

SOME OBSERVATIONS ON LEUCOTOMY AND INVESTIGATIONS BY
PNEUMOENCEPHALOGRAPHY.*

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PART I.—CLINICAL OBSERVATIONS.

Leucotomy studies are now commonplace and this preliminary report on the clinical aspects of our series has probably little to add to existing ideas on the subject. Neither the case material nor our initial approach to the problem differ fundamentally from the observations expressed by various workers at a meeting held at the Royal Society of Medicine on 9 April, 1946.

It is still doubtful, however, if sufficient evidence has yet been obtained to justify rigid conceptions regarding either the selection of patients or the prognostic criteria in any individual case. It is probable that the cardinal "good omens" might apply as with any other form of treatment in psychiatry, but one assumes that few patients with a really good prognosis have been subjected to the operation of leucotomy. We have certainly tried to maintain an uncompromising attitude in this respect and our cases have been selected from material for which no other method of treatment was feasible or where other methods had been unsuccessful. The majority of the patients were mental hospital residents, but a few (mainly obsessionals) had been admitted specifically for operation. Each case was discussed by us in conference to ensure full agreement that leucotomy was justifiable in the hope of relieving a distressing clinical situation.

The positive aspects of our selection are, of course, based on the fundamental hypothesis that the aim of the operation is to relieve emotional tension, and it is possible to divide the cases into two simple categories:

(1) Cases in which tension is obviously associated with distress on the part of the patient.

(2) Cases in which tension is expressed as disordered conduct.

The patients who are overtly distressed are the severe and obdurate depressives and obsessionals and those schizophrenics whose symptomatology is essentially paranoid. The conduct problems are mainly schizophrenics whose personalities show evidence of a variable degree of disintegration. The classification corresponds closely to the four groups distinguished by Cook (1946).

So far no direct reference has been made to the problem of personality in relation to selection and prognosis. On the whole we felt that the more reliable guide is the degree to which personality is affected by the illness and we have not attempted any detailed study of the patient's basic personality. It is frequently difficult, or virtually impossible, to distinguish between basic weak-

* Originally the subject matter of a report to the South-Eastern Division of the Royal Medico-Psychological Association at St. Francis' Hospital, Hayward's Heath, on 4 May, 1948.

ness in the personality structure, and findings which may represent the earlier stages of an insidious process. Furthermore, we are dealing mainly with chronic cases in which the information at our disposal is either inadequate or suffers from the bias imposed by interested parties, who invariably make too vivid distinctions between the past and present state of their unfortunate friends and relatives. Clinical assessment of the two main groups leads to the assumption that personality is relatively intact in the "distressed" patients and much more affected in the "conduct problem" group. Even so, in the latter there has not been complete surrender to the disease process which is still an actively disturbing influence.

The simple sub-division into "Distress" and "Conduct Problem" groups indicates roughly the type of patient and the corresponding need for leucotomy. Subsequent review of the series showed that without some elaboration it did not embrace every case satisfactorily, nor did it allow for sufficient gradation when assessing results in relation to other findings. Thus it did not distinguish between the members of the "Distress" group who showed relatively good preservation and those in whom there were some more definite signs of failure of personality. Likewise, although the majority of the "Conduct Problem" group was apparently disintegrated to an advanced degree, a few showed "islands" of preservation.

Based on overt clinical phenomena there were patients at one end of the scale who showed such features as intense and appropriate affect, preservation of thought and language, and at the lower extreme were those distinguished by symptoms such as apparent loss of affective responses, gross disturbance of language, blind impulsiveness, degraded habits, etc.

Irrespective of the original grouping into "Distress" and "Conduct" the patients were sub-divided into three somewhat empirical grades—A, B, and C, depending on the level they attained in this preservation-disintegration scale.

Bearing in mind these brief theoretical conceptions the actual case material under review should now be examined. This consists of a total of 80 patients (39 males, 41 females) on whom leucotomy has been performed between October, 1946, and April, 1948. Reference will be made to certain additional cases who have had the operation since the latter date, but which are not included in the preliminary review.

In tabular form the classification of these cases, including clinical groups and grade of personality assessment, is as follows :

TABLE I.

Personality grade.	Tension.											
	Distress.									Conduct problems.		
	Depressive.			Paranoid.			Obsessional.			M.	F.	Total.
M.	F.	Total.	M.	F.	Total.	M.	F.	Total.				
A	8	3	11	1	10	11	3	3	6	—	—	—
B	3	2	5	8	10	18	1	1	2	5	2	7
C	—	—	—	—	1	1	—	—	—	10	9	19

The distribution of the cases in this table is largely self-explanatory and according to expectations. It will be seen that, apart from one female patient,

all the "Distress" group are rated A or B in the personality preservation scale. The single exception is a woman who originally displayed a fairly florid paranoid psychosis, but had shown progressive deterioration and would probably have been left untreated but for the insistence of her relatives. Conversely it will be observed that nearly three-quarters of the "Conduct Problem" group are rated C, and the remainder no higher than B.

No exact statistical survey has been made, but in comparing the two sexes such items as age groups and duration of illness seemed to correspond fairly closely. It will be noted from Table II that over 50 per cent. (i.e. a total of 44) of the cases are of 10 or more years' duration.

TABLE II.

		Average age.	Duration.					
			Under 1 yr.	1-2 yrs.	2-5 yrs.	5-10 yrs.	10+ yrs.	
Distress	Depressive	M.	55	1	2	1	1	6
		F.	52	1	—	1	1	2
	Paranoid	M.	44	—	—	2	1	6
		F.	49	—	—	4	8	9
	Obsessional	M.	35	—	—	—	1	3
		F.	33	—	—	—	1	3
Conduct	M.	34	—	3	1	2	9	
	F.	41	—	—	1	4	6	

In assessing results in this series it must be emphasized that this is merely a preliminary survey and no attempt will be made to compare results with other series. There are, however, several points which may be of interest:

Method of recording progress.—We have found it convenient to employ a simple scale of numeral ratings which range from 0, indicating no improvement, to 5, implying recovery. It must be clearly understood that these ratings have no exact definitive value. In assessing improvement the selection and classification of cases and the immediate aims of the operation must influence the criteria on which the results are determined. Subjective relief is obviously a major issue in relation to distressed patients, while ease of management is of equal importance in the cases which are classified as conduct problems. The lower ratings in the scale mainly denote symptomatic improvement, so that the results in the various clinical groups are not strictly comparable, but as the scale is extended towards social recovery a common significance emerges.

Results.—As might be expected, the best results were obtained in the depressive group, although two patients in this group who had made good remissions subsequently relapsed completely. The paranoid group showed a tendency to improvement up to a point, while the results in the obsessional group were variable and, on the whole, are disappointing. The degree of improvement recorded in a fair proportion of the conduct problem cases is a most gratifying feature. Some of these patients surpassed our hopes and showed progress beyond a mere reduction of their behaviour difficulties.

The general pattern of response in the various groups is conveniently illustrated by means of a table (Table III) which shows the peaks reached in terms of the numerical ratings previously mentioned. If these results are examined along with the pre-operative personality grades it will be seen that in certain instances considerable doubt must arise with regard to the accuracy and

validity of purely clinical assessment. It is fair to state that clinical expectations were, for the most part, fulfilled in the depressive group in that all but one of the cases with an A personality grading made much more satisfactory progress than those graded B. In the paranoid group, however, there is little to choose between A and B grades, and the conduct problem group seem to provide the outstanding example of discrepancy between personality grades and the degree of improvement.

TABLE III.—*Progress Peaks.*

		Died.	0.	1.	2.	3.	4.	5.
Depressive	A	1	—	1	—	—	4	4
	B	—	1	1	1	—	1	—
	C	—	—	—	—	—	—	—
Paranoid	A	1	—	1	3	4	1	1
	B	—	2	3	6	5	1	1
	C	—	1	—	—	—	—	—
Obsessional	A	—	1	1	1	2	1	—
	B	—	—	—	—	1	—	—
	C	—	—	—	—	—	—	—
"Conduct"	A	—	—	—	—	—	—	—
	B	—	—	2	3	1	—	1
	C	—	4	4	5	4	2	—

Duration of illness.—There would appear to be no clear correlation between duration and progress, but only three patients who had been ill for more than ten years were ever rated as "recovered." Of these, two (depressives) subsequently relapsed, but one paranoid patient who made a belated remission, has, so far as is known, remained well since leaving hospital. On the other hand, among the conduct problems, several patients who had been ill for more than five years, made surprisingly good remissions.

Pattern of response.—The findings in this series once again illustrate that improvement may be gradual and extend over many months, and in a few schizophrenics improvement was first noted after a latent period. The clinical histories in these latter cases did not suggest that the delayed response might have been spontaneous. In the depressives the response is usually more immediate.

Repeat operations.—In this series we have one intriguing example of the effects of a second leucotomy. The case was that of a male schizophrenic, classified as a conduct problem, who showed a great deal of tension without gross disintegration. The first leucotomy had no effect, but a second operation, performed two years later, produced immediate relief. The only persisting symptom of any significance was the occurrence of brief destructive episodes which seemed just as puzzling to the patient as to ourselves. It was eventually decided that these attacks might be of the nature of epileptic variants. They ceased after epanutin had been prescribed.

TABLE IV.—*C.N.—Progress Chart.*

	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.
1944	L	1	0	0
1945	0	0	—	0	—	0	—	—	0	0	—	—
1946	0	—	—	0	0	—	—	—	—	0	0	L
1947	3	3	3	3	3	3	3	3	3	3	3	5
1948	5	—	5									

L = Leucotomy.

Vegetative functions.—As part of the routine investigation we have been studying some of the apparent alterations in vegetative functions after leucotomy. So far the most interesting finding, and perhaps the item of most practical significance, has been the changes in blood pressure and their possible relationship to kidney function. A fall in blood pressure seems to be invariable, but there is a great deal of individual variation in the degree and duration of this change. The lowest level is generally recorded about the third or fourth day after operation. Frequently the fall seems to be in direct proportion to the pre-operative level, i.e. the most extensive lowering of systolic pressure generally occurs where the initial reading is comparatively high. The duration of these changes is again subject to considerable variation. In some cases the pre-operative pressure may be regained in a comparatively short time, in others it is attained several months after the operation, and in some cases in this series the pre-operative pressure has not yet been re-established.

Another post-operative finding, which again is by no means consistent, is a rise in blood-urea level, which commonly reaches a peak about the third or fourth day. Rise of blood urea has been reported by Cumings (1942) in relation to head injuries. This author postulates a specific toxic factor arising from brain tissue damage and exerting its effect on the renal tubules. The relationship between the rise of blood urea and brain damage is again referred to in a later part of this paper.

At present it is impossible to be dogmatic about the mechanism of either of these findings in our series or to do more than speculate about their conceivable relationship. It can be stated that in some cases the post-operative fall in blood pressure is not accompanied by any rise in blood urea, in others a moderate rise is encountered and in a few instances very high urea levels are reached. Perhaps the most striking example occurred in a female patient whose kidney function had not been suspect until she developed a post-operative fatal uraemia (Fig. 1). Post-mortem revealed an advanced bilateral pyelonephritis. Although impairment of kidney function may be due to Cumings' toxic factor, it is equally reasonable to postulate that it is secondary to the lowering of the blood pressure. It is possible that if there is any pre-existing renal inadequacy it will be unmasked by the fall in blood pressure. The fall in blood pressure as already mentioned, frequently persists for a long time after operation (when any immediate traumatic-toxic factors must have resolved) which certainly suggests that autonomic vaso-motor centres have been affected by leucotomy.

Control of bladder function was interfered with in many of the patients in this series. Broadly speaking, the majority were incontinent for a variable time after operation. There were some who did not appear to be aware of the state or action of their bladders, and others whose incontinence was due to apathy or laziness. Many similar observations have been made in the past, but there may be still further aspects to consider. We have, for example, been puzzled by certain cases in which incontinence did not develop until some days after operation. Partial dehydration may have been a factor, but unfortunately we have no details of actual output in these cases. All that has been noted is that certain patients who used the bed-pan satisfactorily for a

day or two subsequently became incontinent. Another enigma is the incontinent patient who, after leucotomy, eventually becomes dry in habits without showing any significant improvement in other directions. While intensified nursing attention may be a possible explanation of this latter phenomenon, our observations do not suggest it to be so in every instance.

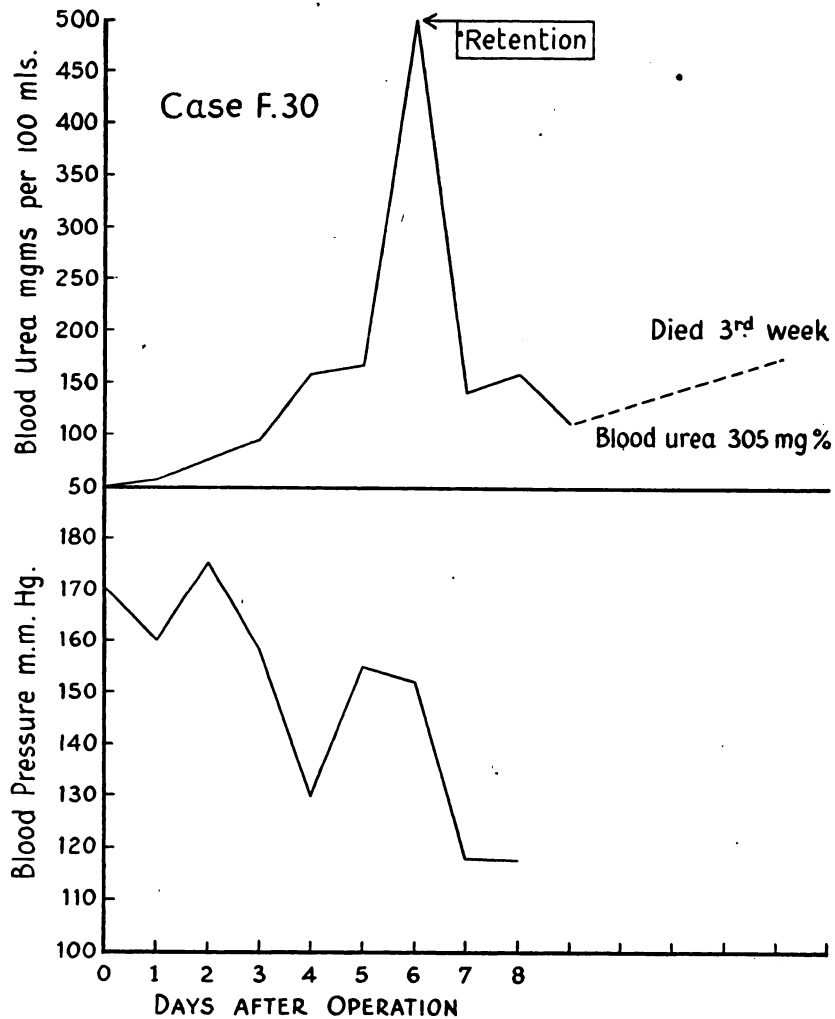


FIG. 1.

Following leucotomy, gain in body weight, often associated with an obvious increase in appetite, has been noted in over half the cases of the series. There is no constant relationship of these findings to mental improvement and their incidence is no less common among those who failed to make significant progress. This might suggest that they are direct results of changes in vegetative centres.

A further communication on these physical aspects of leucotomy is contemplated when certain additional investigations have been completed.

Fits.—A small percentage (4 per cent.) of our patients developed epileptiform convulsions at varying intervals after operation. Our findings in this direction are in keeping with other reports, and do not require special comment.

Deaths.—In this series there have been only two deaths. In both cases uraemia developed. In the first, which has already been discussed, death occurred three weeks after the operation and was due to chronic pyelonephritis. In the second, death occurred seven days after the operation and was due to intracerebral haemorrhage in the region of the leucotomy, and although the blood urea reached a figure of 440 mgm. per cent. the kidneys were normal.

The concluding remarks on this clinical review are mainly concerned with introducing the second part of the investigation. It will have been apparent that in depressive patients and paranoid schizophrenics the results can be understood in terms of reduction of affective disturbance. In the former the affective disturbance is the essential reaction of the illness, whereas in the latter it constitutes only one aspect. Thus, while complete relief may be accorded to a case of pure depression, the same degree of improvement is unlikely to occur in one of paranoid schizophrenia.

These views are in keeping with existing conceptions of the mechanism of leucotomy, and merely emphasize the fact that where emotional tension is directly apparent as affective symptoms, it should be feasible to forecast the progress in most instances. On the other hand, the response in the sort of case which we have classified as "conduct problem" is much more problematical, as our results will have shown. It was therefore considered that, especially in relation to the latter group, fresh evidence must be sought from other sources. With this in view one of us (J. F. D.) began an independent investigation by means of pneumoencephalography, and in describing the results of this study, an attempt will be made to relate them to the clinical findings.

PART II: INVESTIGATION BY PNEUMOENCEPHALOGRAPHY.

The existence of cortical atrophy* in schizophrenia as demonstrated by pneumoencephalography was first reported by Jacobi and Winkler (1927, 1928) and additional reports have come from many sources since then (Moore, 1935; Semrad, 1943; Delay, 1945). Lemke (1935), who studied a series of cases, found that those with the greatest personality disorder occurred in a group showing the greatest ventricular enlargement. That these changes have not received the attention which they probably deserve may be due to the absence of clearly defined histopathological changes to account for them. However, the existence of atrophy in the brain of patients suffering from chronic schizophrenia has been amply supported by observations made by the neurosurgeon during the operation of leucotomy. Often the brain is shrunken from the dura or the sulci are filled with an excess of fluid and the ventricles feel dilated as the exploring needle is inserted. These changes observed at operation, especially those in the cortex, correlate fairly well with those seen in the encephalograms of the same patients.

* The use of the term "cortical atrophy" is not intended in the true histological sense, and possibly "cortical shrinkage" would be more appropriate.

The present encephalographic investigations concern two groups of patients. Group I consists of a series of 19 patients of whom 12 had a further encephalographic study after the operation of leucotomy. Group II consists of 17 patients who had already had a leucotomy operation prior to the commencement of this investigation.

Of the total of 36 patients (18 male and 18 female) who have had encephalograms done, all were suffering from schizophrenia of a duration extending from 2 years to 29 years. Their ages ranged from 16 to 66 years. Seventeen had received other physical treatments (insulin, cardiazol or E.S.T.) previously and 19 had had no physical treatments.

The cases in Group I all show some degree of abnormality in their encephalograms. These abnormalities consist in some of a gross degree of enlargement of the ventricles without any abnormal surface air markings; in some there is a considerable widening of the sulci and of the cisterns, with only minor degrees of enlargement of the ventricles, while in others a combination of both changes is in evidence.

The findings are tabulated below in relation to the age of the patients and the known duration of the schizophrenic illness. An estimate of enlargement of the lateral ventricles was made, and subsequently checked against the ventricular index (Evans, 1942) calculated for each of the encephalograms. In the table there are three grades which compare with the ventricular index as shown.

TABLE V.

Group I. Case No.	Age.	Duration in years.	Degree of enlargement of lateral ventricles.		Ventricular index.			Previous treatments.
			—	+	+	+	+	
16	60	4+	—	+	Less than 0.30 (normal average 0.23).	—	+++	—
4	54	12	+	—	0.30 to 0.32.	+	+	EST
33	54	15+	++	+	0.33 to 0.35.	+	+	—
8	52	15+	+	+		+	+	—
5	52	2	+	+		+	+	—
12	50	29	++	—		+	+	—
26	48	29	+	+		+	++	—
17	47	10+	++	—		+	+++	—
3	45	11	++	—		+	—	—
10	44	13	+	+		—	++	—
13	40	8	++	+		+	—	—
32	38	15	+	—		—	+	—
1	37	15	++	+		+	+	—
6	32	10	+	—		+	+	C
34	30	11	—	—		—	+	C
18	30	7	++	+		+	+	I
29	29	3	+	+		+	—	I
2	24	3	+	—		+	—	EST I
9	16	5+	—	—		—	+	I

EST = electro-shock treatment; I = insulin shock treatment; C = cardiazol shock treatment.

The series of patients examined is too small to make any general deductions from the results, but it can be seen that while none of the patients exhibit an

entirely normal encephalogram the most severe abnormalities tend to be found among the older patients who have a correspondingly longer duration of illness. Most of these older patients have not been given any of the modern physical treatments and this must be taken into account when considering the possibility of atrophic change being a result of physical treatments.

Relation to Progress.

It seems important to establish whether the existence of atrophic cortical lesions as revealed by the encephalogram has any bearing on the progress of the case subsequent to leucotomy. For various reasons it would be premature to form any conclusions from a study of the few cases in Group I who subsequently had a leucotomy operation, although it is perhaps significant that Case 34 (Table V) showed least abnormality in the encephalogram and has improved sufficiently to be discharged home. The other eleven cases all had more marked changes in the encephalogram and at the most exhibit only minor degrees of improvement following the operation.

In cases belonging to Group II, where an encephalogram was made only after the operation of leucotomy, it is impossible to distinguish with certainty between the changes in the encephalogram which can be ascribed to the operation and signs of a pre-existent atrophy. However, the cases are shown in Table VI and an attempt has been made to grade them according to the severity of atrophy shown in the encephalogram although it may well be that some of the cases have been placed in too advanced a grade as a result of general atrophic changes brought about by leucotomy. It is of interest to note that all the major degrees of improvement following leucotomy occur in the first and second grades.

TABLE VI.

Grade I.		Grade II.		Grade III.	
Case No.	Progress.	Case No.	Progress.	Case No.	Progress.
15	5	21	4	20	2
27	3	11	2	30	2
28	2	22	I	24	I
7	2	36	I	25	I
14	0	19	I	23	0
..	..	31	0
..	..	35	0

Plane of Leucotomy.

Dilatation and inequality of the ventricles were both common findings before leucotomy and it is important that this should be realized, as it cannot be assumed that the lateral ventricles, and in consequence the fronto-thalamic radiations, bear a normal relationship to the surface markings of the head in these patients. For this reason it was felt that any estimates of the plane of the leucotomy section made with reference to the coronal suture line were of doubtful validity. At operation the plane of the leucotomy was marked by the insertion of a small length of silver wire into the cut through the white matter. In encephalograms made subsequently the relationship of the plane of the leucotomy to the anterior horns of the lateral ventricles has been esti-

mated by taking several different views, including in many cases stereoscopic pictures. The result of this investigation shows that throughout the series the position of the leucotomy markers varies from just anterior to the tips of the anterior horns of the lateral ventricles to a position well posterior to them.

These variations are summarized in Table VII, and an attempt has been made to correlate the place of section with various features of the progress of the case after operation. The greatest degree of clinical improvement occurred in the two cases with more posterior cuts, but there is a wide individual variation and no constant correlation between the plane of the cut and clinical improvement is evident. Persistent incontinence of urine and a significant fall in blood pressure, either of a duration of more than one month, are also recorded in the table. Although Ziegler and Osgood (1945) came to the conclusion that there was some evidence that a more anterior leucotomy is attended with less incontinence, they admitted that their findings showed only a poor correlation. It is clear that in the present series there is also an absence of a definite relationship between the plane of the leucotomy on the one hand and disturbance of bladder function and vasomotor control on the other. None of the cases developed oedema of the legs after the operation, as described by Ziegler and Osgood, and only one case, No. 14, was complicated by a trophic change in the skin.

Since the operation one case (No. 31) had a very persistent attack of hic-cough and on another occasion had signs of cardiovascular collapse with bradycardia. There were no local lesions to account for these attacks. Although

TABLE VII.

Case No.	Position of leucotomy markers relative to extremity of anterior horns of lateral ventricles.			Final degree of clinical improvement.	Persistent urinary incontinence beyond 1 month.	Fall in systolic B.P. of 10 mm. Hg. and over persisting beyond 1 month.
	Anterior.	Level.	Posterior.			
22	R.	L.	..	1	+	0
13	R.	L.	..	1	0	+
27	..	L.	R.	3	+	+
28	..	L.	R.	1	+	+
11	..	R.	L.	2	0	-
20	..	R.	L.	2	0	0
24	..	R.	L.	1	0	0
23	..	R.	L.	0	0	+
36	..	R.	L.	1	0	+
31	..	R.	L.	0	0	+
26	..	R.	.. L.	0	+	+
19	..	R.	..	0	0	+
16	..	R.	.. L.	0	0	..
34 L.	R.	3	+	+
10 L.	R.	0	0	+
30 L.	R.	1	+	+
4 L.	R.	1	0	+
12 L.	..	1	+	+
5	R. L.	2	0	0
1	R. L.	2	+	0
8	R. L.	2	0	0
21	R. L.	4	0	0
15	R. L.	4	0	+
14	R. L.	0	+	+
25	R. L.	1	+	+
2	R. L.	1	+	+
35	R. L.	0	0	+
18 L.	1	0	0

autonomic disturbances are not uncommon in catatonic schizophrenics it is possibly of significance that in this patient one of the leucotomy markers appears to have moved to occupy a position partially within the lateral ventricle.

Effects of Leucotomy on the Encephalogram.

When the pre- and post-operative encephalograms were compared some of the cases showed little change or changes, confined to a slight enlargement of the frontal horns of the lateral ventricles. Others showed evidence of severer damage, such as large cavitations or deep cortical depressions in the region of the leucotomy cut, or even a generalized dilatation of the ventricles. Although those showing evidence of more severe brain damage were of a higher average age, there were among them two patients whose ages were below the average of those showing little or no change. In all cases the technique of operation was identical. Daily blood urea estimations were made on ten of them during the first week following operation and the rise in blood urea above the pre-operative level is recorded. Each of the patients had a blood urea within normal limits prior to operation. In this series it would appear that there is a certain amount of correlation between the amount of brain damage following leucotomy and the rise in blood urea post-operatively.

TABLE VIII.

With evidence of only minor brain damage.		With evidence of severe brain damage.	
Case No.	Rise in blood urea in mg. per cent.	Case No.	Rise in blood urea in mg. per cent.
8	1	2	11
13	0	16	6
34	0	4	17
10	10	5	7
..	..	26	14
..	..	1	— Not recorded
..	..	12	— „

SUMMARY.

Part I of this paper relates the clinical aspects of 80 cases treated by leucotomy. The main features which have been discussed are :

1. *Selection and classification of case material.*—Two main groups were distinguished. In the first group emotional tension was obviously associated with distress on the part of the patient, and in the second emotional tension was expressed as disordered conduct.

2. *Post-operative progress.*—The results of the operation in the first group appeared to depend largely on the extent to which affective disturbances constituted the original clinical syndromes. The results of the operation in the second group were less comprehensible and indicated the need for further investigation.

3. *Post-operative alterations in vegetative functions.*—In this sphere particular attention was paid to changes in blood pressure and blood urea, and their

possible relationship to kidney function. Various aspects of the problem of post-operative urinary incontinence were also discussed.

Part II is an attempt to throw further light by means of pneumoencephalography on certain of the problems arising under these headings. It correspondingly embraces the following points :

1. *Cortical atrophy in schizophrenia*.—Its existence has been demonstrated in a number of cases, the most severe abnormalities being found among the older patients with a longer duration of illness.

2. *Correlation of findings with clinical results*.—There appears to be some relationship between the degree of atrophy and the post-operative progress in the second clinical group.

3. *Relationship of leucotomy structural changes to alterations in vegetative functions*.—There was no clear relationship between the plane of leucotomy and vegetative changes. The occurrence of cavitation was noted and it appeared to be associated with a greater post-operative rise in blood urea in some cases.

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