them from those in the generality of cases.

The Subcallosal Fasciculus and its Connexions.—It has been suggested by several authorities that the subcallosal fasciculus is made up of overlapping relays of fibres, each running for only a short distance. Mettler (1942) has described fibres which appear to move gradually downwards within it as sections are followed caudally, and he, as well as Papez (1942), have demonstrated neuropil, which appears to pass from its ventral surface into the adjacent caudate nucleus. The bundle is generally supposed to mediate a connexion between the frontal cortex and the caudate nucleus (Levin, 1936; Glees, 1944). The present material would suggest that, if such a fronto-subcalloso-caudate system exists, its integrity in at least one hemisphere is essential to life.

Case No. 56 has been mentioned as an exception to the clinico-anatomical principles revealed in Group II as well as in Group I. There was bilateral involvement of both the posterior quarter of the orbital cortex and the subcallosal fasciculus, yet the patient lived into the ninth month without gross evidence of uræmia and with only terminal development of trophic deterioration. This case, however, was also unique from the anatomical point of view. Both lesions sloped steeply upwards and backwards (Figs. 1 and 4) into area 4 in such a way that, first, the subcallosal fasciculus was cut slightly more posteriorly than in the seven Group II cases dying from trophic deterioration; and, secondly, the rostral half of the head of the caudate nucleus (which was not macerated as in most other cases where affected) was not cut off from areas 8 and 6. The majority of any fibres coursing between that half of the head of the caudate nucleus and these areas, passing through rostral parts of the subcallosal fasciculus, would be uninterrupted, as would be any fibres running between posterior area 47 and rostral parts of the head of the caudate nucleus.

Case No. 86, with bilateral lesions sloping steeply backwards from the most dorsal cortex of area 9

FIG. 4.—Brodmann's standard cytoarchitectural map of the mesial surface of the frontal lobe. The corpus callosum is shown in black. The position and extent of the leucotomy cuts in cases Nos. 56 and 86 are indicated by the interrupted lines.

lesions. This might be a pointer to some principle of practical value in neurosurgery for pain.

into the most rostral part of the angle of the lateral ventricle (Figs. 1 and 4), surviving for 11 months and dying from uræmia without trophic symptoms, would seem to exclude the participation of granular cortex in any fronto-subcalloso-caudate system concerned in fatal trophic deterioration. Again, No. 31 (Fig. 1) and two other cases, with survival periods of 9 months, 16 months, and 18 months respectively, and bilateral deep ventral cuts sweeping upwards into the ventral parts of the anterior horn at about the level of the tip of the caudate nucleus, would seem to exclude the possibility that the "vital" fibres curve round the anterior horn from orbital regions.

Finally, as already pointed out, all patients with bilateral destruction of the subcallosal fasciculus between the levels involved in cases Nos. 56 and 86 died within five months of the operation. All the evidence, therefore, points to the existence of vital structures lying between the rostral half of the head of the caudate nucleus, the related portion of the subcallosal fasciculus and cortex at the level of Brodmann's areas 8 and 6, i.e., the structures lying between the lesions in case No. 86 and case No. 56 as illustrated in Figs. 1 and 4.

If these three regions contributed to a connected vital system one might expect destruction of any one of the elements to be equally fatal. The subcallosal fasciculus, the bottle neck of the system, would be, as suggested by the present material, the point of greatest disruption by a minimal lesion. So far as damage to the caudate nucleus is concerned, although survival in the present series does not appear to vary according to the (macroscopic) amount of its damage, there is no case of its bilateral substantial damage with survival over five months, with the one exception of case No. 87 living for one and a half years after the operation. In this case the damage to each caudate nucleus is confined more than in any other case to its ventricular surface and would not presumably interfere with the majority of any connexions between the head of the caudate nucleus and the cortex. Heath, Freedman, and Mettler (1947), it is interesting to recall, considered that the invariable death of felines subjected to bilateral striatal ablation was most probably due to metabolic dysfunction.

The fact that, within the seven clear cases of fatal trophic deterioration, brevity of survival is directly proportionate, roughly, to the amount of dorsal non-granular region involved in the lesions (see Table), would seem in general to support the conception of such a vital fronto-subcalloso-caudate system. Yet, as is well known, very substantial bilateral destruction of dorsal non-granular cortex is not by itself lethal. This might imply merely that

the system is least vulnerable within its most diffuse, cortical, element. On the other hand, it might indicate that the lethal factor in the dorsal leucotomy lesions lies in a region not usually affected in clinical or experimental surgery on the premotor cortex, namely the adjacent mesial cortex (Fig. 4). That the portion of area 32 lying rostral to the genu of the corpus callosum (and premotor cortex) is not the region concerned, would seem evidenced by the irrelevancy to survival of its involvement or non-involvement in the present series. There has been equal absence of untoward incident, apparently, after fairly full ablation (Pool, 1949 a and b; personal communication, 1950) of this part of area 32, and after undercutting (Scoville, 1949 a and b; personal communication, 1950) of practically the whole area. The cortical end of the presumptive "vital system" cannot therefore be confined to the whole of that area which is regarded as cytoarchitecturally homologous with the cortex (areas 32 and 31) to which all the suppressor areas in monkeys send connexions (McCulloch, 1944). Almost identical arguments are available against area 24 being the only region concerned. Extension of investigations such as those of Meyers and his associates (1949) on electrical activity of the neostriatum might clarify this problem. In the meantime it may be relevant that these workers found such uniformity of electrical activity in the caudate nucleus, the subcallosal fasciculus, and neighbouring parts as to suggest a common source of the discharge.

The essentially metabolic nature of the trophic deterioration might point to importance in its causation of those cortical areas known to be significant in autonomic affairs, such as areas 6 and 24. The connexions concerned would then presumably be fibres such as those which have recently been shown (M. Meyer, 1949) to project from area 6 into the hypothalamus. Most of any such fibres from area 6 or area 24 to the hypothalamus might be expected to take the shortest course through, or immediately around, the subcallosal fasciculus at the level of the head of the caudate nucleus.

Experimental investigation of the subcallosal fasciculus from the point of view of its part in delayed operative death is in progress.

Significance of Grouping in Survival Times.—Whatever the validity of the more tenuous of these deductions from the data, it is clear that the time gap between Groups I and II is due to more than chance, and that a similar gap, or relative attenuation of cases when graded by survival period, is likewise to be expected between Group II and cases dying at

random from intercurrent illness, or from any third group which might emerge in a larger series if there were any tendency for cases with unilateral damage to extra-prefrontal structures to succumb to environmental stresses which are not normally fatal.

Practical Implications of the Findings.—It is not proposed to speculate here on possible physiological mechanisms involved. Much of the relevant experimental work has been referred to in the previous papers quoted, and the elucidation of suppressor and other feed-back mechanisms probably concerned is not sufficiently advanced to bear profitable discussion. My practical concern is to utter a warning regarding two dangers additional to hæmorrhage of blind leucotomy operations: delayed post-operative death from uræmia and from trophic deterioration. The original trans-orbital leucotomy, as well as all the open methods of leucotomy and cortical ablation, are almost* free of all three sources of mortality, but the newly-devised “deep” transorbital cut (Williams, 1949; Freeman, 1949) may ominously increase them. I have seen one such case with unilateral damage to the striatum and subcallosal fasciculus. There would seem no good reason why the striatum and subcallosal fasciculus might not have been equally damaged in both hemispheres, thus determining the patient's death within five months.

Summary

In a series of 22 leucotomy cases dying within six months of the operation, analysis of the causes of death reveals two distinct groups: Group I, dying predominantly from uræmia in the third post-operative week, and Group II, dying predominantly from trophic deterioration (marasmus with trophic skin lesions), between two and five months after the operation. In the latter group blisters or bullæ almost always appeared on the extremities between the fourth and sixth post-operative weeks.

Post-mortem anatomical (mainly macroscopic) analysis of the lesions in the frontal lobes of these 22 cases revealed a striking association of death from uræmia with bilateral damage to the posterior (non-granular) orbital cortex, and of death from trophic deterioration with bilateral cutting of the region of the subcallosal fasciculus at the level of the head of the caudate nucleus.

The orbital cortex concerned in the uræmic deaths appeared to be posterior area 47, not

area 13. Histopathological evidence of nutritional deficiency was not conspicuous among the cases of trophic deterioration.

From evidence supplied by these and other relevant cases, in a total series of 122, it is deduced that connexions between the caudate nucleus and Brodmann's (non-granular) cortical areas 8 and 6 (including their mesial extension towards the corpus callosum), via the rostral parts of the subcallosal fasciculus, may be the structures whose damage determined the fatal trophic deterioration.

The practical intention of the paper is to emphasize the serious danger of delayed operative death from the use of blind leucotomy techniques, including the “deep” transorbital cut.

The writer wishes to express his thanks to Professor Alfred Meyer for his interest in this investigation. For the opportunity to pursue all such studies he is indebted to those medical superintendents and other medical officers who, realizing the potentialities of systematic centralized investigation of such leucotomy material, contributed to the series.

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* One brain has already been examined where the original trans-orbital operation resulted in fatal hæmorrhage from the lenticulo-striate vessels on one side.

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