

THE FUNCTIONS OF THE FRONTAL LOBES.¹

BY JOSEPH SHAW BOLTON, B.Sc., M.D., B.S., M.R.C.P.

Senior Assistant Medical Officer, East Sussex County Asylum, Hellingly.

THE following paper deals with the subject of the functions of the frontal lobes from the standpoint of the morbid anatomy of mental disease, and the general histology of the cerebral cortex in normal individuals and in the subjects of mental disease. That this is not one of the more common methods of studying the question constitutes the writer's excuse for adding the present contribution to an already overburdened literature.

As Monakow's admirable article (15) in the *Ergebnisse der Physiologie* contains a list of 846 publications on the subject of cerebral localisation which have appeared during the past twelve years, the writer proposes to limit himself to such references to literature as are germane to the purpose he has in view, and refers those who desire a full bibliography to the above monograph.

The present paper is especially concerned with the functions of the anterior portions of the frontal lobes, or the prefrontal region of the cerebrum. It is, however, necessary that a few preliminary remarks on general cerebral localisation and on the functions of the posterior parts of the frontal lobes should first be introduced.

Between the years 1842 and 1870, with few dissentients, it was generally accepted, chiefly owing to the writings of Flourens (8), that no localisation of function existed in the cerebrum, and even much later than the latter date Goltz (10) and also Loeb (14) have held that all regions of the cortex possess equivalent functions. Broca (4), however, in 1861,

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pointed out the association which exists between the power of articulate speech and the posterior part of the left third frontal convolution, and Hughlings Jackson (13) in 1864 and Charlton Bastian (1) in 1869 both wrote in favour of functional localisation.

In the year 1870 Fritsch and Hitzig (9) proved that in the dog electrical excitation of certain parts of the cortex cerebri resulted in definite and constant movements.

Ferrier (1873-6), repeated and amplified their observations on the dog, and obtained similar results in the monkey (6). Ferrier's conclusions have not entirely held good, but they have in their main essentials been confirmed and extended by numerous investigators, but especially by Horsley and Beever (12). From the point of view of special movements, and the relation of these to special regions, numerous observations have also been made, and this subject, together with that concerning ablation experiments, possesses in itself an extensive literature. The general area, as eventually mapped out in the monkey, occupied approximately the central convolutions and the posterior parts of the frontal convolutions, together with part of the hemisphere around the upper end of median surface of the fissure of Rolando.

Horsley and Beever also determined the area in one anthropoid ape (an orang-outang), and found that the excitable area was not continuous but was blotchy in character, and that it did not include the first frontal convolution and the upper end of the ascending parietal convolution.

Finally, quite recently Sherrington (20) has shown that in the chimpanzee the area is still further curtailed and lies entirely in front of the furrow of Rolando, *i.e.*, entirely within the frontal lobe. As has been shown by the histological researches of Campbell (5), the human excitable area probably occupies a similarly restricted region.

As long ago as 1870 Hughlings Jackson (13) drew attention to the march of the convulsion in the variety of symptomatic epilepsy which bears his name and is associated with lesions of this region; and numerous isolated clinical observations and occasional examples of cortical stimu-

lation in man have been from time to time published, and support on the whole the localisation which has been worked out by Sherrington in the chimpanzee.

The functions of this region of the cerebral cortex are not yet finally determined.

It is generally accepted that this area subserves the performance of skilled voluntary movements, and the (conscious) learning of such movements. It is, however, not yet proved whether, as is held by Ferrier (6), Schäfer (19) and others, this region is purely "motor," or at most "psycho-motor" in function, or whether with Bastian (1), Mott (16), Munk (17), and many other neurologists of note it is "sensori-motor," and is concerned with the reception of afferent impressions of general sensory and muscular origin. Experimental results and also clinical records supply such contradictory data that the question is as yet unsettled.

It is hoped that the following remarks on this question, though they somewhat anticipate a later portion of the paper, will not, in view of the exhaustive discussion to which the subject has given rise, be considered out of place. It is by no means impossible that neither the "motor," nor the "sensori-motor" view is strictly correct. It may be that the area as now defined bears a similar relationship to some region behind the furrow of Rolando to that which, for example, the visuo-psycho region of the cortex bears to the visuo-sensory. That this is not a proposition without foundation is evident from the fact that whilst Flechsig's projection system for visual impressions occupies the position of, though a greater extent of cortex than, the adult visuo-sensory area, his projection system to the central convolutions bears no such close relationship to the psycho-motor area as now mapped out (figs. 1 and 2, p. 222). In the adult this projection system more probably lies behind the furrow of Rolando than in front of it, judging from the increase of frontal development which takes place as the cerebrum attains its adult characteristics, and from the fact that half the system already lies behind the fissure. If this proposition were true, a lesion of the psycho-motor area would be homologous with one causing

word-blindness or word-deafness, &c.; in other words, this area would be the lower associational centre for kinæsthetic impressions. Such a function for this region, which possesses a direct efferent connection with the motor groups of lower neurones, seems probable in view of the evidence to be brought forward later concerning the functions of the parts of the frontal lobes lying anterior to this area. It is, to say the least, unlikely on developmental grounds that an area of the lowest order, namely, a centre of projection, would lie directly adjacent to such an important centre of association as that in the prefrontal region, and that it would possess at the same time its undoubtedly important motor functions. It is equally unlikely that such a centre, judging from our knowledge of the projection and associational areas attached to the senses of sight and hearing, would singly possess both projection and associational, as well as motor, functions.

Our present knowledge points rather in the contrary direction. As cerebral development proceeds the areas of association increase out of proportion to those of projection, and the psychomotor area becomes elaborated *pari passu* with increasing development of the animal series, and thus resembles the areas of association rather than those of projection. It is consequently not improbable that the psychomotor region is the area of association for kinæsthetic impressions, and is the forerunner of the great anterior centre of association. If this were the case its participation in such important processes of higher association as voluntary attention would be readily intelligible, and the psychomotor area would also fall into series with the posterior centres of association, and not occupy its present anomalous and uncertain position in our scheme of the functions of the cerebrum.

The present paper being chiefly concerned with the functions of the parts of the frontal lobes which lie beyond the limits of the psychomotor area, the latter will not be further referred to, and the former subject will now be introduced.

There is even less consensus of opinion concerning the

functions of the prefrontal region than exists in the case of the psychomotor area.

Ferrier (6) concluded from his experiments that the prefrontal region was the motor centre for movements of the head and eyes to the opposite side, and was hence the centre for attention.

Munk (17) divides the cortex of the monkey into some six "sensory spheres," and looks upon the prefrontal region as the "sensory sphere" of the trunk muscles. He considers that the movements evoked by stimulation of this region are due entirely to a calling up of the sensations which usually accompany these movements.

Numerous writers, notably Wundt (25) and Hitzig (11), have, however, assigned a much more important function to this region of the cerebrum, namely, that it is the centre for the highest psychic processes.

In 1895 Bianchi (2) published his researches on ablation of the frontal lobes in monkeys. His paper contains most careful notes of the psychic and physical condition of the animals operated on. He concludes that "the frontal lobes are the seat of coördination and fusion of the incoming and outgoing products of the several sensory and motor areas of the cortex." . . . "The frontal lobes would thus sum up into series the products of the sensori-motor regions, as well as the emotive states which accompany all the perceptions, the fusion of which constitutes what has been called the *psychic tone* of the individual." (BRAIN, 1895, p. 521.)

Bianchi's paper might seem to settle the question of the functions of the prefrontal region, but unfortunately his results are directly contradicted by the later experiments of Schäfer (19). "It is sufficient to cut off the part to be removed by a subcortical incision." . . . "Operating in this way I have in several cases completely removed in the monkey the whole of the inexcitable area of both frontal lobes without producing the slightest sign of the mental and intellectual dulness and alteration of character which has been regarded as pathognomonic of a lesion of this region." ("Text-book," p. 772.)

From the clinical aspect the numerous published papers

arrive at equally contradictory conclusions. For example, in 1888 Welt (23) collected fifty-nine cases of lesion of the frontal region in man. In twelve cases changes in intellect or character occurred, and in forty-seven no such changes were noted. On the other hand, in 1896 Williamson (24) analysed fifty cases of tumour or abscess of the frontal region, and found mental symptoms in forty-five cases, these being especially marked in thirty-two, and no statement of mental change in five cases. In the thirty-two there were mental dulness, loss of power of attention, loss of memory, loss of spontaneity, and the patient took no notice of his surroundings.

It is doubtful whether in this connection profit results from the collation of data from the numerous published cases of gross lesion of the cerebrum, for whilst on the one hand mental change, especially dulness and loss of memory, may be associated with, or be due to, increase of intracranial tension, on the other the absence of reference to such change may well be due, in at least many cases, to non-recognition of symptoms which would be of more significance to an alienist than to a general physician or even a neurologist.

The question of the functions of the prefrontal region has thus received no solution from the experimental and the clinical points of view, and the contradictory nature of the results is so absolute that a complete deadlock exists.

Fortunately, however, when in 1894 Flechsig (7) began his series of papers on the development of the human cerebrum by a study of the process of myelination, a new method of attacking the problem presented itself; and our knowledge of the functions of the cerebrum as a whole will have been much illumined by the extensive researches of this worker, even though his broad generalisations may not be confirmed in their entirety.

By studying the exact period of myelination of different parts of the cerebrum in the human foetus and infant, Flechsig was enabled to divide the cortex into the two great classes of "*sensory centres*" and "*centres of association.*" The former myelinate earlier than the latter, and possess a

well-marked projection system of fibres. The latter myelinate later and are rich in long systems of fibres of association. The difference is really one of degree only, as Flechsig does not deny that projection fibres exist in the association centres, and that association systems exist in the sensory spheres.

In the whole cerebrum he described in 1898 no less than forty separate myelogenetic fields which develop at different periods.

Of the *sensory spheres* he describes four, namely, for (1) bodily sensibility; (2) visual; (3) auditory; and (4) olfactory and gestatory sensations. (1) has eight separate myelogenetic fields, and each of the others has three each.

Of the *centres of association* he originally described four, namely, the frontal, the parietal, the temporal and the insular. Later he combined the temporal and parietal centres into one, the great posterior centre of association. In 1900, however, owing to his discovery of a centre of projection in the gyrus subangularis, he again separated these centres.

In the temporal and parietal centres of association there exist, according to Flechsig, peripheral zones, which develop earlier, and central zones, which develop later; the former adjoin the sensory centres, and are united to them by numerous arcuate fibres.

In the frontal centre of association similar zones exist, but their disposition is much more complex.

The insular centre of association, and also that in the precuneus, consist of peripheral zones only. Flechsig is of opinion that the peripheral zones may be intermediate types between the central territories of association and the sensory projection spheres.

Hence of the centres of association the *frontal* exhibits the greatest complexity, the *temporal and parietal* are intermediate in structure, and the *insular* and that in the *precuneus* are the least complex of the types (see figs. 1 and 2).

Flechsig's views on the functions of the central territories of the areas of association are as follows:—"The

central territories of the zones of association (especially the middle of the angular gyrus, the third temporal convolution, and the anterior half of the second frontal

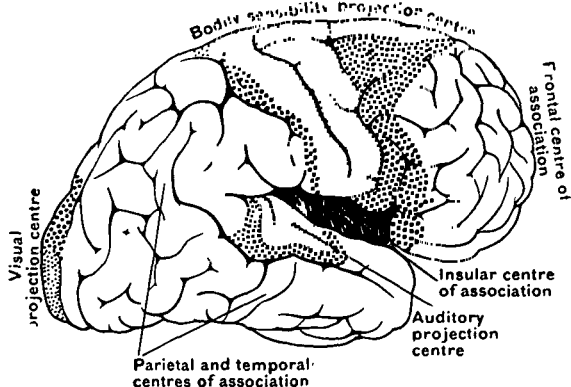


FIG. 1 (AFTER FLECHSIG).

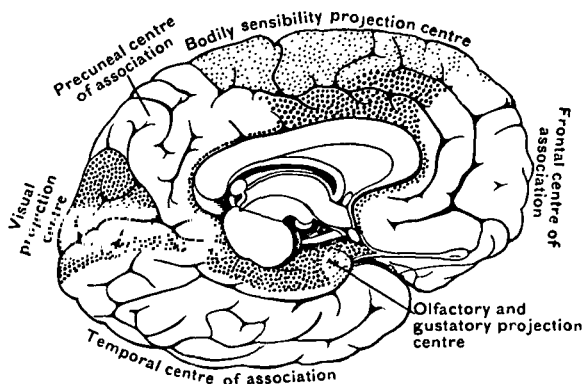


FIG. 2 (AFTER FLECHSIG).

In these figures the "centres of projection" and "centres of association" are mapped out according to Flechsig. The small dots are placed in the chief focus of each centre of projection. Around these chief foci are the regions to which a smaller number of fibres of projection pass; these are indicated by larger dots. These figures, which represent the different cortical spheres as they exist in the human foetus and infant, should be compared with the areas which have been fully defined in the adult cerebrum, *e.g.*, in the case of the psychomotor area, papers by Campbell (5) and Sherrington (20), and, in the case of the visual projection area, by the author (3). See also p. 217 of the present paper.

convolution) are apparently the nodal points of the long systems of association, whilst the peripheral zones only feebly show these characteristics."

"The central territories are terminal territories: they are essentially characteristic of the human brain. Isolated destruction of these is never accompanied by phenomena pointing to disturbance of motion or sensation. Motor phenomena, which occasionally accompany lesions of these territories, must be interpreted as *actions à distance*."

"The central territories of the zones of association are in more or less direct relationship, each with several sensorial zones, some with all."

"After their bilateral removal intelligence is affected, and especially is association of ideas interrupted. These central territories are thus probably of great importance for the exercise of intellectual activity, for the formation of mental images composed of several sensory qualities, for the accomplishment of acts, such as the naming of objects, speaking, &c. These functions are especially interfered with in affections of the posterior centres of association. Clinical observation establishes this fact, and thus justifies the legitimacy of our division of the cerebral cortex into sensory centres (centres of projection) and centres of association." (*Archiv de Neurologie*, ii., 1900, pp. 337-8.)

Flechsig's views have been severely criticised by Hitzig (11), who, however, is disposed to admit their general truth in a less positive form; and by Vogt (21), who directly contradicts many of Flechsig's conclusions, and especially the thesis of the constancy and regularity of myelination of the different systems of fibres. He is inclined to look upon the majority of myelinated fibres as projection fibres. Monakow (15), in his criticism, draws attention to the small proportion which the projection fibres form of the total mass of cortical fibres in any of the convolutions, and he thinks that it is not possible, however roughly it be done, to define the regions which are poor in these fibres and those which are abundantly supplied with them. Sachs (18), whilst admitting that the sense centres are sharply marked off at an early period

from the rest of the cortex, thinks it impossible to prove later, when myelination has advanced, that medullated projection fibres do not pass to the centres of association.

On the whole, however, Flechsig's conclusions in their essential features have been widely accepted, and whilst the projection areas, as has been already pointed out, probably occupy neither the identical position nor the same extent of cortex in the adult brain that they do in the foetus and infant, it may probably be assumed that a great parieto-temporal association centre exists posteriorly, and a more complex prefrontal association centre anteriorly, the insular and precuneal centres being less complex in type, and probably of less importance, than either of the former.

With reference to the functions of the two greatest centres of association, a large body of neurologists, notably Bastian, Hughlings Jackson, Schäfer, and Flechsig himself, are of opinion that gross mental disabilities are more likely to occur in lesions of the posterior centre than of the anterior, whilst Wundt, Hitzig, Ferrier, &c., hold the opposite view.

From the neurological aspect, especially when considering the different varieties of sensory and motor aphasia, the former view is doubtless true, but premising that the posterior centre were concerned with lower associational processes only, general mental disability would still be evident in cases of gross lesion of the hinder part of the hemispheres, as the patient would under these circumstances be unable in many cases to produce satisfactory evidence of general mental soundness. In many other cases, also, such an entire disturbance of perceptive and ideational processes as occurs, would be not unlikely to cause too great a strain on the higher associative functions, and to directly result in the development of symptoms of true mental alienation. This is rendered probable by the fact that no less than one in every 293 of the general population¹ is at present suffering from mental alienation, and that the proportion of potential psychopaths is very much greater.

¹ Report of the Commissioners in Lunacy for 1902.

Hitherto in this connection very little attention has been paid to the cerebral lesions associated with mental disease, though it is very generally recognised, by alienists, that in chronic general paralysis and chronic senile dementia severe prefrontal wasting exists. In the case of the former variety of mental alienation, however, the question is obscured by the thesis that previous syphilitic infection is the chief, if not the essential cause of the disease; and in the case of other varieties of mental disease, whilst their morbid histology has for many years attracted much attention, relatively little care has been bestowed on the *correlation* of the morbid anatomy and clinical features of the different types of mental alienation.

During the past four years the writer has made a careful study of this question, and he has arrived at the conclusion that the great anterior centre of association is the region of the cerebrum which is primarily affected in mental disease, all the neighbouring or bordering regions being concerned to a less extent, probably from chronic atrophy of the related systems of fibres of association.

The summarised evidence on this point which will now be brought forward will be considered from the points of view of (1) *morbid anatomy*, and (2) *general histology*. Fuller details on many points not directly bearing on the subject under discussion are contained in the paper referred to below (3).

(1) MORBID ANATOMY OF MENTAL DISEASE.

In 200 cases of mental disease, recently reported by the writer in the second volume of the *Archives of the Laboratory of the London County Asylums*, it has been demonstrated that the amount of cerebral wasting and the associated morbid changes inside the cranium in these cases vary directly with the amount of dementia existing in the patients. The relationship is much more absolute than might at first appear, probably owing, in the majority of cases of insanity, to a more or less complete removal of the products of degeneration by the time of death. This relationship is less

constant in dementia paralytica (general paralysis of the insane), for whilst in chronic cases the wasting may be more profound even than in corresponding cases of severe dementia, associated with senility and gross vascular degeneration, in acute and rapid cases of the disease, owing to incomplete removal of the products of degeneration, much less wasting exists. The writer has, however, seen several cases in which macroscopic and microscopic *acute* changes were as marked as is the wasting in advanced chronic cases (see later).

In many cases associated with severe vascular degeneration a further complicating factor exists, namely, the presence of local or general atrophies which are directly of vascular origin.

On the whole, however, as has been shown in a previous paper, the relationship is remarkably exact, and the regions of relative wasting can be determined with considerable accuracy. Taken generally, for individual variations exist, the *regions of wasting*, from observation of several hundred cases, are as follows :—

(1) The greatest amount occurs in the prefrontal region (anterior two-thirds or so of the first and second frontal convolutions, including the neighbouring mesial surface, and the anterior third or so of the third frontal convolution).

(2) The wasting is next most marked in the remainder of the first and second frontal convolutions. [In dementia paralytica Broca's convolution should, as a rule, be included here and (2) and (3) should follow (4).]

(3) It is, perhaps, next most marked in the ascending frontal and Broca's convolutions, though this grade should, in many cases at least, follow (4).

(4) It is next most marked in the first temporal convolution and the insula, and in the superior and inferior parietal lobules. In practically all cases it is more marked in the two former than in the two latter.

(5) It is least marked in the remainder of the cerebrum (including the orbital surface of the frontal lobes), particularly the inferio-internal aspect of the temporo-sphenoidal lobe and the posterior pole of the hemisphere.

In the experience of the writer exceptions to this general order are invariably due to vascular or traumatic causes, and should, therefore, be excluded from the ordinary and normal wastings of dementia.

Apart from the necessarily excluded abnormalities of development, which are of vascular or traumatic origin, the *degrees of under-development* follow the order given above, at least as regards (1) and (2). A further statement regarding macroscopical detail cannot be made, as it is more usual to find small and simply convoluted cerebra than brains with average but small convolutions, and it is relatively rare to meet with under-developed brains of average convolutional complexity which show a decrease reasonably comparable with the marked wasting which occurs in severe dementia. The subject of under-development will be more completely considered under the heading of general histology.

It is desirable here to state that from the histological standpoint Watson (22) has recently arrived at almost exactly similar conclusions regarding the comparative degrees of affection of the different regions of the cerebrum in several cases of juvenile general paralysis.

It is unnecessary here to give instances of the morbid conditions under consideration, as numerous examples, with in some cases illustrations, of the respective degrees and types of wasting which occur in mental disease are recorded in the paper already referred to. The following case of dementia paralytica, which has recently come under the notice of the writer, is, however, deserving of record here, owing to its almost unique character, and also to its direct bearing on the subject of the present paper. As will be seen in the illustrations (plate), the association centres of Flechsig are mapped out in this case as clearly almost as in the diagrams (fig. 1 and 2, p. 222). The anterior centre is grossly wasted; the psychomotor area shows some but much less wasting; the great posterior centre of association (temporal and parietal), the insular, and the precuneal, are acutely changed, as is evidenced by the decortication which in this case is *not a post-mortem* phenomenon; and the visual projection area is practically or entirely intact. The

FIG. A. — Photograph of the outer surface of the left hemisphere of Case G. F. (p. 229).

The anterior centre of association is grossly wasted. The psychomotor area shows some, but much less, wasting. The temporal and parietal and the insular centres of association are acutely changed (*post mortem* four and a half hours after death). The upper part of the temporal centre of association, and the anterior part of the parietal, show less acute change and more wasting. The visual projection centre is intact.

This illustration should be compared with the diagram on Fig. 1 (p. 222), and also with the plates in the author's paper in the *Archives of Neurology*, vol. ii.

FIG. B.—Photograph of the inner surface of the same hemisphere.

The anterior centre of association is both grossly wasted and acutely changed. The temporal and præcuneal centres of association are acutely changed. The visual projection centre is intact. There is wasting of the marginal convolution and acute change of the callosal convolution. The acute change in the prefrontal and callosal regions is in the situation where the pia mater of the two hemispheres lies in contact below the falx cerebri, and where, in general paralysis, the earliest and also the most advanced changes are visible.

This illustration should be compared with the diagram on Fig. 2 (p. 222).

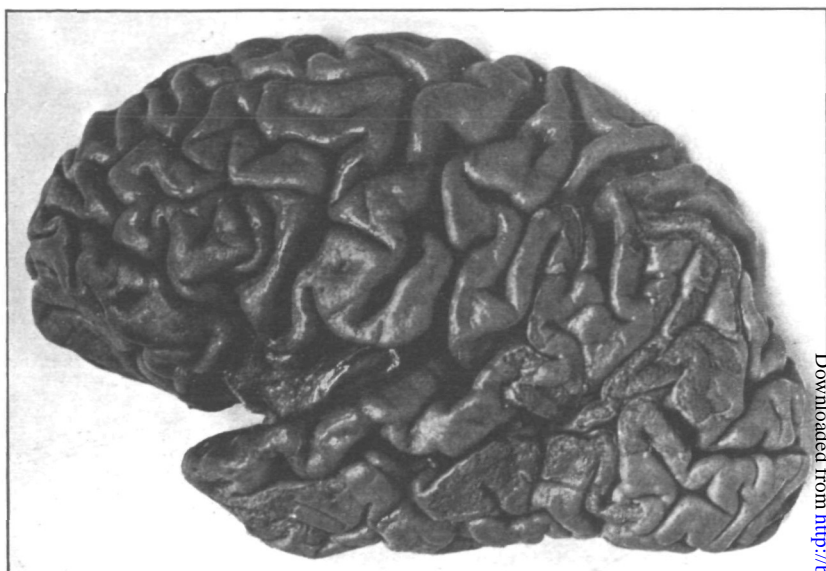


FIG. A.

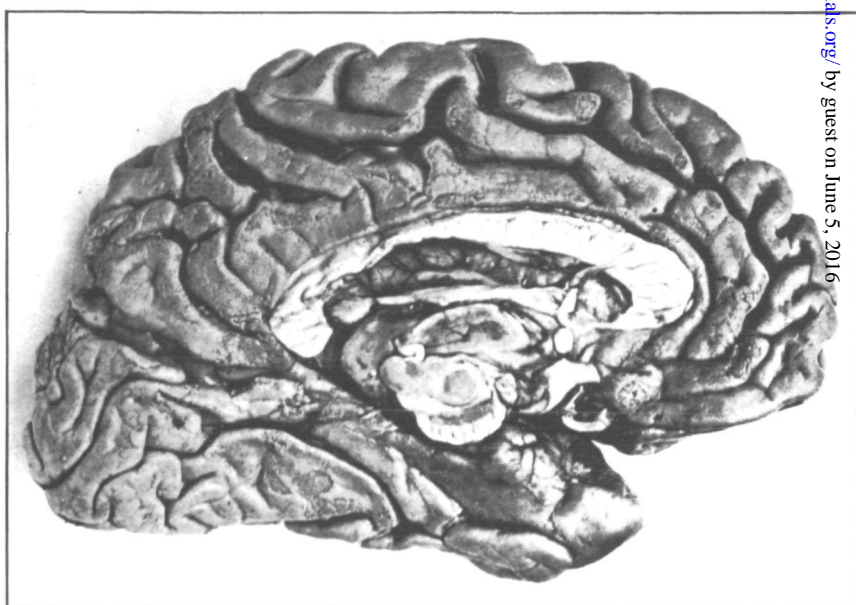


FIG. B.

writer has now seen a sufficient number of similar cases to satisfy him that this condition, though unusual, is normal to a particular type and stage of general paralysis of the insane, granted that the patient dies at the proper time from an intercurrent complication. Such cases illustrate more clearly than do those of any other variety of mental alienation the primary affection of the anterior centre of association, which is followed later on by decay of the posterior centres of association, the projection centres, (especially the visual), which are the first to develop, still remaining relatively unaffected. As a rule the psychomotor area is not markedly affected, though in certain cases commencing with numerous convulsions (*e.g.*, Case 20, in Part II. of the paper above referred to), this region may be early involved in the process of dissolution.

Whilst it is to be regretted that more extensive clinical notes of the following case were not obtained during the four weeks the patient was in the asylum, this was unavoidable owing to the large number of cases under observation, and the impossibility of taking really complete notes even of every severe case of general paralysis.

G. F., admitted March 31, 1903. Died April 28, 1903. Age stated to be 26 years. Single. Private, Rifle Brigade. No satisfactory family or personal history, though heredity of insanity was denied. Was admitted under the following certificate:—"Low demented state. Dirty in habits. Incoherent. Has convulsive seizures and paresis of limbs. Right pupil much dilated. Suicidal. Thinks people are trying to do him an injury and otherwise annoy him. Moping and inert. Sits for hours muttering incoherently. Memory quite fogged."

Physical condition on admission.—Tattoo marks on arms. Tongue tremulous. Incontinence of urine. Pulse small and irregular. Heart weak. Right pupil larger than left. Both irregular and neither reacts to light or accommodation. Both undergo irregular rhythmic movements and become eccentric at irregular intervals. Knee jerks, + +. All the limbs undergo chronic contractions and sometimes enter a pseudoclonus. Continual masticatory movements of lower jaw.

Mental condition on admission.—Patient lies in bed with his limbs flexed and rigid. He does not understand anything when

he is spoken to but at times makes inarticulate noises, especially if he is touched. He willingly takes his food from a feeder. He seemed to recognise his brother when he visited him, and tried to speak but could not be understood.

April 15, 1903.—His pupils vary as on admission and his limbs vary in position and degree of rigidity, but apparently quite irregularly. No data can be obtained from him regarding his mental condition, but he tends to resist examination though he is otherwise quite helpless.

April 28, 1903.—Died of right lobar pneumonia.

Post Mortem (Four and a Half Hours after Death).

Dura mater natural. Subdural deposit:—A non-hæmorrhagic film, the thickness of tissue paper on the right vault. Remarkable excess of subdural fluid. Pia:—Extremely opaque, and almost universally thickened. Marked mid-line pre-frontal adhesions below the falx cerebri. Great excess of sub-arachnoid fluid, especially in the pre-frontal region. Lateral ventricles immensely dilated, and granular. Third ventricle granular. Fourth ventricle very granular throughout, but especially so in calamus. Vessels apparently natural. Weight of encephalon 975 grammes. Right hemisphere, unstripped, 395 grammes. Left hemisphere, unstripped, 395 grammes, ditto, stripped, 350 grammes. Cerebellum, pons and medulla 157 grammes. There is extreme wasting of the prefrontal region, relatively little of the psychomotor area and the post-central convolution, and none of the occipital pole and the visuo-sensory area. The pia-arachnoid strips very readily over the frontal region. There is extreme decortication of the parietal, temporal, and insular association centres externally and of the precuneus and the inner part of the temporo-occipital region internally. There is also decortication scattered irregularly throughout the callosal convolution, but the visuo-sensory area is practically free from decortication. There are no absolute *post-mortem* signs of syphilis, but the density of the liver, spleen, and kidneys is increased.

Cause of Death:—Right lobar pneumonia. General paralysis.

(2) GENERAL HISTOLOGY (NORMAL AND MORBID) OF THE CORTEX CEREBRI.

Regarding the special cellular elements of the cortex cerebri which are affected in mental disease, it is a well-

known histological fact that the most commonly affected cells are those of the pyramidal layer. The writer is, however, able, as the result during the past seven years of an extensive study of the cortex cerebri by the method of micrometric measurement, to make a number of very definite statements concerning the development and retrogression of the cellular elements of the cortex cerebri, both in normal individuals and in the subjects of mental disease. His conclusions are derived from the examination of many thousands of micrometric measurements of the different cell layers of the cortex, which have been published in more or less complete detail in previous papers.

The cortex cerebri in the regions referred to above as the centres of association of Flechsig, consists in the adult of five primary layers; of these, two, the first or superficial, and the fourth, are essentially nerve fibril layers. The remaining three, namely, the second, the third and the fifth, containing respectively the pyramidal, the granule, and the polymorphic cells, are essentially nerve-cell layers. The writer makes no attempt to sub-divide the second or pyramidal layer, which is structurally single, into layers of small and large pyramids, and he considers that the ganglionic or Betz cells, which lie in certain regions of the cortex cerebri, belong to the fourth layer or inner line of Baillarger, that they are homologous with the solitary cells lying in this layer in other regions of the cortex, and that they are not "pyramidal cells" at all.

In the investigation from which the immediately following data are derived, the cortex made use of was taken from, as it were, the focus of the wasting referred to above, namely, from the anterior pole of the hemisphere in the region of the second frontal convolution, and at right angles to the (constant) transverse fissure of Wernicke. The region employed was as far as possible of the same relative size in all the brains examined; serial sections were made, and as far as possible mathematical accuracy was attempted, both in the choice of sections and in the micrometric measurements prepared from them.

In the prefrontal region of the cerebrum lamination

begins about the sixth month of foetal life by the separation off of the fifth or polymorphic layer of nerve-cells, and the fourth layer (of fibres) or inner line of Baillarger, and both these layers are very little below (about three-quarters of) the normal depth almost from the first appearance of the lamination. The third layer, or layer of granule cells, next develops, and at the period referred to is only about one-half the normal depth. At this period the second layer, or layer of pyramidal cells, is only one-fourth of the normal depth.

The development of the layers of the cerebral cortex thus takes place first in the deepest part of the originally indifferent neuroblasts and the more superficial layers develop later; in other words, the process takes place from within outwards.

At birth the second or pyramidal layer is but little more than one-half of the depth of the adult layer, the third or granule layer has now become three-fourths of the adult depth, and the fourth and fifth layers are rather more than three-fourths of the adult depth.

In the normal adult prefrontal cortex the depth of the third, fourth, and fifth layers is practically constant in different individuals, but differences exist in the depth of the second or pyramidal layer of nerve-cells. This layer of cells is, of all the cortical layers, the easiest to measure accurately, and hence these differences actually exist.

In congenital amentia (idiots and imbeciles) degrees of under-development of the prefrontal cortex exist which vary inversely with the mental power of the individual concerned.

In chronic and recurrent insanity without dementia, the third, fourth, and fifth layers of the prefrontal cortex are approximately of the normal adult depth, but degrees of under-development of the pyramidal layer of nerve-cells exist.

In dementia, and in dementia paralytica, degrees of wasting or retrogression exist in the layers of the prefrontal cortex which vary directly with the amount of dementia present. When the mental power of the patient is that of the new-born child all the cortical layers are, as regards depth, approximately in the same condition as in the

latter. This fact is graphically shown in the following table, in which the results of micrometric examination of the pre-frontal cortex of certain cases is summarised :—

Type of case.	LAYER I. Superficial nerve fibrils.	LAYER II. Pyramidal cells.	LAYER III. Granule cells.	LAYER IV. Inner line of Bailarger.	LAYER V. Polymorphic cells.	Total depth of cortex in millimetres.
	mm.	mm.	mm.	mm.	mm.	mm.
Normal (average of cases 1, 2 and 3)	·3005	·8312	·2288	·2303	·3098	1·9006
Still-born infants (average of cases 6 and 7)	·2024	·5047	·1661	·1663	·2270	1·2665
Gross dementia (average of cases 19 and 20)	·2858	·6568	·1748	·1581	·2130	1·4885

When the neuroglial and vascular proliferation which exists in the first two layers of the third series is allowed for, the last two series show a marked resemblance to one another, as do the corresponding mental conditions; and as a child under the age of a few months is still relatively helpless and mindless, an even closer parallel of measurements might be made than the above. The two series given, however, representing as they do the condition of the cortex at *birth*, when mentation is about to begin, and *at death in the final stage of primary decay of the prefrontal cortex*, with the mind practically gone, are sufficiently striking.

The above data concern the prefrontal cortex in normal individuals of different ages and in the subjects of the different types and grades of mental disease.

The writer has, however, also mapped out and similarly examined the whole visuo-sensory region, or region of the cortex to which visual impressions primarily pass, and also a considerable portion of the adjoining cortex. The following data thus serve to illustrate similar features of the projection and posterior associational areas of the cerebrum.

In the visuo-sensory cortex (projection centre) the pyramidal layer of nerve-cells is developed earlier than is the corresponding layer in the surrounding visuo-psychic cortex (centre of association). For example, in children of one and three months respectively, the pyramidal layer of nerve-cells

in the visuo-sensory region is relatively little below the normal adult depth, whilst in the surrounding cortex in the child of three months the pyramidal layer is much below the normal adult depth, and in the child of one month it is less than two-thirds of the latter.

This fact constitutes an important proof of the associational function of the pyramidal layer of the cortex surrounding the visuo-sensory region, and it agrees with Flechsig's discovery that the fibres passing to the primary visual area myelinate earlier than those to the surrounding cortex. The fact also that the pyramidal layer of nerve-cells of the visuo-sensory region is in the adult only five-ninths of the depth of the corresponding layer in the surrounding cortex, also supports the thesis of the associational function of this layer in the latter region of the cerebrum.

On the other hand, in the dementes examined, though the amount of dementia differed in the different cases, the decrease present in the pyramidal layer in all the cases was practically the same and very slight, in this differing from the results obtained in the prefrontal region, where it varied with the amount of dementia. The pyramidal layer was also actually as much, and relatively to its depth more, decreased in the visuo-sensory region than in the visuo-psychic. This agrees strikingly with the fact that in dementia the loss of recognition and of recent memory is more obvious than that of remote memory, though naturally little stress can be laid on this detail. It is certain, however, that whilst in *all* cases the depth of the pyramidal layer of nerve-cells in the prefrontal region varies directly with the mental powers of the individual, this is not the case in the primary visual and neighbouring visuo-psychic regions, though here, as has already been stated, the pyramidal layer develops earlier in the former than in the latter region.

From the above data the following conclusions may be drawn concerning the cortical cell layers:—

- (1) *The second or pyramidal layer of the cortex cerebri.*
 - (a) *The prefrontal region.*—The pyramidal layer is the last cell-layer of the cortex to develop during the process

of lamination, and it is also the first to undergo retrogression in dementia. It is the only layer which appreciably varies in depth in normal brains; the degree of its development in normal foetuses and infants, and in congenital aments of every grade, varies directly with the mental power of the individual; and the degree of its retrogression in demented patients varies directly with the amount of dementia existing in the respective patients.

(b) *The visuo-psychic region.*—The pyramidal layer reaches practically the same adult depth as in the prefrontal region, but it does not vary in depth according to the degree of dementia, though a small and practically constant decrease in depth is evident. This layer develops much later than does the pyramidal layer in the visuo-sensory region, and in a child of one month it is less than two-thirds of the adult depth. (c) *The visuo-sensory region.*—The pyramidal layer in this region is in the adult only about five-ninths of its depth in the regions above referred to. It, however, develops much earlier, being in infants of one and three months very little below the adult depth.

The pyramidal layer, therefore, subserves the "psychic" or associational functions of the cerebrum. This is pre-eminently the case in the prefrontal region, less so in the visuo-psychic region, and least of all in the visuo-sensory region. These three regions are therefore of different grades in the hierarchy of cerebral function.

(2) *The third, or granule layer,* is developed before the pyramidal layer. In the primary visual area the optic radiations end in the midst of the hypertrophied and duplicated granule layer. *This layer, therefore, probably, reasoning by analogy, subserves the reception or immediate transformation of afferent impressions, whether from the sense organs, or from other parts of the cerebrum.*

(3) *The fifth or polymorphic layer* is the first layer to be differentiated during the process of lamination, and it is the last to fail in the retrogression of dementia. A decrease in this layer exists in extreme aments (normal or otherwise), and in demented who are unable to carry on the ordinary animal functions, such as attending to their own wants, &c.

This layer, therefore, probably subserves these lower voluntary functions of the animal economy.

The *first and fourth layers* of the cortex cerebri, being primarily cell-process layers, occupy a different position. It is, however, of great interest that these layers are laid down in neuroglia long before fibrils can be detected in them, *e.g.*, in the prefrontal region the first layer exists as an irregular line of varying thickness in the fourth month of foetal life, and the fourth layer develops during the sixth month of foetal life. It is not intended by the above to deny that the relatively small number of cells, which, in the adult state of the cortex especially, are contained in these layers, may and probably do possess important though minor functions in the processes of cerebration. In the psycho-motor area, for example, the Betz cells, which really belong in the opinion of the writer to the fourth layer or "inner line of Baillarger," and are therefore not "pyramidal" cells at all, constitute the origin of the important efferent tract for skilled voluntary movement. Probably the "solitary cells" of Meynert in the occipital cortex possess a somewhat analogous function, and perhaps the same may be stated concerning the more or less pyramidal-shaped cells which lie in the fourth layer or inner line of Baillarger, in other regions of the cerebrum. It is probably hardly justifiable to endeavour to assign a function to the few cells which lie in the first or superficial layer of the cortex cerebri, but perhaps, reasoning on general grounds, it is not unfair to suggest that they possess associational functions similar to those of the pyramidal layer, above which they lie, and with which, in order of time, they appear to be developed.

CONCLUDING REMARKS.

The evidence above adduced, which is derived from a study of the general histology of the cerebral cortex in normal individuals, and of the morbid anatomy of the cerebrum and the general histology of the cortex cerebri in the subjects of mental disease, points, in the opinion of the writer, irresistibly to the conclusions that *the anterior centre*

of association of Flechsig is the region concerned with attention and the general orderly coördination of psychic processes, and that the cellular elements throughout the cortex which are especially concerned in the performance of associational functions are those of the pyramidal layer of nerve-cells.

From the standpoint of morbid anatomy the writer considers it proved, with the necessary restrictions already referred to, that the amount of cerebral wasting present in any case varies directly with the degree of dementia existing, and that this wasting has its maximum focus in the pre-frontal region.

Still more definite and positive results have, however, followed his study of the general histology of the cortex cerebri by the micrometric method. The pyramidal layer of nerve-cells develops *pari passu* with the development of the psychic powers of the individual, whereas the other cell-layers of the cortex develop earlier and soon reach their adult depth. In the visuo-sensory area (a type of the centres of projection), the pyramidal layer develops earlier than in the visuo-psychic region (a type of the posterior centres of association) and even soon after birth is relatively little below the adult depth, which is only about five-ninths of the depth of the layer in the centres of association. In the visuo-psychic region the pyramidal layer attains the same depth as in the pre-frontal region, but the decrease in depth in dementia is small and does not vary with the degree of dementia. Further, in the pre-frontal region, in the different types of mental alienation grading from the idiot to the chronic or recurrent lunatic without dementia, the pyramidal layer exhibits degrees of underdevelopment which vary inversely with the mental power of the individual: and it is the only cell layer of the pre-frontal cortex which varies appreciably in depth in normal individuals, although of all the layers of the cortex cerebri it is the easiest to measure accurately, which fact proves that these differences are not accidental. Finally, in dementia (which term is used to connote the mental condition of patients who suffer from permanent psychic disability) the amount of thinning of the pyramidal layer of nerve-cells in the pre-frontal region varies directly with the degree of dementia present.

The writer hence considers it proved that *the great anterior centre of association lying in the prefrontal region is underdeveloped on the one hand in all grades of primary mental deficiency, and on the other undergoes primary atrophy pari passu with the development of dementia; it is therefore the region of the cerebrum which is concerned with the performance of the highest coördinating and associational processes of mind.*

From the point of view of pure alienism this thesis receives illustration in the impulsive and irrational acts of many types of lunatic, and in the mechanical and stereotyped mental processes of the dement. Further illustrations are found in the absence of self-consciousness (as regards the presence of others), in the extreme vanity, and in the callous and selfish behaviour, which are common characteristics of the insane; but especially by a study of the development of delusional states. The delusional state is a secondary development, having as its basis a deficient power of coördination of psychic processes, and an inability to correctly interpret and suitably coördinate present experience in the light of past. In the paranoiac the capacity to develop it is present long before accident of environment determines the particular variety, and also the content of the, at first temporary but finally permanent, delusional state which ensues. The primary causal factor, however, progresses more rapidly than does the delusional state, and hence in some cases mild and in others more marked dementia eventually becomes evident. In a typical example this may ensue in the absence of hallucinations, in which case it may be presumed that there is only a relatively slight affection of the lower centres of association. This variety of mental disease may thus, perhaps, be considered to be in some respects a connecting link between, on the one hand, the different grades of primary mental deficiency, and on the other, the cases of more or less simple progressive dementia.

It is not desirable to enter further into this matter in the present paper, but it has been thought worth while to introduce the above remarks in illustration of the writer's

thesis concerning the functions of the pre-frontal region of the cerebrum.

That the study of gross lesions of the cerebrum has resulted in such contradictory conclusions concerning the functions of this region is readily explicable on the ground that such lesions, whether the symptoms resulting from them be direct or indirect or due to a general disturbance of the cerebral functions, do not necessarily interfere seriously with the functions of the complex associated groups of neurones focussed in the pre-frontal region. It is probably only when the whole complex system of neurones is under-developed or when it is undergoing general primary decay, namely, in the different types and degrees of mental alienation, that a satisfactory insight into its functions can be obtained; and even under these conditions, owing to the highly intricate systems of association which connect the pre-frontal region with the other parts of the cerebrum, the resulting lesion is not pure, but is merely focussed in the anterior parts of the frontal lobes.

Again, that the results obtained from experimental interference with the pre-frontal region in monkeys are equally contradictory is explicable on similar grounds. If the lesion were complete, owing to the close association between, if not the actual overlapping of, the pre-frontal and psychomotor regions, motor phenomena would necessarily invalidate the results, and any less extensive lesion cannot, in the opinion of the writer, be considered conclusive. Still more important, however, is the immense difference which exists between the psychic powers of even the highest monkeys and those of human beings; and apart even from this difference, it is probable that a general primary decay of the pre-frontal associated systems of neurones is the only condition which, even in the monkey, could enable a satisfactory solution of the problem to be obtained.

Our knowledge of the structure and mode of development of the cerebral cortex in the different members of the animal kingdom is still in its infancy and it is probable that future research in this direction will be fruitful with reference to the functions of the cerebrum both in man and in the lower animals.

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