different structures of the body in different persons. The whole question was one of alcohol attacking the *locus resistentiæ minoris*. In asylums they hardly ever saw a case of cirrhosis of the liver, showing that drunkards, when insane, usually gave way on their nerves and brain side rather than on the side of other organs, and that the nervous system in the insane was the *locus resistentiæ minoris*.

Dr. Bevan Lewis, in replying, thanked those who had spoken and those who had listened so attentively to the discussion of a subject which he felt must be a trifle obscure.

Amentia and Dementia: a Clinico-Pathological Study.

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PART III.—DEMENTIA.

INTRODUCTION.

The present and final division of this paper contains a description of those types of mental disease which are classed by the writer under the heading "Dementia." Under this term

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he includes all cases which agree, from the psychic aspect, in the possession of a decreased or decreasing mental capacity, and from the physical, in the existence of a distinct and permanent loss of cortical substance in those regions of the cerebrum which especially serve as a physical basis for the carrying on of (voluntary) psychic processes.

Whilst a large number of such cases are examples of natural involution of the cortical neurones, occurring at such individually diverse periods of life as are determined by their inherent capacity of resistance to the process of decay, in many, perhaps even in the majority of the cases falling into the group, both the actual point of time at which the process of dissolution commences, and also the extent and degree to which it proceeds, are largely influenced by extraneous factors.

These consist, on the one hand, of the various influences which combine to produce the normal and relatively harmless environment of sane individuals, and on the other, of more variable and accidental factors of, usually, a toxic or a nutritional nature. If the process of neuronic dissolution be one of normal involution, or if it be excited by permanently existing and progressive factors—*e.g.*, degeneration of cerebral vessels, etc.—it continues more or less slowly until death occurs. If, however, it be excited by non-progressive, temporary, or removable causes, whether these belong to such extreme types as cerebral lesion, alcoholic excess, or puerperal toxæmia on the one hand, and what constitutes the normal "stress" to which all healthy cortical neurones are subjected in a civilised community on the other, cessation of the causative influence may result in an arrest of the process of neuronic dissolution, and the patient may live for years in a practically stationary condition of mental enfeeblement.

The writer thus employs the term "dementia" to connote in the widest sense *the mental condition of patients who suffer from a permanent psychic disability due to neuronic degeneration following insufficient durability.*

In dealing with the subject of *amentia*, in the second part of this paper, the 283 cases, classified as suffering from deficient or subnormally aberrant neuronic development, are grouped on a symptomatological basis, as these types of mental disease are of developmental origin, and, apart from the incidence of cerebral dissolution, possess no morbid anatomy. Cases of amentia,

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however, viewed from the standpoint of developmental anatomy, exhibit various types and grades of cerebral deficiency, which future research will in all probability associate with the differences in symptomatology which are clinically observable in the various groups under which they have been provisionally classified. Further, in the case of high-grade amentia, for reasons which have already been sufficiently elaborated, neither the age of the patient nor the emotional tone of the general symptomatology possesses an essential significance.

In dealing with the subject of *dementia*, however, an entirely different method of treatment is necessary, for reasons which will now be briefly detailed. In the first place, cases of dementia exhibit naked-eye *post-mortem* morbid appearances which vary in severity according to the degree of dementia present. From the naked-eye point of view, this statement holds good in a general sense, even when the progress of the mental enfeeblement has been very rapid, and when, therefore, the removal of the products of neuronic degeneration is incomplete. In the case of apparent exceptions to this general statement it can be demonstrated by histological methods that degenerative changes of an acute nature exist, and that these correspond in degree with the grade of dementia present. Further, dementia differs from amentia in the facts that its symptomatology varies in degree rather than in kind, and that the type of its precursory symptomatology (mental confusion) depends to some extent on its immediate causation. On the other hand, in the case of amentia the symptomatology depends rather upon the cerebral organisation of the individual than upon the exciting cause of the attack of insanity. Again, the times of onset in cases of dementia, where the neuronic degeneration is of the nature of a primary involution, or is precipitated by a temporary or removable cause, are largely focussed at, and associated with, certain "critical" periods of life, namely, pre-maturity (puberty), maturity, pre-senility (climacteric), and senility. In the case of amentia, on the other hand, the attacks are excited by accident of environment, and are in many cases merely exaggerations of the permanent mental conditions of the patients. Moreover, the occurrence of dementia, where the neuronic degeneration is of a secondary and progressive nature, largely depends upon the time-onset of the exciting cause—*e.g.*, previous syphilis, senile or pre-senile vascular degeneration, etc. Further, certain dementias of special origin—*e.g.*, those following sense-deprivation and cerebral lesions—require different treatment from that meted to the analogous types of amentia, as in the latter these influences either occur at such an early period of life that the mental symptomatology is not peculiar, or they result in the incidence of dementia.

It is thus evident that as dementia differs from amentia in possessing a morbid anatomy, in its uniform symptomatology, and, lastly, in its more intimate relationship to definite causative or precipitating agents, one of which is the age of the patient, the former subject requires different treatment from that which was adopted in the case of the latter in the second part of this paper.

It is also obvious that a part at least of the evidence on which the writer is endeavouring to erect a rational pathology of mental disease (namely, that dealing with morbid anatomy) has a more direct bearing on the subject of dementia, in which morbid appearances are present, than in that of amentia, in which the place of these is taken by degrees and types of developmental deficiency.

The writer, therefore, purposes, as a preliminary to the consideration of the subject of dementia, briefly to review the naked-eye and histological evidence which he has published in previous papers, and on which he has based a subdivision of mental disease into amentia and dementia, as defined and classified in the present communication. The description of the general pathology of mental disease which is inserted in the following section thus contains little that the writer has not previously published. He hopes, however, to be successful in presenting his conclusions in a more readily intelligible form than that which he was compelled to adopt in the more lengthy individual papers. If, in his endeavour to attain lucidity, he should appear to dogmatise and to ignore the labours of others, he trusts to be pardoned by the reader, who will find, should he desire it, sufficient reference to these in the earlier contributions.

THE GENERAL PATHOLOGY OF MENTAL DISEASE AND THE FUNCTIONAL REGIONS OF THE CEREBRUM.

Though much has been written of late years on the minute anatomy and functions of the grey mantle of the cerebrum, and remarkable progress has been made in the correlation of cortical structure with psychic processes, to the reader who is not a professional neurologist and psychologist it is still difficult to retain even an elementary appreciation of the present state of knowledge. The writer, therefore, hopes to be excused for his apparent lack of courtesy in referring at times to elementary details.

The cerebral cortex consists in essence of a sheet of grey matter which, as has been shown by the writer from a study of its mode of development from a layer of indifferent neuroblasts, is composed of five primary laminæ, the lower four of which separate off in turn from the deep surface upwards. Of these five laminæ, three, the second or the pyramidal (outer cell layer), the third or the granule (middle cell layer), and the fifth or the polymorphic (inner cell layer), the numbers being from the superficial surface downwards, are originally in essential structure nerve-cell layers. The remaining two, namely, the first or the superficial (outer fibre layer), and the fourth (inner fibre layer), which corresponds with the "inner line of Baillarger," are, on the other hand, originally in essential structure nerve-fibre layers, and contain relatively few cellular elements. In a fœtus of four months the cortex consists solely of a superficial indifferent layer and of a deeper layer of neuroblasts. As development proceeds the fifth, fourth, third, and second laminæ become respectively and in this order separated off from one another. From this original five-layered basis the more complex adult cortex cerebri is developed and specialised.

As has been shown by the embryological researches of Flechsig, whose studies on the order of myelination of the fibre-complexes which constitute the white matter of the cerebrum are classical, certain regions of the grey mantle at a relatively early period become connected by myelinated fibre-tracts with the base of the brain. These regions, called by him *projection centres* or *sensory spheres*, subserve the conveyance of afferent impulses from the several organs of special sense, namely, those concerned with (1) bodily sensibility, (2) vision, (3) hearing, and (4) olfactory and gustatory sensations. These regions of the cerebrum myelinate earlier than the remainder and possess well-marked projection systems of fibres. The remainder of the cerebrum, which myelinates at a later period, is especially rich in long systems of fibres of association, and is divided by Flechsig into a number of *centres of association.* Of these centres of association the chief are the frontal, the parietal, the temporal, and those in the insula and the precuneus. 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 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. "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 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."

Though later research has shown that the projection centres probably occupy neither the identical position nor the same extent of cortex in the adult brain that they do in the fœtus and infant, Flechsig's conclusions concerning them must be accepted in their essential features; and, further, it may be considered proved that a great parietal and temporal association centre exists posteriorly, a more complex prefrontal association centre anteriorly, and two less complex and less important centres in the insular and precuneal regions respectively.

The writer of this paper, by his researches on the general histology of the cortex cerebri in health and disease, has endeavoured to further demonstrate that the grey mantle of the brain may be subdivided into three groups of regions which occupy increasingly important positions in the hierarchy of cerebral function, namely:

(1) *The projection spheres*, or the regions to which afferent

sensorial impressions primarily pass, namely, those for bodily sensibility, sight, hearing, smell, and taste.

(2) *The regions of lower association*, which lie in the immediate neighbourhood of each of the areas included in the first group, and which subserve the elaboration of the different varieties of sensorial impressions into simple perceptions, and the association of these psychic units into higher complexes.

(3) *The region of higher association and co-ordination*, which subserves the grouping of these higher complexes into harmonious series of concepts by means of voluntary attention and selection. This region of the cortex is therefore concerned with the carrying on of the highest processes of mind. It is also the part of the cerebrum which is especially affected in the subjects of mental disease. It is the last part of the cerebrum to be evolved, and it is under-developed in amentia of all grades. It is the first part of the cerebrum to undergo dissolution in dementia.

These three groups of functional regions will now be briefly considered, with especial reference to the writer's own researches, owing to the direct bearing of these on the general pathology of mental disease.

(1) THE PROJECTION SPHERES—THE VISUO-SENSORY AREA.

For the purposes of this paper it will be sufficient to refer here to that cortical sensory sphere with which the writer is especially familiar, namely, the region of the cortex concerned with the reception and immediate transformation of visual impressions.

During the latter half of the last century clinical and experimental evidence more and more clearly pointed to the region of the calcarine fissure, the cortex of which possesses a characteristic structure owing to the existence in the centre of the grey matter of a white line, as the visual projection centre. This line, which is readily visible to the naked eye, was first described by Gennari in 1776. The exact anatomical and histological limits of the region containing it were mapped out by the writer in a previous research, in which this area was proved to be connected with vision, and was named the "visuo-sensory area" as the result of a detailed examination of normal

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brains and of cases of long-standing and of congenital blindness.

The lamination of the cortex cerebri in this region is specialised from the five-layered type already referred to, and consists of the following layers:

(I) The superficial layer of nerve-fibres (*outer fibre lamina*).

(II) The layer of pyramidal cells (*outer cell lamina*).

(III A) The outer layer of granules.
(III B) The middle layer of nerve-fibres or "line of Gennari," containing solitary cells of Meynert.
(III C) The inner layer of granules.
} *middle cell lamina.*

(IV) The inner layer of nerve-fibres or "inner line of Baillarger," containing solitary cells of Meynert (*inner fibre lamina*).

(V) The layer of polymorphic cells (*inner cell lamina*).

The specialisation of the visuo-sensory cortex consists, therefore, in essentials, in a duplication of the third primary lamina of the cortex, and in the interposition between the double layer of a layer composed of nerve-fibres. Of this triple layer, Layer III A is an additional feature; Layer III B is an exaggeration of a thin fibre band, the "outer line of Baillarger," which in the adult cortex lies between the second and third primary laminæ; and Layer III C is the original third primary lamina increased in depth (see Fig. 9, p. 261).

In congenital or long-standing blindness the depth of Layer III B is decreased by nearly 50 *per cent.*, and that of Layer III A is decreased by more than 10 *per cent.*, owing to atrophy of the optic radiations. The other layers of the cortex are unchanged in depth by the existence of blindness.

These facts prove that the cortical region under consideration is the projection centre for visual impressions or the "visuo-sensory area."

Further, and equally important, data which bear on the development and functional importance of the second or pyramidal layer (outer cell lamina) were obtained during this research. These will be referred to later during the discussion of the position of the cortical projection spheres, from the point of view of psychic function, in relation to the areas of lower association and the region concerned with higher association.

(II) THE REGIONS CONCERNED WITH LOWER ASSOCIATION—THE VISUO-PSYCHIC AREA.

As in the case of the projection areas of the cerebrum, it will suffice to consider one only of the regions of lower association, that concerned with the elaboration of visual impressions.

At the periphery of the visuo-sensory area, where it passes in each direction into the neighbouring cortex, termed by the writer "visuo-psychic," an abrupt change in lamination takes place, Layer III B, the line of Gennari, suddenly ceasing, and Layers III A and III C, the two layers of granules, running into one and becoming Layer III of the visuo-psychic region. This region thus consists of a five-layered type, namely:

(I) The superficial layer of nerve-fibres (*outer fibre lamina*).

(II) The layer of small and large pyramidal cells (*outer cell lamina*).

(III) The layer of granules (*middle cell lamina*).

(IV) The inner layer of nerve-fibres or "inner line of Baillarger," containing large and frequently solitary cells (*inner fibre lamina*).

(V) The layer of polymorphic cells (*inner cell lamina*).

Congenital or long-standing blindness causes no modification of the lamination of the visuo-psychic region.

In this region, however, many important facts bearing on the functions of the second or pyramidal layer (outer cell layer) were derived from the data obtained by the writer during his investigation. These data are summarised graphically in Fig. 9, p. 261, which shows the relative depths of the outer cell laminæ in the visuo-sensory and the visuo-psychic regions respectively of the six cases investigated.

On examination of this table it will be seen that in the visuo-sensory region of Cases 6 and 5, from infants æt. one and three months respectively, the pyramidal layer is somewhat below the normal adult thickness, and that this layer is decreased also in the visuo-sensory region of Cases 2, 3, and 4, from patients suffering from chronic insanity with dementia. In the visuo-psychic region, however, whilst in the cases of chronic insanity with dementia the pyramidal layer is decreased in depth to some extent, in the child of three months it is very much under-developed, and in the child of one month its depth is less than two thirds of that of the normal adult.

In other words, in the visuo-sensory region of infants æt. one and three months the pyramidal layer of nerve-cells is equally but not fully developed (in spite of the congenital blindness of the former), whereas in the visuo-psychic region it is much under-developed in the infant of three months, and it is still more under-developed in the infant of one month.

This fact constitutes an important proof of the associational function of the latter cortical region, and also indicates the relatively low "psychic" importance of the pyramidal layer of the visuo-sensory region. Attention may here be drawn to the confirmatory detail that in the normal adult brain the depth of the pyramidal layer in the visuo-sensory area is only five ninths of the depth of this layer in the visuo-psychic region.

This subject will be further referred to during the consideration of the cortical region concerned with higher association. In the meantime it is only necessary to state that the facts above cited prove that the visuo-sensory area is concerned with a lower grade of psychic function than that performed in the visuo-psychic region of the cortex, and that they afford independent proof of the correctness of Flechsig's thesis, that the cortex cerebri is divisible into the two great classes of "sensory spheres (centres of projection)" and "centres of association." The writer, however, goes a step further, as the result of his study of the morbid anatomy and general histology of mental disease, and, as has already been stated, divides the "centres of association" into areas of lower association in relation with the several "sensory spheres" and a great anterior centre of higher association situated in the prefrontal region of the cerebrum. The proofs on which he bases this thesis will now be referred to as briefly as is consistent with clearness of exposition.

(III) THE CORTICAL REGION CONCERNED WITH HIGHER ASSOCIATION.

As a preliminary to the consideration of this subject it may be stated that much difference of opinion exists amongst authorities with reference to the respective functions of the anterior and posterior centres of association of Flechsig. A large body of neurologists and psychologists, notably Bastian, Hughlings Jackson, Schäfer, and Flechsig himself, consider that gross mental disabilities are more likely to occur in lesions of the posterior than of the anterior of these centres, whilst Wundt, Hitzig, Ferrier, etc., 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 apparent 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. For instance, to take a gross case, a severe example of sensory aphasia is frequently, through the maiming of his capacity for visual and auditory perception, in as impossible a condition for the determination of his mental state (from an alienistic point of view) as would be a man without sense organs for the investigation for his ability to form perceptions. On the other hand, in certain of the purer cases of sensory aphasia, where the capacity for visual or auditory perception is intact, it is easy to determine that the general mental functions are relatively or absolutely sound. Again, in other cases of lesion of the posterior centre of association, it is likely that such an entire disturbance of perceptive and ideational processes as exists would cause too great a strain on the higher associational functions and directly result in the development of symptoms of true mental alienation. This is rendered the more probable by the facts that no less than 1 in every 285 of the general population is at present in seclusion owing to alienation of the mental functions, and that the proportion of potential psychopaths who are living at large is very much greater.

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 in 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 this disease; and in the case of other varieties of mental disease, whilst their morbid histology has for many years attracted much attention, little or no care has been bestowed on the *correlation* of the morbid anatomy with the clinical symptomatology of the different types of mental alienation.

During a number of 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 adduced will be considered from the points of view of (*a*) *morbid anatomy*, and (*b*) *general histology*. Fuller details on many points not directly bearing on the subject under discussion will be found in previous papers.

(A) *Morbid Anatomy of Mental Disease.*

The writer has demonstrated, as the result of a careful comparison of the clinical symptomatology with the *post-mortem* intra-cranial appearances of several hundred cases of mental disease, that the amount of cerebral wasting and the associated morbid changes found inside the cranium in these cases vary directly in degree with the amount of dementia existing in the patients. The relationship is much more absolute than might be expected, and it is hence probable that in the majority of cases of insanity a more or less complete removal of the products of neuronic degeneration has occurred by the time of death. Reference will be made later to certain cases which at first sight appear to be exceptions to the general rule.

The majority of the morbid appearances which occur in many cases of mental disease are well known and may be dismissed here with a passing reference, as, except from the point of view of the assistance they afford in the determination of the grade of morbid change which exists in the interior of any particular cranium, they have no especial bearing on the purpose of the present description. These changes are, in brief, morbid conditions of the dura mater, subdural deposits (pachymeningitis hæmorrhagica), excess of subdural fluid, morbid conditions and modes of stripping of the pia-arachnoid, excess of subarachnoid fluid, and dilatation and granularity of the lateral and

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fourth ventricles; and their significance has been fully and individually considered in previous communications.

Certain other morbid appearances, but especially the weights and degrees of wasting of the cerebral hemispheres, will now be referred to in such detail as is necessary to demonstrate the object in view.

For purposes of comparison during his study of the morbid anatomy of mental disease, the writer divided the cases clinically into five groups, namely, (1) cases without dementia, (2) cases with appreciable dementia, (3) cases of insanity with moderate dementia, (4) cases of dementia which still show symptoms of insanity, and (5) cases of gross dementia.

These groups agree remarkably closely with the following five classes, which are based on the relative severity of the morbid appearances which are present: (1) cases without morbid changes and where the pia-arachnoid strips naturally; (2) cases with slight morbid changes and where the pia-arachnoid strips rather more readily than natural; (3) cases with moderate morbid changes, with subdural excess to the level of the tentorium, and where the pia-arachnoid strips readily; (4) cases with marked morbid changes and where the pia-arachnoid strips very readily; and (5) cases with very marked morbid changes and where the pia-arachnoid strips like a glove from the hemisphere.

It may be noted here that the difference between Groups I and II is not very marked, that both these differ considerably from Group III, and that this differs even more from the again similar Groups IV and V.

Groups I and II contain the majority of the cases of amentia, though several scattered cases with senile or pre-senile involution of the cerebrum occur in the later groups. Group III is composed largely of cases of the dementias of maturity and prematurity (dementia præcox), but contains many senile and pre-senile cases, which, had they lived, would have passed into Groups IV and V. Finally, Groups IV and V contain cases of advanced involution of the cerebrum of either a primary nature or due to the primary factors referred to in Part I (vol. li, 1905, p. 278), under the second group of causes of mental confusion.

The weights of, and the abnormal anatomical characters presented by, the cerebral hemispheres of the cases classified into these several groups will now be considered from the point of view of their bearing on the pathology of dementia and amentia respectively.

Weights of Stripped Hemispheres in Relation to Amentia and Dementia.

In the following table the weights of the stripped hemispheres belonging to 417 consecutive cases of mental disease (excluding

FIG. 1.

	Males.	Females.
	Normal average . 589 grs.	Normal average . 534 grs.
GROUP I, 61 cases (no morbid appearances)	Ordinary . (16) . 553 grs. Epileptic imbeciles . (5) . 548 grs.	Ordinary . (36) . 499 grs. Epileptic imbeciles . (4) . 472 grs.
	Total . (21) . 552 grs.	Total . (40) . 497 grs.
GROUP II, 95 cases (slight morbid appearances)	Ordinary . (14) . 565 grs. Epileptics . (7) . 561 grs.	Ordinary . (66) . 480 grs. Epileptics . (8) . 524 grs.
	Total . (21) . 564 grs.	Total . (74) . 485 grs.
GROUP III, 96 cases (moderate morbid appearances)	Ordinary . (27) . 551 grs. Epileptics . (4) . 617 grs.	Ordinary . (59) . 482 grs. Epileptics . (6) . 484 grs.
	Total . (31) . 560 grs.	Total . (65) . 482 grs.
GROUP IV, 90 cases (severe morbid appearances)	Ordinary . (27) . 509 grs. Epilepti-form cases (11) . 516 grs.	Ordinary . (44) . 455 grs. Epilepti-form cases (8) . 460 grs.
	Total . (38) . 511 grs.	Total . (52) . 456 grs.
GROUP V, 75 cases (gross morbid appearances)	Total . (25) . 513 grs.	Total . (50) . 437 grs.
Grand total . 417	Grand total . 136 males	Grand total . 281 females

dementia paralytica) are analysed and classified. It has been considered desirable, owing to their varying and usually greater weight, to separate the epileptic hemispheres from the remainder. Apart from this detail, the table contains the average weights of the hemispheres belonging to the several groups above

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referred to, in order that they may be compared with one another, and with the normal average weights of stripped male and female hemispheres. The latter figures have been estimated from Marchand's statistics by the aid of Huschke's ratio of the relative weights of the conjoined cerebellum and pons and of the cerebrum.

In this table it is probable that the average weights in the right-hand column are the more reliable, owing to the greater number of the female hemispheres. As, however, both sets of figures support the same conclusions, and, indeed, differ very little in detail, any departure from relative average accuracy which may exist is not of importance.

The following facts are readily elicited from the table:

The weights throughout are considerably below the average normal, and this statement applies even to Group I, where no wasting exists, and to Group II, where little or no wasting has occurred.

In the case of Group III, however, it is possible that the wasting which has occurred may be sufficient to account for the decrease in average weight, on the supposition that this originally reached the average normal.

In Groups IV and V, in which much wasting exists, it is difficult to estimate the original weights of the brains, which may or may not have been up to the average normal.

It is clearly shown in the table that the cases in Group III originally possessed a greater weight than those in Groups I and II.

The cases in Groups I and II are therefore, macroscopically, cases of "amentia," as defined by the writer.

Regions of Wasting of the Cerebrum in Mental Disease.

The cases in which wasting of the cerebrum exists may approximately be divided into three categories—those in which the wasting is chiefly or wholly due to involution of the cortical neurones, those in which it is chiefly or wholly due to local, or fairly general, atrophies which are directly of vascular origin, and those in which both these conditions exist.

The mixed cases will not be further referred to, and it is sufficient with reference to the cases of vascular origin to state that all degrees, from definite old or recent softenings to extensive or quite local secondary atrophies of convolutions, often with vermiform or cross-striated markings, are included. The cases which are chiefly or entirely due to retrogression or involution of the cortical neurones will, however, be more fully considered.

In cases belonging to the last category the relationship of the degree of wasting to the degree of dementia is, on the whole, very definite, and the regions of relative wasting can be determined with considerable accuracy. Taken generally—for individual variations exist—the *regions of wasting* of the cerebrum in dementia, as ascertained by personal study of over a thousand cases, are as follow:

(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.

Reference may here be made to the researches of Watson, who independently, and from the histological standpoint, has arrived at almost exactly similar conclusions regarding the comparative degrees of affection of the different regions of the cortex cerebri in several cases of juvenile general paralysis. In this investigation, though he does not explicitly state the fact in his paper, Watson made the necessary allowances for differences in the type of fibre wealth in the several regions examined, by a comparison of sections of each area with corresponding sections taken from the same areas of normal brains. It may also be added that Schaffer, working on different lines, has arrived at very similar conclusions regarding the respective degrees of affection of the different regions of the cortex cerebri in ordinary general paralysis of the insane (dementia paralytica).

Regions of Under-Development of the Cerebrum in Mental Disease.

Apart from the necessarily excluded abnormalities of development which are of vascular or traumatic origin, the degrees of under-development of the cerebrum in amentia follow the order given above, at least as regards (1) and (2). A further statement regarding macroscopic 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 cerebra of average convolutional complexity which show a decrease reasonably comparable with the marked wasting which occurs in severe dementia. The question, in fact, of the functional value of an *under*-developed cerebrum requires for solution microscopic rather than macroscopic study, and, as the writer will demonstrate in the next section of this paper, the micrometric method applied from the lamination standpoint affords a ready means of determining the degree of departure from the normal. One case of idiocy, for example, which was published by the writer in a previous paper, and in which the brain, though somewhat below the average weight, appeared to the naked eye perfectly normal except for slight simplicity of convolutional pattern and a somewhat decreased development of the prefrontal region, when investigated by the micrometric method, gave general average measurements which were almost identical with those obtained from a female stillborn infant. Again, the writer has recently measured for Dr. Campbell the prefrontal cortex of a case of macrocephaly. The patient was a male adult idiot who died in Rainhill Asylum, and the encephalon weighed 1775 grammes. The result of micrometric measurement is as follows:

	Macrocephalic idiot.	Average normal (see Fig. 3).	Difference.	Percentage difference.
Layer I	0·278 mm.	0·301 mm.	−0·023 mm.	− 7·6
" II	0·663 "	0·831 "	−0·168 "	−20·2
" III	0·212 "	0·229 "	−0·017 "	− 7·4
" IV	0·236 "	0·230 "	+0·006 "	+ 2·6
" V	0·295 "	0·310 "	−0·015 "	− 4·8
Total . .	1·684 mm.	1·901 mm.	−0·217 mm.	−11·4

In this case, where the cortex cerebri might reasonably have been expected to be of at least average depth, the measurements demonstrate that the condition is one of idiocy (*cf.* Fig. 5, p. 254).

The Chief Causes of apparently Aberrant Morbid Appearances in Mental Disease.

It is not necessary to consider here the different factors which may produce morbid appearances that at first sight appear exceptions to the general statements just made. The writer, however, proposes briefly to refer, for illustrative purposes, to certain conditions which might appear to contradict his description.

Amongst cases suffering from more or less pure senile or pre-senile involution of the cortical neurones it is by no means exceptional to find idiots and severe imbeciles. Such patients, even at the age of 40, are frequently markedly senile, and, without any particularly obvious modification of their already low intelligence, may, on *post-mortem* examination, show distinct morbid appearances, including cerebral wasting of a more or less general type.

On the other hand, recent cases of marked mental confusion with dementia who certainly suffer from severe cerebral disintegration may show relatively slight macroscopic chronic morbid appearances, owing to incomplete removal of the products of neuronic degeneration. In these cases, however, as the writer has repeatedly observed, well-marked macroscopic and microscopic *acute* degenerative changes are invariably present.

In the severer grades of dementia, which frequently but not necessarily occur in patients of advanced age, it is common to

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find extensive degeneration of the cerebral vessels. It might, therefore, appear probable that the age was the cause of the vascular degeneration and that this, again, was the cause of the dementia, which last would thus not necessarily be associated with neuronic involution, but would be the result of vascular lesions. The writer has, however, shown that the relationship between the presence of degeneration of the cerebral vessels and the development of dementia may be summed up as follows: "In a cerebrum which has begun to break down, or where degeneration has progressed to the 'moderate' stage (Group III), the presence or incidence of gross degeneration of the cerebral vessels will cause rapid progress of the neuronic degeneration, with gross dementia." Cerebra are, of course, frequently met with in which more or less marked macroscopic lesions exist as the result of vascular degeneration, but these fall into a different category and belong equally to the sane and the insane.

Finally, certain morbid appearances are commonly present in cases of mental disease as the result of the systemic diseases which are the cause of death. Of these the most usual in all types of case, whether of dementia or of amentia, is œdema of the pia-arachnoid and the cerebrum. In systemic tuberculosis, for example, this morbid appearance occurs with a frequency of over 30 *per cent.*, and it is also found in many patients who have died of progressive cardiac failure, of the different toxæmias and infections, or of these conditions combined.

Summary.

It is evident from the macroscopic data contained in the above description that the average weight of the cerebral hemispheres in amentia is below that of the normal average. Such cerebra, moreover, frequently show signs of under-development, as, for example, a small prefrontal region and a more or less marked simplicity of convolutional pattern. Cases of amentia of vascular or traumatic origin are not included in this category.

It is in dementia, however, that macroscopic study of the intra-cranial contents is of especial value. In addition to morbid conditions of the cerebral membranes and intra-cranial fluid, macroscopic wasting of the cerebrum is visible; and all these abnormal appearances vary in degree with the amount of dementia present. The region of the cerebrum in which wasting has occurred is of peculiar significance. It has its focus in the prefrontal region, in the middle of which lies the nodal point of Flechsig's anterior and most complex centre of association, and it exists to a lesser degree in the neighbouring fronto-parietal and temporal regions. Hence, even in the absence of the histological evidence now to be adduced, the facts already cited demonstrate that in dementia the anterior centre of association of Flechsig is atrophied, and that this atrophy apparently extends to the systems of fibres of association which pass to the neighbouring regions of the cerebrum.

(B) *General Histology of Mental Disease.*

(1) *The Cell and Fibre Architecture of the Prefrontal Cortex Cerebri.*

The cortex made use of for the following description, and that employed for the preparation of the micrometric data here summarised, was obtained from the focus of the cerebral wasting referred to above, namely, from the neighbourhood of 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 area selected for micrometric examination 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 selection of the sections and in the preparation of the micrometric measurements from these.

The cortex cerebri, in the region referred to, consists in the adult of the five primary laminæ to which reference has already been made, and in this detail, except as regards unobvious specialisation which is probably connected with differences in function, resembles that of the other zones of association of Flechsig.

Of these five laminæ the first or superficial and the fourth or "inner line of Baillarger" are essentially fibre-layers. The remaining three, namely the second, the third, and the fifth, which contain respectively the pyramidal, the granule, and the polymorphic cells, are essentially nerve-cell layers. The writer

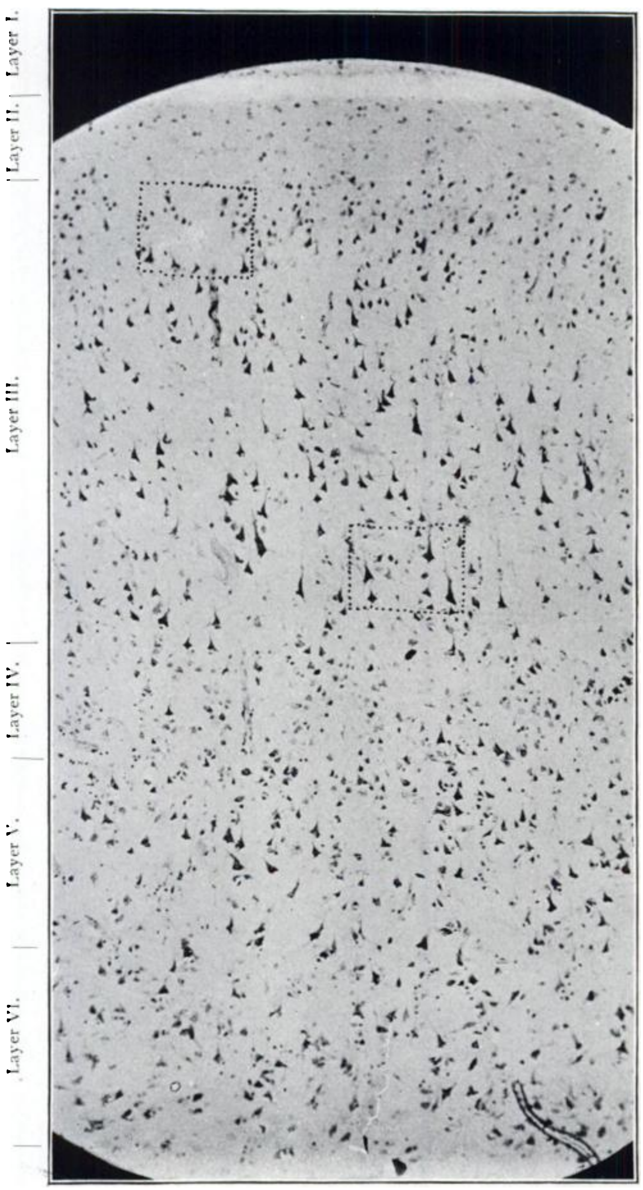

FIG. 1. 82 Diameters.

FIG. 2. 85 Diameters.

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PLATE I.

Microphotographs of the prefrontal cortex cerebri just behind the pole of the hemisphere. The sections were made at right angles to, and across the middle of, the (constant) transverse fissure of Wernicke. The part of the section shown in the photographs is the " side " of the fissure, at a point midway between the lips and the bottom.

FIG. 1.—82 diameters. The cellular elements of the prefrontal cortex. High-power microphotographs of the upper and lower regions of Layer II are given on Plate II, figs. 3 and 4, and the exact position of these is indicated by the dotted areas.

Layer I. Superficial or outer fibre lamina.
Layer II. " Pyramidal " or outer cell lamina.
Layer III. " Granule " or middle cell lamina.
Layer IV. Inner line of Baillarger or inner fibre lamina. In this layer numerous large pyramid-shaped or irregular cells lie singly or in clusters (homologues of Betz cells and solitary cells of Meynert in the pre-central and occipital regions respectively).
Layer V. " Polymorphic " or inner cell lamina.
The well-developed condition of the cellular elements of the prefrontal cortex is clearly visible even in this low-power microphotograph.

FIG. 2.—85 diameters. The fibre-architecture of the prefrontal cortex. This microphotograph is introduced to show the position, indicated by dotted lines, of the high-power illustration on Plate IV, fig. 6, and thus demonstrate the existence, as high up as Layer III, of relatively coarse medullated fibres. Owing to the blood-vessel which appears in the illustration, the columns of Meynert are not visible in the central portion of the photograph, and, for the same reason, large pyramidal cells are absent from the lower part of Layer II.

PLATE II.

Fig. 3.—615 diameters. Microphotograph of the upper part of Layer II, in the position indicated in Plate I, fig. 1. The pyramidal and triangular cell-elements of this part of the layer are well developed, and their apical processes and numerous basal dendrites are clearly visible.

Fig. 4.—615 diameters. Microphotograph of the lower part of Layer II, in the position indicated in Plate I, fig. 1. The figure shows three large pyramidal cells with complex apical processes and numerous and well-developed basal dendrites.

Nerve-cells in a better condition of development would, to say the least, be difficult to demonstrate in any region in the cortex cerebri.

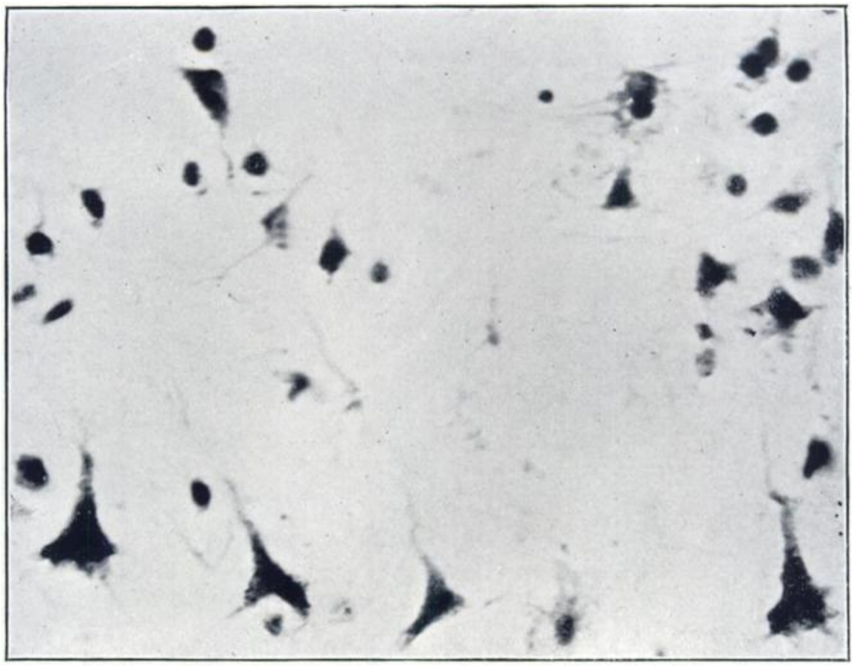

FIG. 3. 615 Diameters.

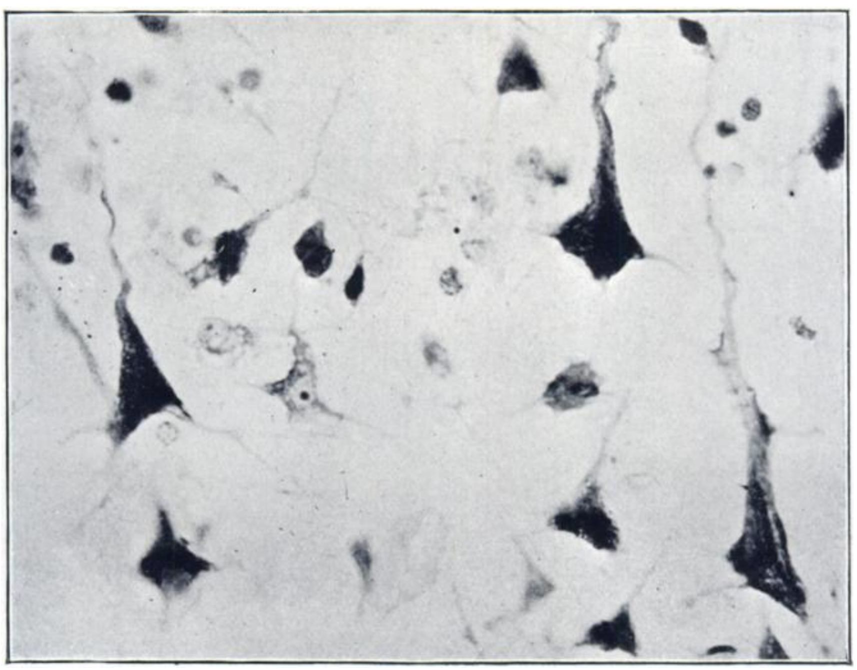

FIG. 4. 615 Diameters.
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makes no attempt to subdivide the second or pyramidal layer (outer cell lamina), which is structurally and developmentally single, into artificial layers of small, medium, and large pyramidal cells.

In the following description the cellular elements of the prefrontal cortex will first be referred to. An account will then be given of the nerve-fibre architecture of this region. Finally, the structure of the prefrontal cortex cerebri will be briefly considered from the micrometric aspect.

(A) *Cellular Elements of the Prefrontal Cortex.*

Lamina I.—Superficial layer. Molecular layer. Outer fibre layer. This layer resembles the corresponding layer in other regions of the cortex in possessing few and insignificant cellular elements.

Lamina II.—Layer of pyramidal cells; outer cell layer. This layer is well developed, and is of practically the same average depth as in the visuo-psychic region of the cortex (a posterior zone of association), namely, ·83 mm. This depth is somewhat greater than that of the combined third, fourth, and fifth laminæ, which is ·77 mm., and in this respect the cortex of the prefrontal region again resembles that of the visuo-psychic area. These facts, as is shown in the next section (p. 251), which deals with the mode of evolution of the cortex cerebri, prove that the layer under consideration is as well developed as is the corresponding layer in the visuo-psychic region (a posterior zone of association).

The nerve-cells in this layer are well developed and pyramidal in shape, and those in its lower half are large and well formed and possess well-marked and complex apical processes and numerous basal dendrites. In the upper third of the layer the cells are smaller and more closely packed, but even here well-formed cells, of a triangular rather than a pyramidal shape, and possessing well-marked apical processes and basal dendrites, are present.

Microphotographs of the deep larger and of the superficial smaller cells are figured on Pl. II, figs. 3 and 4, and in the low-power microphotograph on Pl. I, fig. 1, the respective parts of the layer in which these cells lie are illustrated.

Lamina III.—Layer of granules. Middle cell layer. This layer is well developed and resembles in its average depth and in its cellular elements the corresponding layer in the visuo-psychic region (a posterior zone of association).

The nerve-cells in this layer are small and closely packed. They are of irregular shape, but as a whole are rounded in outline, or are triangular with convex sides, and they possess two or three short, thin processes.

In the upper and lower limits of the lamina the special cells belonging to the layer are encroached upon by scattered cellular elements belonging to the adjacent laminæ (II and IV).

Lamina IV.—Inner line of Baillarger. Inner fibre layer. This layer, in average depth and general characters, resembles the corresponding layer in the visuo-psychic region (a posterior zone of association).

The cellular elements contained in it are scattered and of a mixed type. In the upper part of the layer, however, triangular or pyramidal-shaped cells of considerable size lie singly or in clusters (homologues of Betz cells and of solitary cells of Meynert in the precentral and the occipital cortex respectively), and similar solitary cells lie here and there in the lower part of the layer.

Lamina V.—Layer of polymorphic cells. Inner cell layer. This layer, in average depth and general characters, again closely resembles the corresponding layer in the visuo-psychic region (a posterior zone of association).

The cellular elements are numerous and irregular in shape, and lie in all directions. They, on the whole, possess at any rate from two to five well-developed processes. As in other regions of the cerebrum, their shape varies considerably with the part of the convolution under examination. At the "side" of the convolution (parts in contact between the surface of the brain and the bottom of a fissure) they are mostly irregular in shape. At the "bottom" of a fissure they are often fusiform in shape and lie parallel to the surface. At the "apex" of a convolution (part where an abrupt twist occurs at the lip of a fissure, etc.) they are largely fusiform in shape and radiate towards the surface of the brain between the "radiations of Meynert." Finally, on the "flat" external surface of a convolution their shape and arrangement are intermediate between those on a "side" and those at an "apex."

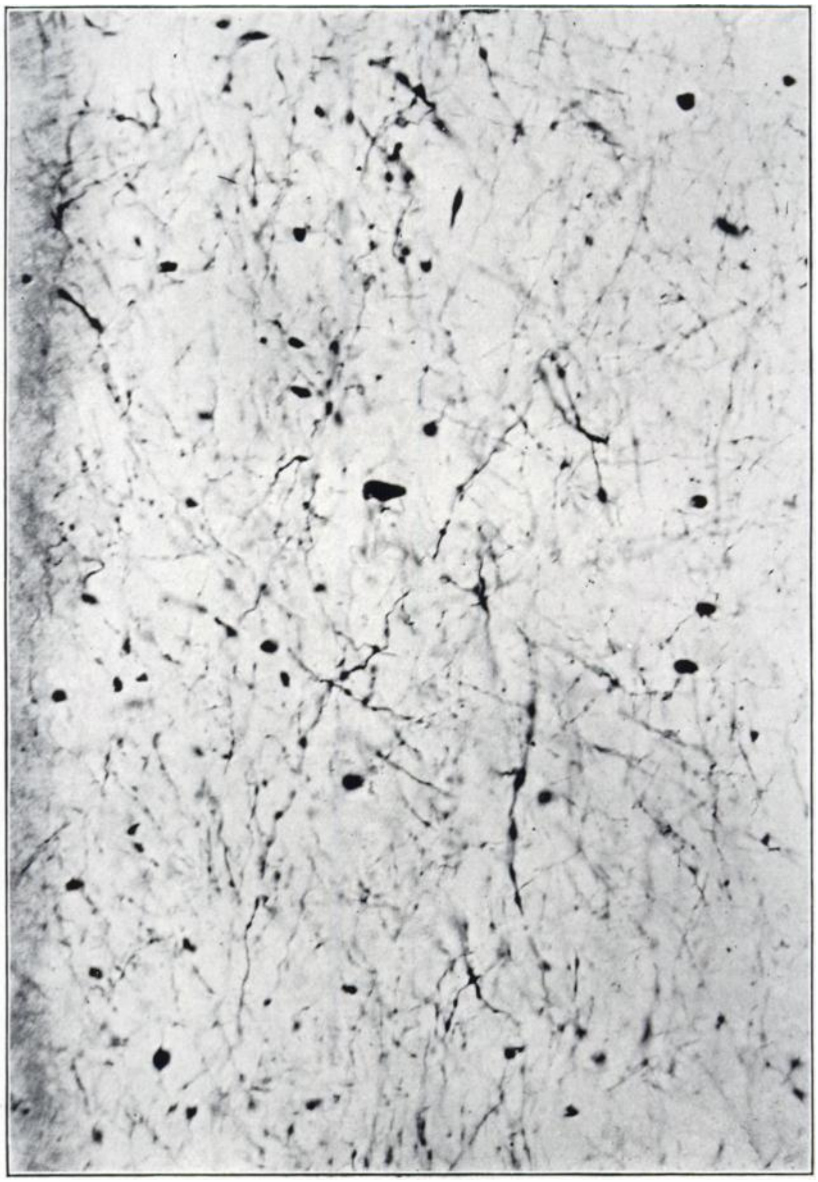

FIG. 5. 385 Diameters.
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PLATE III.

FIG. 5.—385 diameters. Microphotograph of the upper half of Layer I, the superficial or outer lamina of the cortex. The outer covering of neuroglia is shown at the top of the figure as a more darkly stained portion.

The complex meshwork of varicose fibrils which exists in this layer is well illustrated in the figure. The photograph, however, gives but a poor idea of the great fibre wealth which is visible in an actual section, owing to the technical difficulties which attend the reproduction of a mass of delicate fibrils lying in many planes.

PLATE IV.

FIG. 6.—385 diameters. Microphotograph of the columns of Meynert and the intra-radiary fibre plexus in the exact position indicated by the dotted lines in Plate I, fig. 2. Even as high in the cortex, therefore, as lamina III, the granule layer, relatively coarse medullated fibres, which lie both vertically and obliquely, are common. The illustration admirably demonstrates the great fibre wealth of the intra-radiary plexus in this region, though multitudes of the finer fibrils have been lost during the process of reproduction.

FIG. 7.—385 diameters. Microphotographs of the columns of Meynert and the intra-radiary plexus in the lower part of Lamina IV. Numerous relatively coarse medullated fibres lie in the columns and run obliquely across the field, and the plexus is of remarkable complexity and delicacy.

The illustrations on these plates indisputably prove the great cell and fibre wealth of the prefrontal region of the cortex cerebri, and form the best reply to the criticism of the writer's researches which Dr. Campbell appears to have founded on his conclusion that "The structural development of the 'prefrontal' cortex is exceedingly low. It presents an extreme of fibre poverty; all its fibre elements are of delicate calibre, and its association system is particularly deficient. Its cell representation is on a similar scale. The cortex is also shallow."

FIG. 6. 385 Diameters.

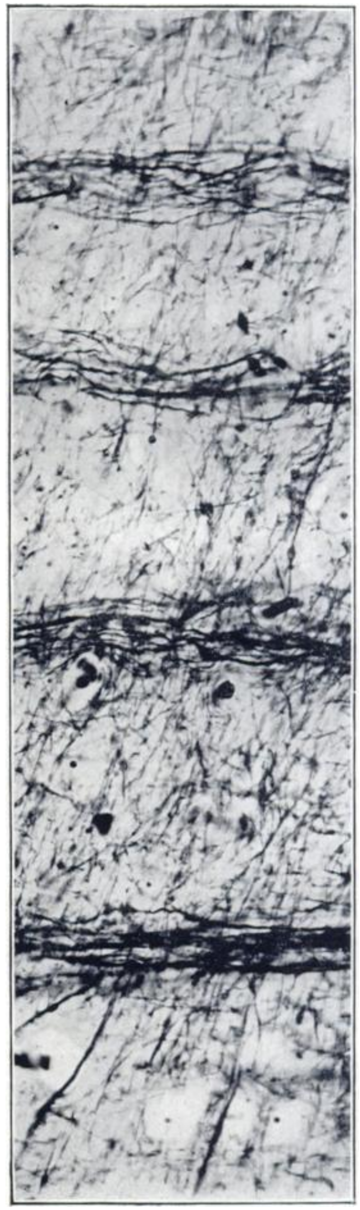

FIG. 7. 385 Diameters.

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(B) *The Nerve-Fibres of the Prefrontal Cortex.*

For convenience of description the fibre-architecture of the prefrontal region will be considered as far as possible under the laminæ of the cortex cerebri which have been already referred to.

(1) *Superficial or molecular layer, first lamina.*—Throughout the whole of this layer, excepting the thin outer neuroglial covering, is a very complex and delicate meshwork of fine varicose fibrils. These fibrils interlace in every direction, though a considerable proportion lie approximately parallel to the surface. Many, of rather coarser calibre, pass vertically or obliquely into and from the subjacent pyramidal or outer cell layer (Lamina II). This meshwork is traversed obliquely by scattered medium and even coarse varicose fibrils. Beneath the outer fibreless covering is a definite but imperfect layer of medium and coarse varicose fibrils, the continuity of which increases with the thickness of the section. Lastly, in the deeper part of the layer, just before it passes into the pyramidal or outer cell layer, a sufficiently distinct decrease in the complexity of the fibrillar meshwork exists to enable the line of separation between the two laminæ to be detected even if the nerve-cells of the latter are invisible. In Plate III, Fig. 5, the nerve-fibrils of the upper half of this lamina are illustrated.

(2) *Pyramidal or outer cell layer, second lamina.*—Through the lower boundary of this layer the terminations of the radiations of Meynert, composed of fine and medium and also several coarse medullated and varicose fibrils, pass upwards, and some of the fibrils can be traced through the upper confines of the layer into the outer or first lamina of the cortex.

Lying throughout the lamina under description is an intricate meshwork of mixed fibrils, which is coarser below, and attains its maximum delicacy and complexity about the upper trisection of the lamina and below the aggregated smaller pyramidal cells. In the outer part of the lamina which is occupied by these cells the meshwork is complex, delicate, and wavy, owing to the manner in which the fibrils interlace in every direction between the individual cells.

(3) *Third, fourth, and fifth laminæ; middle or granule cell-layer, inner fibre-layer, and inner or polymorphic cell layer.*—

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Owing to the fact that no exact relationship exists between the fibre-structure of this part of the cortex cerebri and the three primary laminæ of which it is composed, the whole will be included under one description.

This region of the cortex is traversed vertically by the radiations of Meynert, and lying horizontally in it are two fibre-plexuses. The outer and more delicate of these is situated at the junction of the pyramidal layer (second lamina) and the granule layer (third lamina), and encroaches on the latter. The inner and denser of these horizontal fibre-plexuses lies in the region of the fourth lamina (inner fibre layer of primary cortical structure).

Radiations of Meynert.—These columns are composed of medullated and varicose fibrils of different calibre, and include many coarse medullated fibres (see Plate I, fig. 2, and Plate IV, figs. 6 and 7).

Interradiary plexus.—This plexus is of remarkable and delicate fibrillar wealth, and is traversed obliquely and horizontally by numbers of coarse medullated and varicose fibres. In the two regions above referred to a distinct band is produced by a horizontal condensation of the fibrillæ. Of the two bands the inner (fourth lamina) is the more dense, and the outer (plexus lying between the second and third laminæ and encroaching on the latter) is the more delicate. Even in the latter, however, many coarse medullated and varicose fibres lie obliquely and horizontally, and these may be followed at times for considerable distances (see Plate IV, figs. 6 and 7).

The interradiary plexus is of the least density in the lower part of the granule layer (third lamina), but even here is of great and delicate fibre wealth, and in structure is homologous with the band of fibres lying directly above it at the junction of the second and third laminæ. The interradiary plexus is of rather coarser composition, and forms a dense meshwork round the nerve-cells in the fifth lamina (polymorphic or inner cell layer), and in structure is homologous with the fibre-band lying immediately above it in the fourth lamina (inner fibre layer of primary cortical structure).

The horizontal fibre bands of the prefrontal cortex.—In order to avoid misinterpretation in one of the most difficult details of the fibre architecture of the cortex, it seems desirable, finally, to refer, in the form of a summary, to the exact position of the horizontal fibre bands of the prefrontal region.

Of the five primary laminæ of the cortex cerebri, two—the first and the fourth (outer and inner fibre layers)—are in essential structure fibre-layers. These laminæ are laid down in the developing cortex before nerve-fibres appear, and are not to be confounded with the fibre-bands of the adult cortex.

The horizontal fibre bands of the adult cortex are four in number, and, as a whole, decrease in thickness from below upwards.

The fourth and deepest fibre-band.—Inner line of Baillarger. This band occupies the position of the fourth primary lamina of the cortex. In specimens stained for nerve-fibres this band is usually visible in sections prepared from the centres of association, but is commonly invisible in sections taken from the sensory spheres, owing to the immense number of projection fibres which traverse the cortex vertically in these regions. In the prefrontal region (centre of association) it is, as a rule, readily discerned in carefully differentiated specimens.

The third fibre-band.—Outer line of Baillarger. This band is much thinner than the last described; it lies between the second and third laminæ (pyramidal or outer and granule or middle cell layers), and it somewhat encroaches on the latter of these. It is usually readily visible in sections taken from nearly any part of the cortex cerebri. It is especially prominent in the visuo-sensory area of the cortex (the most definite sensory projection sphere), it has received the name "line of Gennari," and it is here separated from the second lamina (pyramidal or outer cell layer) by an additional layer of granules. This fact proves its connection with the third lamina (granule or middle cell layer); and the association of the third lamina, including this fibre-band, with the optic radiations, is demonstrated by the fact that in long-standing or congenital blindness the outer layer of granules is decreased in thickness to the extent of more than 10 *per cent.*, and the fibre-band to the extent of nearly 50 *per cent.*

The second fibre-band.—Superradiary fibre-band. This fibre-band is thinner than the last described. It is usually readily demonstrated in sections taken from nearly any part of the cortex cerebri, though its position appears to vary somewhat in different regions. In the prefrontal cortex it consists of a delicate fibre-band, which in structure is a condensation of the general fibre meshwork of the second lamina, and lies approximately at the outer trisection of this lamina (pyramidal or outer cell layer) and below the aggregated smaller pyramidal cells.

The superficial or first fibre band.—Tangential layer of fibres. This fibre-band lies in the outer part of the first or outer lamina (outer fibre layer) of the cortex, just beneath the thin outer neuroglial covering. The coarseness of its constituent fibre elements varies in different regions of the cortex. In the prefrontal region it consists of a definite but imperfect layer of medium and coarse varicose fibrils, the continuity of which increases with the thickness of the section.

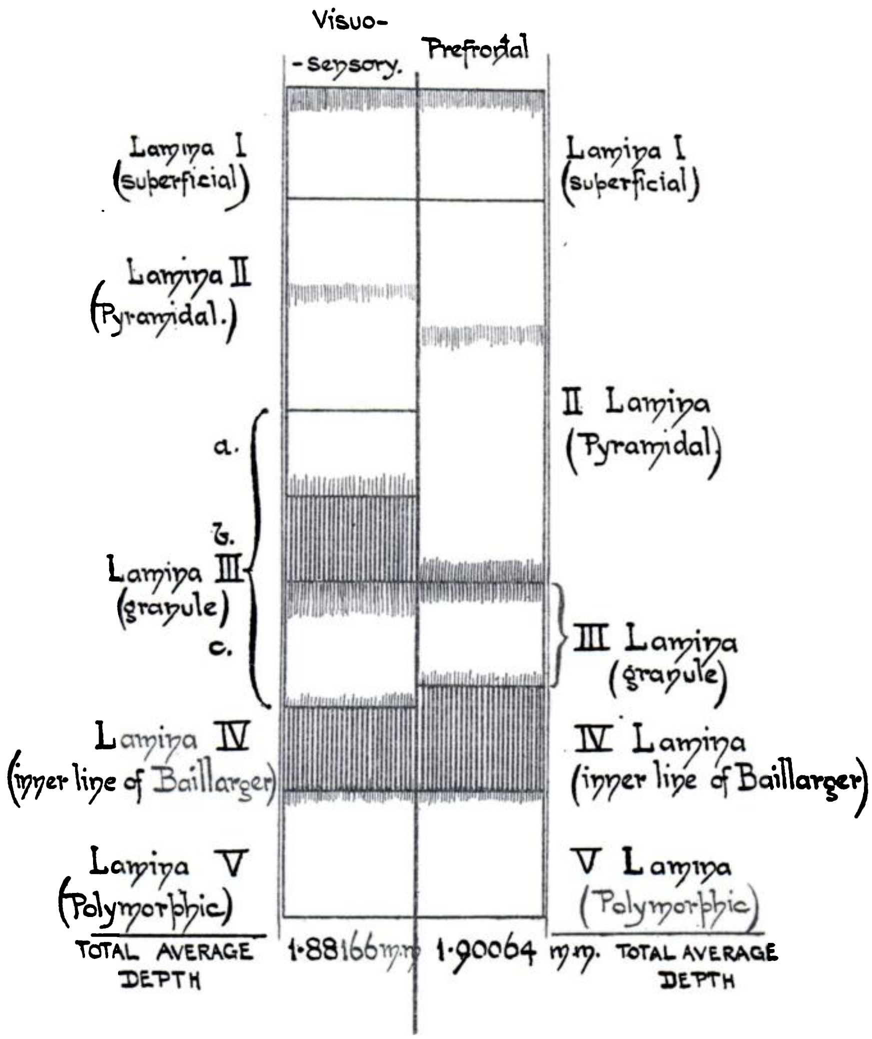
The horizontal fibre bands of the cortex in the visuo-sensory and prefrontal regions are compared in the following diagram, which approximately represents their relative positions and in a gross manner their respective depths.

It is finally desirable to add, for the sake of clearness, that the fibre-architecture of the cortex depends for its chief characters on the lamination and relative development of the cell-elements. In other words, the fibres lie wherever there is room for them, and their arrangement depends upon the position, size, and number of the pre-existing cells. In the fourth lamina, where cells are relatively few, a dense plexus develops and forms a definite horizontal band. Between the second and third laminæ, where the large pyramids are more or less definitely separated off from the subjacent granules, another band, which there is reason to believe is closely associated with projection fibres, is usually quite definite. In the upper part of Lamina II, below the smaller and frequently aggregated pyramidal or triangular cells, around which a wavy plexus of fibres exists, a more or less definite condensation of fibres is usually perceptible as a further horizontal band. Finally, in Lamina I, the fibres which it contains form a fairly definite horizontal condensation in the outer part of the lamina, and this is probably a natural mechanical arrangement which has occurred during the growth of the fibres into the lamina.

The above account of the fibre structure of the prefrontal region differs so absolutely, both generally and in detail, from that recently published by Campbell, in his *Histological Studies on the Localisation of Cerebral Function*, that an explanation of

FIG. 2

Rough diagram of the
FIBRE BANDS OF THE CORTEX CEREBRI



NOTE.—This diagram is not intended to show either the exact thickness of the bands or the relative number of fibres contained in them.

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this difference is necessary. The description given by this author is briefly as follows:

"'*Zonal layer of fibres.*' In the 'prefrontal' area the development is so poor that a few scattered, short, wavy fibrils alone remain to denote the existence of the layer" (*cf.* on the other hand Pl. III, fig. 5).

"'*Supra-radiary layer.*' When we come to the 'prefrontal' area only a few short and irregularly scattered fibres can be seen. But since nerve-cells, although small, are present in abundance in the same situation, and it is impossible to think of nerve-cells without accompanying nerve-fibres, I should qualify my statement by saying that scarcely any fibres are present which even a delicate method like that we owe to the ingenuity of Wolters and Kulschitzky, will reveal."

"'*Line of Baillarger*'" (= outer line of Baillarger or outer of the two inter-radiary fibre bands). "In the 'prefrontal area' . . . the formation is found to be very weak; it contains no large fibres at all, scarcely any which can be designated medium-sized, and the delicate elements which do compose it are both short and scarce."

"'*Radiations of Meynert.*' Coming to the 'prefrontal' cortex the attenuation is more pronounced, and large and medium-sized fibres having disappeared, the fasciculi are composed entirely of delicate varicose elements" (*cf.* on the other hand Pl. IV, figs. 6 and 7).

"'*Interradiary plexus and association fibres.*' The 'prefrontal' plexus in turn differs from the 'frontal' in being still more open, and in containing no fibres of large calibre. The latter feature is one which I regard as of great histological importance" (*cf.* on the other hand Pl. IV, figs. 6 and 7).

In his summary Campbell adds:

"(5) The structural development of the 'prefrontal' cortex is exceedingly low. It presents an extreme of fibre poverty; all its fibre elements are of delicate calibre, and its association system is particularly deficient. Its cell representation is on a similar scale. The cortex is also shallow."

The cause of the discrepancy between Campbell's and the writer's descriptions lies in the difference of method adopted. The writer, by the methods he employs, is able to stain the nerve-fibrils which are present, and is even able to state positively that the variation in fibre architecture which occurs in the several regions of the cortex is not so much a difference in fibre wealth as a difference in coarseness of fibre structure. Campbell, on the other hand, has throughout used the Wolters-Kulschitzky modification of the Weigert-Pal process for the staining of his fibre preparations.

Several years ago the writer conducted a lengthy investigation into the chemistry of the Weigert-Pal method (*Journ. Anat. and Phys.*, 1897 and 1898), and showed that this process "is not a specific method for the staining of medullated nerve-fibres with hæmatoxylin, but is a method of dyeing fibrils, which comprises three distinct operations—the mordanting of the fibrils, the formation of a lake in them, and, finally, the removal of the stain by oxidation from nearly every other part of the complex tissue under treatment." In his papers he classified the several lakes, formed by hæmatoxylin with various metallic salts, according to their relative value, and eventually, in his later investigations on cortical structure, made use of ammonium molybdate and iron alum as the most trustworthy mordants. As every technical dyer is aware, unless a fabric is properly mordanted (in the staining of woven fibres with basic dyes) no amount of dyeing will give a satisfactory result, and it is in this detail that the Wolters-Kulschitzky method is untrustworthy, as it depends for its results on the staining rather than on the mordanting part of the process.

In the staining of nerve-fibrils, as the delicacy and complexity of the meshworks of these become greater, the process of mordanting must be more and more thoroughly carried out. Of all the regions of the cortex, the fibre-plexuses are the most delicate and complex in the prefrontal region, and there is a corresponding difficulty in obtaining a satisfactory result. In this part of the cerebrum especially, the mordanting and staining processes require to be carried out most thoroughly and the oxidising process most carefully. To a worker unaccustomed to the particular processes referred to, the earlier results are almost certain to be disappointing, as both practice and persistence are necessary in order to take advantage of the full staining capabilities of the tissue. In some brains, even after repeated and persistent attempts, a more or less complete failure results, and this is in all probability due to some chemical alteration in the tissues of either *ante-* or *post-mortem* occurrence. The writer has therefore prepared his photographs from specimens which were kindly lent to him by Dr. Watson, in order to provide independent confirmation of the superiority of the staining processes he advocates.

This, then, is the reason of the discrepancy between the above descriptions, and it is a matter of regret to the writer that such an extensive investigation as that conducted by Dr. Campbell should have lost much of its value owing to a preventable cause, and that this author should have founded on an untrustworthy basis his very positive statements concerning the fibre architecture of the prefrontal cortex.

(c) *The Prefrontal Cortex from the Micrometric Aspect.*

The general structure of the prefrontal cortex from the micrometric aspect is derived from an examination of three normal brains. The average depths of the different layers of which the cortex is composed were obtained by a method already published in detail in a previous paper. They are shown graphically in percentages in Fig. 10, p. 263, and are stated in millimetres in the following table.

FIG. 3.

		Case I.	Case II.	Case I I.	Average of Cases I, II, and III.
Layer I	Outer fibre layer	0·27713 mm.	0·34141 mm.	0·28308 mm.	0·30054 mm.
Layer II	Outer cell layer	0·83616 „	0·90143 „	0·75590 „	0·83116 „
Layer III	Middle cell layer	0·24117 „	0·21953 „	0·22579 „	0·22883 „
Layer IV	Inner fibre layer	0·23592 „	0·22271 „	0·23233 „	0·23032 „
Layer V	Inner cell layer	0·30166 „	0·31033 „	0·31737 „	0·30979 „
Total depth . .		1·89204 mm.	1·99541 mm.	1·81447 mm.	1·90064 mm.

Of the three cases, Case 2 gives higher and Case 3 lower results than Case 1: and the average of the three cases is practically identical with that of Case 1. It will be noticed in the table that such differences as exist occur in the first and second laminæ only. Lamina II, the pyramidal or outer cell layer, is of all the cortical layers the easiest to measure accurately. This layer, therefore, varies in depth in different normal individuals, a fact, as will be seen later, of the very greatest significance. In the case of Lamina I, the superficial or outer fibre layer, whilst every care was taken to obtain accurate results, it is certainly the portion of the cortex most likely to sustain injury during the process of preparation for microscopic examination. As, however, the mode of development of this layer demonstrates that, after attaining a certain depth, it afterwards increases *pari passu* with Lamina II, it is probable that the two laminæ are structurally and functionally associated.

(2) *The Mode of Development of the Primary Cell and Fibre Laminæ of the Prefrontal Cortex Cerebri.*

The micrometric basis for this description is derived from an examination of five selected cases, namely, two fœtuses of about four and six months respectively, two stillborn infants (male and female), and one child of the age of six weeks. The results are displayed graphically in percentages of the normal adult depth in Fig. 10, p. 263.

In the fœtus of four months lamination has not begun, and the cortex consists solely of a superficial indifferent layer and of a deeper layer of undifferentiated neuroblasts. The average depth of the former is 0·154665 mm., and of the latter 0·67758, a total of 0·832245 mm., which is less than half the normal adult general average depth.

For simplicity of exposition, the process of development will be first described in the case of each separate layer, and the results will then be summarised.

PRIMARY FIBRE LAYERS OF THE CORTEX.—*Lamina I: Superficial layer, outer fibre layer.*—At the fourth month of fœtal life the cortex consists of this layer and of a deeper undifferentiated mass of neuroblasts. The layer under description is already about one half of the adult depth, and it remains unchanged until the development of lamination in the sixth month. At birth, however, it has attained to a depth which is about two thirds of the adult normal. It is probable that its further development to the normal adult depth occurs in association with that of the subjacent second, pyramidal, or outer cell layer.

Lamina IV.—Inner fibre layer, inner line of Baillarger.—This layer appears in the sixth month of fœtal life, and almost at once attains to nearly the normal adult depth. The cleavage of the partially differentiated neuroblasts of the cortex into an upper and a lower portion by the development of this layer is the most striking feature of the process of lamination. In view of what will be stated later concerning the functions carried on by the inner cell layer, this cleavage of the neuroblasts is an occurrence of the greatest significance.

PRIMARY CELL LAYERS OF THE CORTEX.—*Layer II: pyramidal layer, outer cell layer.*—The pyramidal layer is the last cell layer to develop during the process of lamination. In a fœtus of six months this layer is separable from the subjacent middle cell layer owing to the less differentiated condition of its cell elements, and it is at this period only one fourth of the depth to which it attains in the adult. At birth and in early infancy it is still little more than one half of the adult depth.

Layer III: granule layer, middle cell layer.—The granule layer develops in the sixth month of fœtal life, and at this period it is separable from the superjacent outer cell or pyramidal layer owing to the more differentiated condition of its cell elements. At this period it is already one half of the adult depth, and by the time of birth it has attained to a depth which is nearly three fourths of this.

Layer V: polymorphic layer, inner cell layer.—The polymorphic layer is separated off, as has already been stated, from the rest of the partially differentiated neuroblasts by the development of the fourth or inner fibre lamina at the sixth month of fœtal life. The polymorphic layer is already, at the period referred to, about three fourths of the adult depth, and it undergoes a slow further development until after birth. In a child of six weeks it has attained a depth which is within 18 *per cent.* of the adult normal.

Summary.—The *inner cell layer*, therefore, appears before the others and is almost at once of a depth which is about 75 *per cent.* of the adult normal. It remains almost of a stationary depth until after birth. Its depth in a child of six weeks is 82 *per cent.* of the adult normal.

The *middle cell layer* appears next in order and is almost at once about one half of the normal adult depth. It gradually increases in thickness, and at birth it has attained to a depth which is 75 *per cent.* of the adult normal.

The *outer cell layer* is the last layer of the cortex to be developed, and at this time it is only one fourth of the normal adult depth. It gradually increases in thickness, and in an infant of six weeks it has attained to a depth which is about 60 *per cent.* of the adult normal.

The functional significance of the facts contained in this section will be referred to later, after the consideration of the condition of the cortical laminæ in amentia and dementia respectively.

(3) *The Prefrontal Cortex in Amentia.*

(*a*) *Low-grade amentia.*—The micrometric basis for the facts to be adduced concerning the condition of the prefrontal cortex in low-grade amentia is derived from an examination of four cases which exhibited different grades of idiocy and imbecility. In one of the cases both hemispheres were examined, as an additional means of checking the results. The measurements obtained from these hemispheres showed throughout a remarkable similarity, such a resemblance, in fact, that it was quite easy after all the figures had been worked out, to pick them out as belonging to the same cerebrum. The general average measurements of this case are as follows:

FIG. 4.

Low-grade amentia.		Right hemisphere.	Left hemisphere.
	Outer fibre layer	0·27598 mm.	0·28955 mm.
II	Outer cell layer	0·72886 „	0·77021 „
III	Middle cell layer	0·20053 „	0·19929 „
IV	Inner fibre layer	0·19327 „	0·19941 „
V	Inner cell layer	0·27231 „	0·27444 „
Total		1·67095 mm.	1·73290 mm.

It will be noticed that the general average measurements in the two columns are practically identical except for the fact that the second or outer cell layer is somewhat deeper in the left hemisphere.

In all the cases the depth of the cortex varied according to the mental capacity of the individual. In the lowest case, an idiot, it was 72·94 *per cent.* of the normal, and in the highest, a mild imbecile, it was 89·95 *per cent.* of the normal. The chief

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factor in the production of the difference in depth was in all the cases the thickness of the second, pyramidal or outer cell layer.

In the following table the general average measurements of the combined cases are compared with those of the combined normal cases which are given on p. 250 (Fig. 3). In the table the actual and the percentage decreases in depth are shown in the third and the fourth columns respectively.

FIG. 5.

		Average normal.	Average low-grade amentia.	Decrease.	Percentage of decrease.
Layer I	Outer fibre layer	0·30054 mm.	0·25576 mm.	0·04478 mm.	15 %
„ II	Outer cell layer .	0·83116 „	0·66858 „	0·16258 „	20 %
„ III	Middle cell layer	0·22883 „	0·19277 „	0·03606 „	16 %
„ IV	Inner fibre layer.	0·23032 „	0·19925 „	0·03107 „	13 %
„ V	Inner cell layer .	0·30979 „	0·27491 „	0·03488 „	11 %
Total		1·90064 mm.	1·59127 mm.	0·30937 mm.	16 %

On examination of this table it will be seen that more than half of the actual decrease in depth occurs in the second or pyramidal layer (outer cell layer). In the last column the percentage decrease of each separate layer is stated, and this, when compared with the section on the mode of development of the primary laminæ of the prefrontal cortex cerebri (p. 251), affords absolute proof that the cortex of the cases just referred to is in a condition of arrested development. The percentage decrease is the smallest in the fourth or inner cell layer, and it is the largest in the second or outer cell layer, that in Layer III, the granule or middle-cell layer, occupying an intermediate position. In the case of the primary fibre laminæ also the decrease is more marked in Layer I, the outer, than in Layer IV, the inner. All these facts agree exactly with the order and mode of development of the different laminæ of the cortex cerebri.

The prefrontal cortex cerebri in low-grade amentia is, therefore, in a state of arrested development, and this arrest especially affects the second or pyramidal layer (outer cell layer), which is the last lamina of the cortex cerebri to be evolved.

(β) *High-grade amentia.*—The three cases employed for the preparation of the micrometric data here considered are examples of recurrent and chronic insanity without dementia, which showed no intra-cranial morbid appearances on *post-mortem* examination.

The total depth of the cortex cerebri in these cases varies from 89·45 to 94·4 *per cent.* of the normal, and the chief factor in the production of the decrease in depth is the condition of the second, pyramidal, or outer cell-layer.

In the following table the general average measurements of the combined cases of high-grade amentia are compared with those of the combined normal cases, and the actual and the percentage decreases in depth are shown in the third and fourth columns.

FIG. 6.

		Average normal.	Average high-grade amentia.	Decrease.	Percentage of decrease.
Layer I	Outer fibre layer	0·30054 mm.	0·26150 mm.	0·03904 mm.	13 %
„ II	Outer cell layer.	0·83116 „	0·72599 „	0·10517 „	13 %
„ III	Middle cell layer	0·22883 „	0·21823 „	0·01060 „	5 %
„ IV	Inner fibre layer.	0·23032 „	0·21811 „	0·01221 „	5 %
„ V	Inner cell layer.	0·30979 „	0·30106 „	0·00873 „	3 %
Total		1·90064 „	1·72489 „	·17575 „	9 %

On examination of this table it will be seen that considerably more than half the actual decrease in depth occurs in the second, pyramidal, or outer cell-layer. If the percentage decrease in each separate layer be compared with those in Fig. 5, p. 254, and with the description of the mode of development of the primary laminæ of the cortex cerebri, it will again be seen that the condition is one of arrested development. In high-grade amentia, however, compared with low-grade amentia, the decrease in depth is proportionately more marked in the second, or outer cell-layer. The fifth, or inner cell-layer shows the least decrease, and the third, or middle cell-layer shows very little more. The major portion of the decrease exists in the second, or outer cell-layer, which is the last of the cell laminæ to be evolved. In the case of the primary fibre laminæ, the decrease is much more marked in Layer I (the outer) than in

Layer IV (the inner), which fact also agrees with the mode of development of the cortical laminæ. As has already been shown, though Layer I is first existent, Layer IV rapidly attains almost to the adult depth, whereas Layer I continues to increase in depth *pari passu* with the development of the second lamina (the outer cell layer).

Hence *the prefrontal cortex cerebri in high-grade amentia is in a condition of arrested development*, which especially affects the second, pyramidal, or outer cell layer, which is the last of the cell-layers to be evolved; *and this arrest of development has occurred later in life than has the corresponding arrest in low-grade amentia.*

(4) *The Prefrontal Cortex in Dementia.*

(*a*) *Chronic insanity with dementia* (the ordinary chronic lunatic with dementia).—The micrometric data employed as a basis for this description are derived from two cases of chronic insanity with dementia, which at the *post-mortem* examination exhibited a moderate degree of morbid change in the intra-cranial contents—namely, moderate excess of intra-cranial fluid, moderate thickening of the pia-arachnoid, and moderate wasting of the cerebrum.

The total depth of the cortex cerebri in these cases was respectively 87·17 and 88·81 *per cent.* of the average normal.

In the following table the general average measurements of the combined cases are compared with those of the combined normal cases, and in the third and fourth columns are respectively stated the actual and the percentage decreases in depth.

FIG. 7.

		Average normal.	Average chronic insanity with dementia.	Decrease.	Percentage of decrease.
Layer I	Outer fibre layer	0·30054 mm.	0·25260 mm.	0·04794 mm.	16 %
Layer II	Outer cell layer.	0·83116 „	0·69245 „	0·13871 „	17 %
Layer III	Middle cell layer	0·22883 „	0·21041 „	0·01842 „	8 %
Layer IV	Inner fibre layer	0·23032 „	0·21652 „	0·01380 „	6 %
Layer V	Inner cell layer.	0·30979 „	0·29282 „	0·01697 „	5 %
Total		1·90064 mm.	1·66480 mm.	0·23584 mm.	12 %

On examination of the table it will be seen that more than one half of the actual decrease in depth, which is here chiefly or entirely due to cortical wasting, occurs in the second, pyramidal, or outer cell-layer. The percentage decrease is least in the fifth, or inner cell-layer, which is the first to be developed, and greatest in the second, or outer cell layer, which is the last to be evolved, that in the third, or middle cell layer occupying an intermediate position. In the case of the fibre laminæ the first, or outer, follows, as before, the second, or outer cell layer, and shows the greater decrease; and the fourth, or inner, shows the lesser, and in this follows the fifth, or inner cell layer.

Hence, during the process of cortical involution the layers which are the latest to be developed undergo the greatest degree of retrogression, and those which are the earliest undergo the least. In other words, the order of involution of the primary laminæ of the cortex cerebri is exactly the reverse of that of their evolution. The neurones of the cerebral cortex therefore conform to the general biological law with regard to the processes of evolution and involution.

The prefrontal cortex cerebri in chronic insanity with moderate dementia has therefore undergone dissolution in the reverse order to that of its evolution, the layers which have developed the latest being the most involuted, and those which have appeared the earliest being the least.

(β) *Gross dementia and gross dementia paralytica.*—Of the three cases examined micrometrically, two were cases of gross dementia and one was a case of gross dementia paralytica (general paralysis of the insane). In these cases the mental power of the patients was at its lowest ebb, and at the *post-mortem* examination gross morbid changes existed in the intra-cranial contents, namely, great excess of intra-cranial fluid, extreme thickening and opacity of the pia-arachnoid, and extreme wasting of the cerebrum.

The total depth of the cortex cerebri in these cases varies from 84·06 to 77·53 *per cent.* of the average normal.

Marked wasting exists in all the layers of the cortex, but an exact determination of the respective degrees in the different cell and fibre laminæ is impossible owing to the amount of chronic neuroglial and vascular proliferation which exists, especially in the first or outer fibre and the second or outer cell layers, and hence increases their depth.

In the following table the general average measurements of the combined cases of gross dementia are compared with those of the combined normal cases and with those of the combined stillborn infants.

FIG. 8.

		Normal. Average of cases 1, 2, and 3.	Stillborn infants. Average of cases 6 and 7.	Gross dementia. Average of cases 18, 19, and 20.
Layer I	Outer fibre layer .	0·30054 mm.	0·20238 mm.	0·26996
" II	Outer cell layer .	0·83116 "	0·50471 "	0·66709
" III	Middle cell "	0·22883 "	0·16610 "	0·18748
" IV	Inner fibre "	0·23032 "	0·16631 "	0·17092
" V	Inner cell "	0·30979 "	0·22696 "	0·22705
Total		1·90064 mm.	1·26646 mm.	1·52250

Allowing for the neuroglial and vascular proliferation which exists in the first two laminæ of the cortex of the gross dements, the second and third columns of figures in the table show a marked resemblance to one another, as do the corresponding mental conditions; and as children under the age of a few months are still relatively helpless and mindless, an even closer parallel of measurements might be obtained by the employment of such cases.

The two series given, however, representing as they do the condition of the cortex cerebri *at birth*, when the mental processes are about to begin, and *at death in the final stage of decay of the prefrontal region*, with the mind practically gone, are sufficiently striking.

(5) *The Neopallium of the Mammalia, and the Functional Significance of the Primary Cell Layers of the Human Cortex Cerebri.*

As has been stated, the human cerebral cortex is composed of five primary laminæ, of which the first or superficial and the fourth are, in essential structure, fibre-layers, and the second, third, and fifth are essentially nerve-cell layers.

The undifferentiated cortex cerebri consists of a superficial layer and of a deeper layer of neuroblasts. From this basis are first developed the fifth, polymorphic or inner cell layer and the fourth, inner line of Baillarger or inner fibre layer. These laminæ rapidly attain almost to the adult depth and form a primary or "lower level" basis for the exercise of cerebral function. The third granule or middle cell layer develops next in order, and as has been seen in the description of the visuo-sensory cortex, this lamina is related in an important manner to the projection fibres for visual impressions. There is reason to believe that this association is not a peculiar one, and that the granule layer bears a similar relationship to the afferent fibres in the other projection spheres. Differentiation of the granule or third lamina is followed by the evolution of the second, pyramidal or outer cell layer, *pari passu* with which occurs a further development of the first, superficial or outer fibre layer. The last two of these layers constitute a second or "higher level" basis for the further development of cerebral function; and the degree of evolution of the second, pyramidal or outer cell layer is a direct index of the amount of general psychic capacity possessed by the individual.

Thus the fifth, polymorphic or inner cell layer deals with the lower organic and instinctive activities, and the second, pyramidal or outer cell layer with the higher psychic functions. The third, granule or middle cell layer, as will be pointed out later, deals with the reception and immediate elaboration of (? conscious) afferent impressions originating primarily in the sense organs.

The grounds on which the above description is founded have been already summarised and will be further referred to. It is, however, here desirable to briefly refer to the evidence, bearing on the subject, which has been adduced by Watson as the result of his elaborate study of the cerebral cortex of the mammalia, and which forms the complement of the writer's researches. Watson has shown that in the mammalia generally the neopallium is composed chiefly of the layers which have been referred to above as the third, granule, or middle-cell layer, the fourth, or inner-fibre layer, and the fifth, polymorphic or inner-cell layer, the second, pyramidal, or outer-cell layer being in a rudimentary condition. For convenience of description he refers to the combined fourth and fifth laminæ as the "infra-granular" portion of the cortex, and to the second lamina as the "supra-granular;" but, apart from this difference in terminology, his account of the lamination of the mammalian neopallium is a confirmation of that which was originated by the writer in the case of the human cortex cerebri.

In his recently published papers on the Insectivoræ (*Proc. Roy. Soc.*, 1905, and *Arch. Neurol.*, vol. iii, 1906) Watson has shown that the second, pyramidal, or outer-cell layer, or, as he terms it, the "supra-granular," is in a rudimentary condition, whereas the combined depth of the remaining laminæ of the cortex differs little, in the mole, for example, from that of these laminæ in the human infant. He has made a careful study of the habits of the members of the order which he has examined, and he has discussed the relationship which exists between their psychic functions and the structure of their neopallium.

Watson, in his further and as yet unpublished work, has shown that the second, pyramidal, or "supra-granular" lamina develops *pari passu* with the increasing degree of intelligence which appears in the different orders of the mammalia, and he has correlated this physical basis with the educability and general intelligence of the respective animals. For example, the "supra-granular" lamina is better developed in the Rodents than it is in the Insectivoræ; it is again better developed in the Ungulates and the Carnivores than in the Rodents; and it is strikingly more developed in the Primates than in the Carnivores. On the other hand, the "infra-granular" portion (Laminæ IV and V of the writer) is for practical purposes equally developed in all these orders.

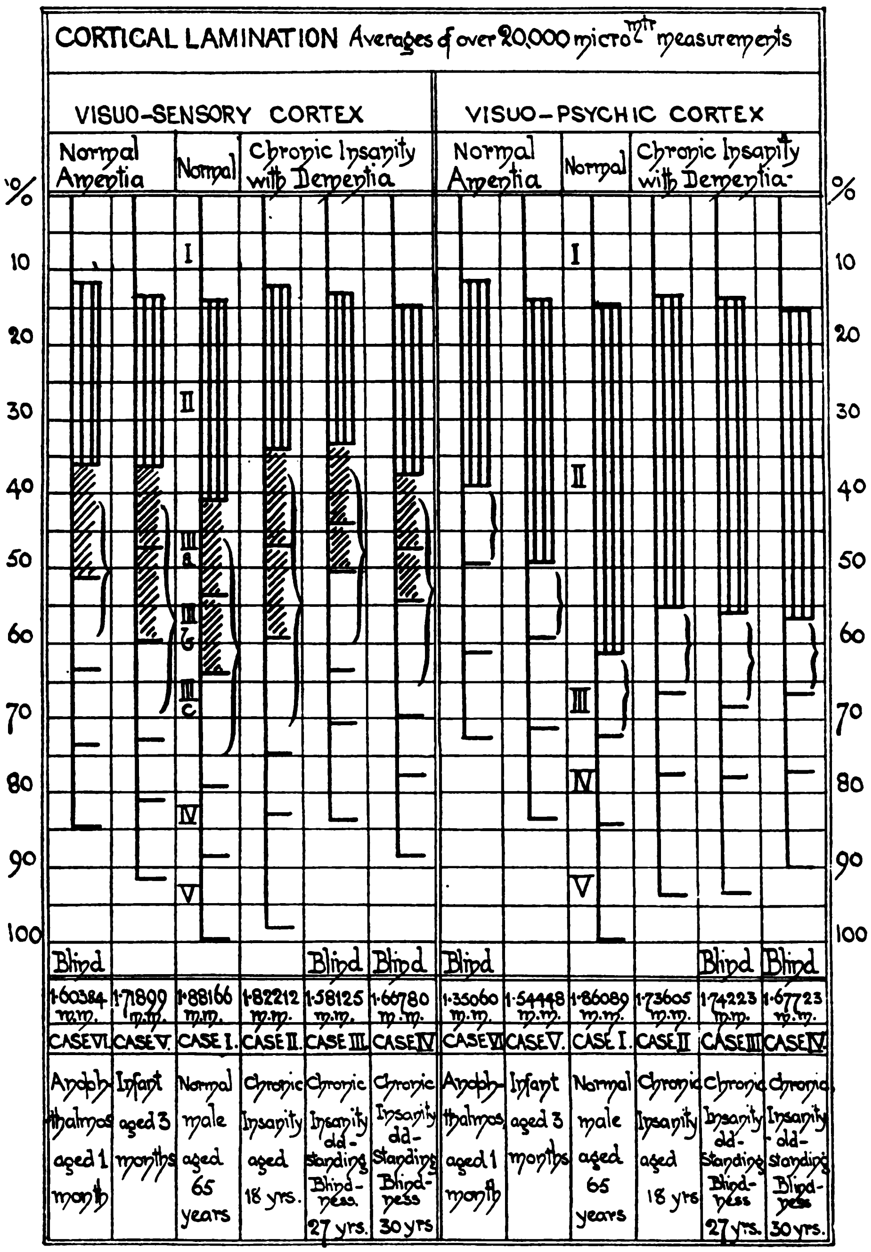
In other words, the primary or "lower-level" portion of the cortex cerebri above referred to is the only part which is fully developed in the lower orders of the mammalia, and in these it constitutes the most important cell-formation of the neopallium.

Watson, therefore, correlates the "infra-granular" portion of the neopallium with the instinctive activities in contradistinction to the educability existing in the different types of mammal.

These conclusions of Watson concerning the functional sig-

Note (Fig. 9).—The micrometer measurements on which this table is based have been already published (*Phil. Trans.*, 1900, pp. 165—222). The subdivisions from above downwards refer to the cell-layers described in the text. In the first half of the table Layers III A, III B, and III C are bracketed together, and are equivalent to Layer III in the second half, which has a bracket opposite to it. The shaded portion represents the additional "visual" layers, which are decreased in depth in long-standing blindness.

Fig. 9.



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nificance of the primary cell laminæ of the mammalian neopallium agree with, and form the complement of, those already published by the writer in the case of the human cortex cerebri.

The functional significance of the three primary cell layers of the cortex cerebri, together with the evidence on which this is based, will now be briefly summarised.

Certain of the micrometric data which the writer has obtained during the past ten years, and from which he has developed the following description, are shown in graphic form in Figs. 9 and 10, and these may be usefully referred to by the reader of the account which follows.

It may be remarked here that it was at one time the purpose of the writer to obtain more complete data concerning the age-periods of development of the cerebral cortex in fœtal life and childhood. He found, however, considerable variations in the degree of development of different cases at stated ages, and therefore, in the absence of any data as to the respective degrees of intelligence in the different cases, was unable to pursue the subject to a satisfactory conclusion. He consequently confined his studies to cases in which it was possible to co-ordinate the mental states and the micrometric data. The results which he has obtained during these investigations are so absolute as to make very definite statements possible regarding the correlation of the degree and mode of development and the functional significance of the primary cell-laminæ of the cortex cerebri.

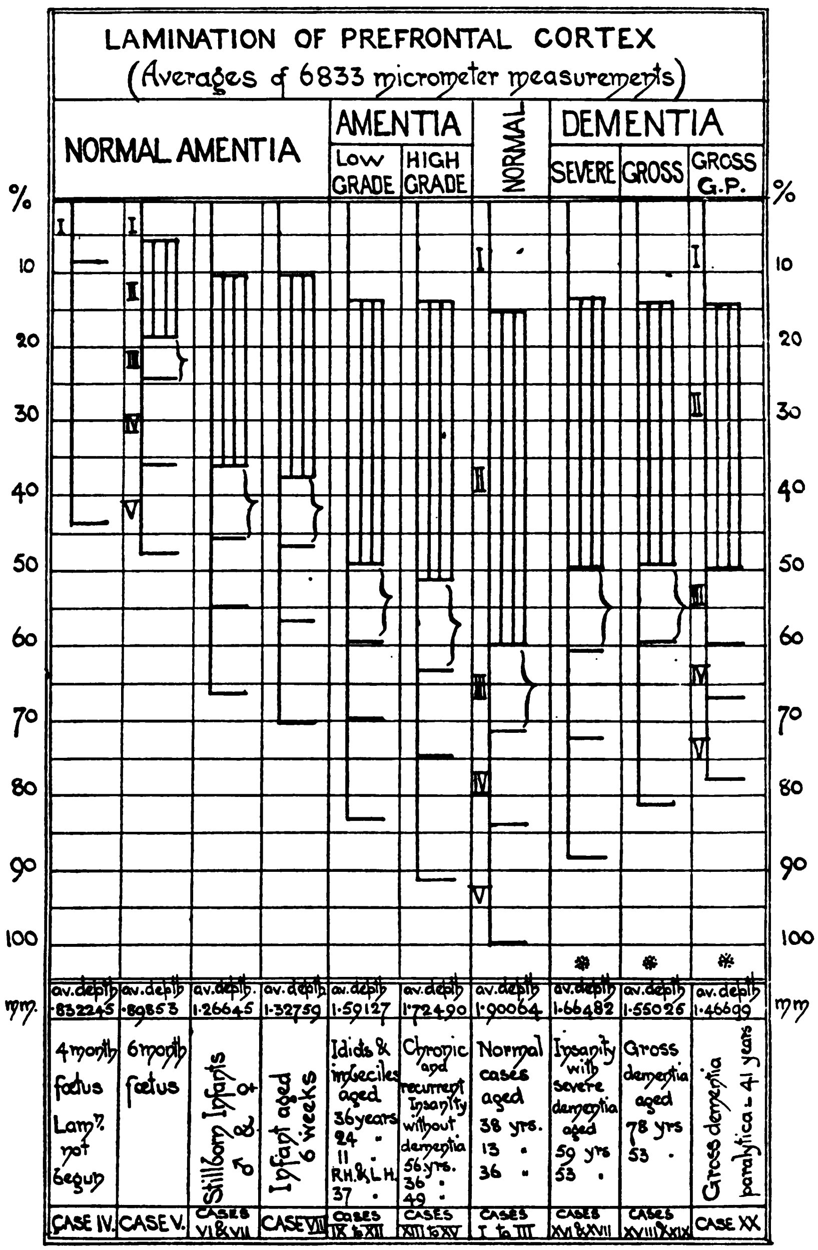
The fifth, polymorphic or inner cell layer.—This layer is the first cell-lamina of the cortex cerebri to be differentiated during the progress of lamination. In the prefrontal region of a fœtus of six months it is separated off from the rest of the cortex by the fourth or inner fibre lamina, and is already within 29 *per cent.* of the normal adult depth. In a child of six weeks it has advanced to within 18 *per cent.* of the normal adult depth.

It is of extremely constant average adult depth.

A very slight decrease in the depth of this layer exists in cases of high-grade amentia and of chronic insanity with

Note (Fig. 10).—The micrometer measurements on which this table is based have been already published (*Archives of Neurology*, vol. ii, 1903, pp. 424—620 B).
* In the first two layers of these columns, particularly the "Gross" and "Gross (G.P.)," vascular and neuroglial proliferation causes the depth to be greater than would have been the case if a formation of repair tissue had not accompanied the decay of the neurones.

FIG. 10.


LAMINATION OF PREFRONTAL CORTEX
(Averages of 6833 micrometer measurements)
NORMAL AMENTIA
AMENTIA
LOW GRADE
HIGH GRADE
NORMAL
DEMENTIA
SEVERE
GROSS
GROSS G.P.
%
10
20
30
40
50
60
70
80
90
100
mm
av. depth ·832245
av. depth ·89853
av. depth 1·26645
av. depth 1·32759
av. depth 1·59127
av. depth 1·72490
av. depth 1·90064
av. depth 1·66482
av. depth 1·55026
av. depth 1·46699
4 month foetus Lamⁿ. not begun
6 month foetus
Stillborn Infants 0+ & ♂
Infant aged 6 weeks
Idiots & imbeciles aged 36 years 24 · 11 · RH.&LH. 37 ·
Chronic and recurrent Insanity without dementia 56 yrs. 36 · 49 ·
Normal cases aged 38 yrs. 13 · 36 ·
Insanity with severe dementia aged 59 yrs 53 ·
Gross dementia aged 78 yrs 53 ·
Gross dementia paralytica - 41 years
CASE IV.
CASE V.
CASES VI & VII
CASE VIII
CASES IX to XII
CASES XIII to XV
CASES I to III
CASES XVI & XVII
CASES XVIII & XIX
CASE XX

moderate dementia. A considerable decrease, on the other hand, exists in more marked aments (whether normal aments or idiots and imbeciles), and in gross dements who are unable to carry on the ordinary animal functions, such as attending to their own wants, etc.

As has been shown by Watson, the "infra-granular" region contains the important cell-layers of the neopallium of the lower mammalia, and is very little inferior in depth to the normal adult human depth of the conjoined fourth and fifth laminæ.

The fifth, polymorphic or inner cell layer, therefore, in association with the fourth or inner fibre layer, subserves the lower voluntary and instinctive activities of the animal economy, and thus forms a lower level basis for the carrying on of cerebral function.

The third, granule or middle cell layer.—This layer is developed after the fifth, polymorphic or inner cell layer, and before the second, pyramidal or outer cell layer. In the prefrontal region of a fœtus of six months it has just become differentiated, by commencing specialisation of its constituent cells, from the superjacent second or outer cell layer, and it is already one half of the normal adult depth. In a child at birth it has become three fourths (73 *per cent.*) of the normal adult depth.

In the visuo-sensory area the optic radiations end in the midst of a hypertrophied and duplicated third or granule layer. The duplication is due to the interposition in the midst of the hypertrophied third or granule layer of a well-marked fibre band, the line of Gennari, which fibre-band, as has already been stated, is a hypertrophy of the outer of the two horizontal inter-radiary fibre plexuses of the adult cortex, namely, the "outer line of Baillarger." In old-standing or congenital optic atrophy the outer (and additional) of the granule layers is decreased in thickness by more than 10 *per cent.* and the line of Gennari is decreased in thickness by nearly 50 *per cent.*

As has been pointed out by Watson, a hypertrophied third, granule or middle cell layer appears to be characteristic of the projection areas of the cerebrum. In the case of the visuo-sensory area (visual projection sphere) the third or granule layer first becomes definitely duplicated in the order Primates, though slight indications of duplication occur in the higher Carnivores.

The third, granule or middle cell layer, therefore, primarily sub-

serves the reception or immediate transformation of afferent impressions, whether these arrive directly from the lower sensory neurones, or indirectly through other regions of the cerebrum.

The second, pyramidal or outer cell layer.—The data which have been advanced by the writer with reference to the functions of this layer will be considered under the regions of the cortex cerebri from which they have been derived, namely, the prefrontal, the visuo-psychic, and the visuo-sensory areas.

(*a*) *The prefrontal region.*—The pyramidal or outer cell layer is the last layer of the cortex cerebri to develop. It is visible owing to the undifferentiated condition of its constituent elements in a fœtus of six months, and is at this time only one quarter of the normal adult depth. In infants at birth and at the age of six weeks it is still less than two thirds of the normal adult depth.

It is the only cell layer of the cortex cerebri which varies definitely in depth in normal brains.

It is under-developed to different degrees, not only in idiots and imbeciles, in the severer grades of which its depth is only two thirds of the adult normal, but also, and here to a lesser extent, in chronic and recurrent lunatics without dementia. The degree of its retrogression in demented patients varies directly, and to an equally marked degree as its subdevelopment in the case of amentia, with the amount of dementia existing in the respective cases.

(*β*) *The visuo-psychic region.*—The second, pyramidal or outer cell layer develops earlier in this region than in the prefrontal. In infants of one and three months it is respectively nearly two thirds and more than three quarters of the normal adult depth.

It reaches practically the same adult depth as in the prefrontal region.

It does not vary in depth according to the degree of dementia existing in the patients, though a small and practically constant decrease in depth, which may be due to either subdevelopment or retrogression, is evident in such cases.

(*γ*) *The visuo-sensory region.*—The second, pyramidal or outer cell layer develops much earlier in this area than in the visuo-psychic and prefrontal region. In infants of one and three months respectively its depth is already 84 *per cent.* of the adult normal.

In the normal adult this cell layer in the visuo-sensory area is only about five ninths of its depth in the visuo-psychic and prefrontal regions of the cerebral cortex.

The second, pyramidal or outer cell layer of the cortex cerebri therefore subserves the "psychic" or associational functions of the cerebrum. These functions are pre-eminent in the prefrontal region, they are less important in the visuo-psychic region, and they are of least importance in the visuo-sensory region. These three areas are, therefore, of different grades in the hierarchy of cerebral function.

The second, pyramidal or outer cell layer, in association with the first, superficial or outer fibre layer, thus forms a "higher level" basis for the carrying on of cerebral function. It is superadded on a "lower level" basis, consisting of the fifth, polymorphic or inner cell layer and the fourth or inner fibre layer, which subserves the lower voluntary and instinctive activities of the animal economy.

As a complement to the above facts concerning the regional variations in, and the development and retrogression of, the second, pyramidal or outer cell layer of the human cortex cerebri, and its functional significance, the writer will now draw attention to the data concerning this layer which have so far been obtained by Watson during his histological investigation of the mammalian neopallium. He finds that in the Insectivora the pyramidal or outer cell layer is in a rudimentary condition, though the lower layers of the cortex approximate to the normal human adult depth. Further, the pyramidal or outer cell layer is better developed in the Rodents than in the Insectivores; it is, again, better developed in the Ungulates and the Carnivores than in the Rodents, and it is strikingly more developed in the Primates than in the Carnivores.

He therefore functionally correlates this layer with the educability and general intelligence which appear in an increasing degree during the ascent of the mammalian scale.

(IV) SUMMARISED EVIDENCE BEARING ON THE FUNCTIONAL REGIONS OF THE CEREBRUM AND ON THE GENERAL PATHOLOGY OF MENTAL DISEASE.

The evidence which has been briefly detailed in the preceding pages will now be summarised in order to demonstrate its bearing on the geography of the cortex cerebri in relation to function, and on the general pathology of mental disease.

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 cases of mental disease varies directly with the degree of dementia present, and that this wasting has its maximum focus in the prefrontal region of the cortex cerebri.

Still more detailed and positive results have, however, followed his study of the general histology of the cortex cerebri by the micrometric method. The pyramidal or outer cell layer increases in depth *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, or outer cell 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 five ninths of the depth of this layer in the centres of association.

In the visuo-psychic area the pyramidal or outer cell layer develops earlier than, but attains the same adult depth as, in the prefrontal region. The layer decreases in depth in dementia, but this decrease is small and constant, and does not vary with the grade of dementia.

Further, in the prefrontal region, in the different types of mental alienation, grading from the idiot to the chronic and recurrent lunatic without dementia, the pyramidal or outer cell layer exhibits degrees of under-development, which vary inversely with the mental power of the individual. In this region the pyramidal, or outer cell layer is the only layer of the cortex cerebri which varies appreciably in depth in normal individuals. Finally, in dementia (which term is used to connote the mental condition of patients who suffer from permanent psychic disability due to neuronic degeneration following insufficient durability) the amount of thinning of the pyramidal or outer cell layer in the prefrontal region varies directly with the degree of dementia present.

Hence, throughout the regions of the cortex cerebri which have been examined by the writer the cellular elements which are especially concerned with the performance of associational functions are those of the pyramidal or outer cell layer.

This associational function of the cerebrum is pre-eminent in the prefrontal region, it is less marked in the visuo-psychic region (a posterior centre as association), and it is least of all evident in the visuo-sensory area (a centre of projection). There are therefore three grades in the hierarchy of cerebral function, namely:

(1) *Projection spheres*, or regions to which afferent sensorial impressions pass from the parts of the body devoted to the appreciation of the types of specialised sensation, namely, vision, hearing,* bodily sensibility, smell, and taste.

* The writer is of opinion, as will be seen from the following excerpt from a previous paper, that the projection area for bodily sensibility lies in an at present undefined region of the cortex behind the furrow of Rolando, and that the "excito-motor" area is the centre of lower association in relation with this. "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-psychic 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 psychomotor area as now mapped out. 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 psychomotor area would be homologous with one causing word-blindness or word-deafness, etc.; in other words, this area would be the lower association 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" (*Brain*, Summer, 1903). The practical absence of a granule or middle cell layer from the psychomotor area, and the high development of this layer in the post-central region, accord with this view of the functional significance of these regions. Further, amongst others, Tschemak's experimental studies on the cat, and Campbell's recently published histological investigations, are both in favour of the existence, behind the psychomotor area, of a projection sphere for bodily sensibility.

(2) *Centres of lower association*, which lie in the immediate neighbourhood of each of the areas included in the first group, and which subserve the elaboration of the different varieties of sensorial impression into simple perceptions and the association of these psychic units into higher complexes.

(3) *The centre of higher association and co-ordination* in the prefrontal region, which subserves the grouping of these higher complexes into harmonious series of concepts by means of voluntary attention and selection. This region of the cortex cerebri is thus concerned with the performance of the higher processes of mind.

Though it is not the purpose of the writer to describe in detail the differences in degree of development and in structure which exist between the cerebrum of man and those of the anthropoid primates, it is desirable to indicate here briefly the chief of these. It consists in the immense development of the anterior and posterior zones of association which has occurred in the human brain. Concurrently with this increase in the extent of the great zones of association there has developed in man the power of abstract thought and the employment for this purpose of highly complex articulate and written language. As the centres of lower association in the anthropoid primates differ from those of man in extent and complexity, so do the percepts of the former differ from the highly complex lower psychic units of the latter. Equally does the rudimentary prefrontal region of the anthropoid primates, which imperfectly marshals the relatively simple lower psychic units of these animals, differ from the existing and still developing prefrontal lobe of man, the capacity of which for co-ordinating the infinitely complex lower psychic units, which are compounded in the human mind, into harmonious series of concepts by means of voluntary attention and selection, is only limited by the degree of functional development of this lobe in any particular individual of the race. The lower associational centres of man, which represent the physical basis of the content of mind, are thus co-ordinate in development with the centre of higher association and co-ordination, which represents the physical basis of the capacity

The writer would add, as his excuse for intruding the above remarks, that the delimitation of the excitomotor area by Sherrington and Grünbaum to a region lying entirely in front of the fissure of Rolando has necessarily reopened the vexed question of the significance of the "motor" area of the cortex, and thereby brought into prominence many investigations the results of which did not accord with the sensorimotor doctrine and area.

to voluntarily group into a harmonious and connected sequence the higher psychic units of the mind.

The latest-developed and most important portion of the grey mantle of the human cerebrum, namely, the prefrontal area, is the region which is especially affected in the subjects of mental disease.

In the conception of the general pathology of mental alienation, to the elaboration of which this paper is devoted, no hard-and-fast line is drawn between sanity and insanity. On the one side of the normal all degrees of subnormal mental power exist without any gap, from the intelligence possessed by the lowest example of low-grade amentia, though that existing in the different types of low- and high-grade amentia, directly up to that of the normal "sane," who individually vary considerably in mental capacity. On the other hand, all degrees of loss of mental power exist from the stereotypism of mental processes in many normal individuals, down through all grades of dementia from the mildest degree in some "sane" persons to the severest grade in the gross dement.

Insanity, from this point of view, is neither an obscure entity which attacks at random certain unfortunate members of an otherwise sane stock, nor a disease of the cerebrum of microbic, or at any rate toxic, origin, which might be cured or prevented by some method of sanitary or preventive medicine.

The *potential* lunatic (and the actual low-grade ament) is born, not made. The *actual* lunatic is an individual who is temporarily or permanently so out of accord with the environment of the sane as to require segregation, owing either to his inherent inability to cerebrate normally under the "stress" to which the cerebra of the civilised sane are without injury subject, or to the development of cerebral dissolution and dementia under its influence.

Mental disease, thus interpreted, becomes a unit under a fundamental natural law, that of arrest and decay of vital structures; the mind is as young or as old as the brain. The high-grade ament is a man who is required to do a man's work with a child-brain; the dement is a man unable to do a man's work with a (prematurely) worn-out brain. The former may fail and try again; the latter has tried for the last and perhaps also the first time and has failed.

This conception of the general pathology of mental disease

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being accepted, the writer hopes that future research will result in the elaboration of a special pathology for the various types and degrees of amentia and dementia.

It is probable that, in most cases of insanity, not only is the capacity for the performance of higher associative and co-ordinative functions deficient, but the carrying on of these is hampered by the existence of aberrant (normally or subnormally) types and grades of lower associational processes, and even in some cases of an aberrant or imperfect capacity for the appreciation of primary sensorial impressions. As possible examples of the latter may be cited the occurrence of illusions and hallucinations, and of the former the development of delusions by aberrant ideational processes founded on false or imperfectly appreciated premisses.

That the elaboration of a special pathology is possible for at any rate some of the types of mental disease the writer is convinced, though he does not suggest that the elucidation of a physical basis for such symptom-complexes as those of "mania" and "melancholia" could be carried out by any methods at the command of the morbid anatomist or histologist. For example, he has formed the opinion from his *post-mortem* experience in different parts of the country that the convolutional pattern and general cerebral development are on the whole less highly evolved in the emotional types of high-grade amentia than in the classes of "cranks and asylum curiosities," and of "systematised delusional cases." Further, considering the subject from a more extended point of view, he is of opinion that a relatively larger proportion of small and simply convoluted cerebra occur in certain rural and agricultural districts than are found amongst the mixed lunatics of the metropolis, and that a relatively larger proportion of such cerebra exists amongst the latter than is seen in the insane belonging to certain of the larger northern centres of population. In clinical agreement with this opinion are the undoubted truths that the delusional types which constitute the higher grades of amentia are more common in the second of the classes referred to than in either of the others, and that dementia of all types and grades, unfortunately too often precipitated by alcoholic excess, is most common in the last and least common in the first of these classes.

Reply to a Criticism of the Writer's Researches by Dr. Campbell in his "Histological Studies on the Localisation of Cerebral Function."

Whilst it is the duty and the privilege of scientific investigators to correlate their own conclusions with those already published, to make full use of the researches and results of other workers, and where necessary to criticise and correct such results, there are certain hard-and-fast lines beyond which such criticism becomes unfair and even discourteous. Dr. Campbell in his recently published book has, in the opinion of the writer, transgressed the rules of fair criticism to such an extent as to compel him, in justice to his own work, to make a public reply and remonstrance.

Owing to the direct bearing of Dr. Campbell's remarks on the subject which has just been considered, the writer hopes to receive pardon for the unusual course which he is adopting in defending his researches through the medium of a scientific communication.

Dr. Campbell has produced a book which in some respects is unique. For the fisrt time an attempt has been made by modern methods to map out the entire cortex cerebri according to the differences in histological structure which exist in its several regions; and this attempt has, from the general aspect, been successful. Dr. Campbell has done good work, from a comparative point of view, in that he has applied the same histological methods to the whole of the cortex cerebri, and though the greater part of his research has resulted in a confirmation of the conclusions arrived at by previous investigators, his patient industry and the success which has crowned his efforts are worthy of all commendation.

This is not the place for a criticism of his individual descriptions of histological structure or of the methods which he has adopted, and therefore only such reference will be made to these as is necessitated by the purpose the writer has in view.

It is proposed to refer here to two chapters only—those dealing with the "visuo-sensory and visuo-psychic areas" and with the "frontal and prefrontal areas," as these chapters contain the criticism to which reference has been made.

In a paper which was published in the year 1900 in the *Philosophical Transactions of the Royal Society*, the writer defined

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by histological methods a cortical area, which he described as the "visuo-sensory area." This area was mapped out minutely in six hemispheres, two of which were obtained from cases of long-standing blindness, and one of which was from a case of anophthalmos. As the result of an extensive micrometric examination of the whole of the cortex contained in this region, as well as of the surrounding cortex, he was able to prove that the area above referred to was the visual projection centre. The surrounding and differently specialised cortex in which old-standing optic atrophy causes no modification of the lamination was described by him under the term "visuo-psychic." This investigation was an extensive one, and required nearly four years for its completion. The writer, in fact, found it necessary to divide each occipital lobe into nearly as many separate blocks as Dr. Campbell appears to have divided a whole hemisphere, and he therefore cordially endorses this author's remark, that "the occipital lobe is of such an awkward shape that it is almost impossible to divide it into a series of sections, all of which will show the cortex cut at right angles to the plane surface and free from the damaging effect of obliquity."

In view of the *proof* which the writer adduced that the region referred to was not merely a special cortical area but was also the visual projection centre or "visuo-sensory area," it is somewhat surprising to find the following statements in Dr. Campbell's monograph: "Examining in serial sections the occipital lobes of the brains of five cases of old-standing total blindness and one of anophthalmos, and using as a criterion the atrophy and disappearance of certain nerve-cell and fibre elements, Dr. Bolton was able to map out with the greatest distinctness, an area which corresponds in all important respects with that which clinico-pathological, developmental, and experimental researches have indicated as the visuo-sensory area.

"It will be unnecessary for me to describe the limits of the area defined by Dr. Bolton, for on referring to his diagrams and descriptions it may be found that if I did so I should merely reiterate what I have said already regarding the limits of my visuo-sensory area, but as we agree that the area over which the line of Gennari is distributed represents the cortical visuo-sensory centre, it obviously follows that it is unnecessary to resort to pathological material for a definition of the field, and as a matter of fact it can be determined in a normal brain even without the aid of a microscope."

The writer can only conclude that Dr. Campbell has not carefully read the paper, in view of the fact that he seems to think that the investigation was restricted to cases of blindness and was confined to a mere delimitation of the cortical area referred to. This area can readily be defined by the naked eye, but the writer would emphasize the point that such a definition *proves* nothing regarding the functions of the area.

Dr. Campbell's histological studies have enabled him to more or less definitely map out several cortical areas, but on what rests the proof of their functions? Not on Dr. Campbell's work, but on the observations of previous investigators. In spite of his apparent obtuseness to the difference between histological delimitation and proof of function, Dr. Campbell has himself, in fact, endeavoured to adduce proof of the functions of the pre-central and post-central convolutions by the examination of cases of amputation and of tabes dorsalis respectively.

The sentence, "It will be unnecessary for me to describe the limits of the area defined by Dr. Bolton, for, on referring to his diagrams and descriptions, it may be found that if I did so I should merely reiterate what I have said already regarding the limits of my visuo-sensory area," is a somewhat quaint mode of putting the cart before the horse, and this is not the only instance in the monograph of an inversion in order of time.

The writer has thought it desirable in common fairness to make the above reference to the chapter dealing with the visual region of the cortex, though the extracts he has cited caused him amusement rather than annoyance.

Dr. Campbell's remarks concerning the writer's work on the prefrontal region, however, distinctly pass the limits of fair criticism. These will now be briefly considered.

The section in the monograph which deals with "histological data" concerning the "frontal and prefrontal" areas consists, except for a few lines, entirely of a criticism of the investigations carried out independently by the writer and Schäfer, and concludes with the following warning:

"I have digressed more than I intended to discuss these conclusions of Bolton and Schäfer, but I have felt that it was important to take more than a passing notice of them, because they might be converted into unsound capital by those, unpractised in histological research, who are investigating the functions of the brain and particularly those of the frontal lobe."

The writer does not propose to reply, as he might justifiably do, by warning his readers against Dr. Campbell's researches, but prefers rather to consider seriously this author's chief criticisms and statements. Amongst the latter is the following sentence:

"Without for a moment discrediting the accuracy of Bolton's observations, and while admiring the work for the care bestowed on it, I must, nevertheless, say that his arguments seem to rest on frail premisses."

This remark appears from what follows to mean that Dr. Campbell does not question the accuracy of the writer's observations regarding the morbid anatomy of dementia, but that he objects to the deductions drawn from these. Dr. Campbell appears to think (1) that the regions in which wasting is visible in cases of dementia have no bearing on the functional significance of the parts wasted; (2) that the wasting in dementia, or at any rate in dementia paralytica (general paralysis) is due to a morbid process affecting all parts of the cerebrum equally; (3) that the parts of the cerebrum which show the most wasting really do so because they are built up "with attenuated and collapsible radiations and an interradiary network untraversed by strong fibres"; and (4) that wasting in the regions stated may be assisted by "physical disease, causing general body emaciation," "the nutritional supply of the brain, and the influence of gravity."

Before considering this criticism of his conclusions, the writer proposes to join issue with Dr. Campbell on two important subjects, the cell and fibre structure of the prefrontal region, and the regional distribution of the morbid process in general paralysis. Dr. Campbell appears to shelve the distribution of the lesion in dementia and leaves the reader to infer either that it is unknown or that it is the same as occurs in general paralysis, namely "ubiquitous."

As the former of these subjects has been fully referred to on pp. 240–250, it is unnecessary here to do more than remark that the writer directly negatives the views expressed in the following paragraph:

"(5) The structural development of the prefrontal cortex is exceedingly low. It presents an extreme of fibre poverty; all its fibre elements are of delicate calibre, and its association system is particularly deficient. Its cell representation is on a similar scale. The cortex is also shallow."

With reference to the distribution of the morbid process in general paralysis, Dr. Campbell states:

"Indeed, in the dementia of general paralysis, one of the conditions which he (*i.e.*, the writer of the present paper) has selected for study, we have very good reasons for supposing that the morbid process has a tendency to be ubiquitous, and yet in given cases of this disease in which our microscopic examination proves the universality of the cortical affection, we might still be correct in describing the prefrontal region, etc., as the parts which to the naked eye exhibit most atrophy, and the same might apply to ordinary forms of dementia."

The writer has arrived at very different conclusions regarding the distribution of the morbid process in this disease. He has shown that the centres of association are more severely affected than are those of projection, and that the prefrontal centre of association is by far the most severely affected region of the cerebrum. He would add that a similar remark applies to the distribution of the lesion in dementia. In other words, in cerebral dissolution the order of retrogression is the reverse of the order of evolution. For reasons of space he refers any interested reader to his previous papers for a description of his researches regarding the pathology of dementia paralytica, and also to the papers of Watson and of Schaffer, both of whom have independently arrived at similar results to his own.

Turning now to the warning and criticism, the writer would point out that, as in the case of the visual area, so here Dr. Campbell seems to be unaware of the extent and minuteness of his researches concerning the correlation between the mental conditions and the macroscopic and microscopic appearances of amentia and dementia. That Dr. Campbell's theoretical objections have no substantial basis in the case of dementia is proved by the fact that the writer has obtained corresponding histological results in the case of amentia, in which macroscopic morbid appearances are not present, and to which, therefore, such objections do not apply. As the writer's researches are available in a summarised form in the present communication, it is unnecessary here to make further reference to them.

With regard to the question of cortical architecture, Dr. Campbell is unaware of the complexity and delicacy of the fibre structure of the prefrontal region, as the method which he has adopted has not enabled him to demonstrate it. Dr. Campbell has therefore not appreciated the significance of the evidence on which the writer has demonstrated that this region of the cortex cerebri is well developed and extremely complex in structure, and is the latest part of the cerebrum to be evolved, the highest in function, and the first to undergo dissolution—in other words, that it is not a cortical area with a possible future, but one with an actual and important present and a certain future.

In summary, the writer considers that Dr. Campbell's warning against his work is discourteous in the extreme; that his criticism is unfair in that he has obviously not read the papers carefully, if at all; and that his objections are baseless and are due to his lack of knowledge of the clinical and pathological evidence on which the conclusions are founded. He also joins issue with Dr. Campbell regarding the histology of the prefrontal region by directly denying the alleged poverty of structure of this part of the cerebrum, and by advancing photographic proof of its cell and fibre wealth. He regrets that Dr. Campbell should have so overrated his own personal investigation, which from a general point of view is of great value, as to claim the right, as the result of a relatively coarse and wholesale method of examination of the entire cerebrum, to warn his readers against the researches of another worker, which are more limited in scope, have occupied a longer time for even their partial completion, and are more elaborate in method and detail than his own.

(*To be continued.*)