

# Johnson Symington (1851–1924)

President of the Ulster Medical Society

1896–97

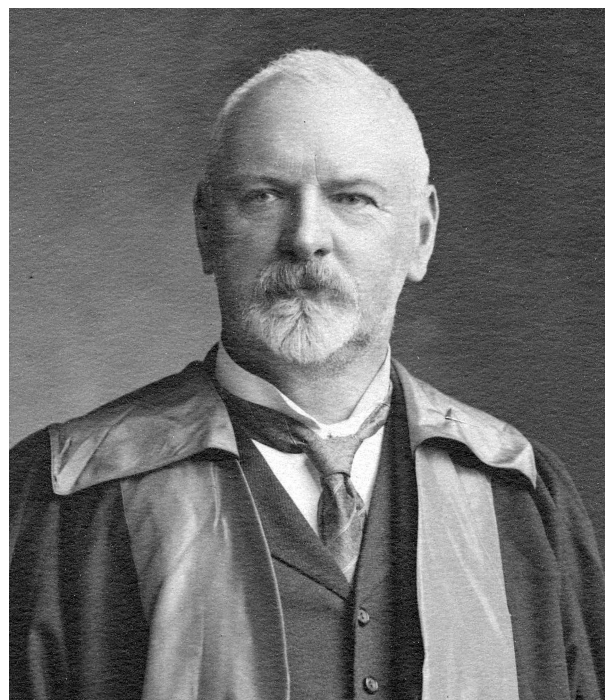
**Presidential Opening Address**  
Ulster Medical Society  
5th November 1896

Ladies and Gentlemen, My first desire on entering upon the duties of President of the Ulster Medical Society, is to offer its members my warmest thanks for the great honour they have conferred upon me in electing me to this important position.

When our genial and energetic Secretary asked me to allow my name to be proposed as your President for this Session and assured me that it was the desire, not only of the Council of the Society, but also of the members generally, that I should accept the office, I could not but feel gratified at such a marked expression of confidence and esteem on the part of my professional brethren.

It is only three years since I came to Belfast an entire stranger to almost every member of your Society. I am not a practitioner, either general or special, and cannot like my predecessors in this position, bring to bear upon your discussions and deliberations the knowledge acquired by an extensive experience of the clinical aspects of disease. My personal claims to the honour are of the slenderest. Even my association with the Queen's College did not appear to me to explain your choice, as within the last three years two members of its teaching staff have occupied the Presidential Chair, and the warmest partisan of our College could not say that this Institution had been neglected. I accepted your generous offer as a compliment to the subject I have the honour to teach, and regarded your invitation as a proof of your sympathy with, and interest in, the purely scientific departments of medicine.

I have selected as the subject of my address this evening, a review of some of the recent advances in our knowledge of the structure and functions of the cerebral cortex. This theme appears to me to fulfil two important, if not essential conditions, which ought to be observed in choosing a topic for a Presidential Address, in that it deals with problems of special interest to every member of the Society, while at the same time it lies within the province of the speaker's special work. If man be held to be the highest evolution and the crowning glory of organic



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nature that claim rests upon the enormous development and complexity of his higher nerve centres. It is unnecessary in addressing a medical audience that I should insist upon the importance of the cortex as a regulator and controller of every function of the body. The influence of the mind, or in other words, the mental cortex, upon all the ordinary physiological actions of the body is a matter of every day experience to all of us, and this age of almost universal mental strain and worry is one in which no physician can afford to overlook its wide and varied actions.

The problems that confront neurologists in their investigations on the Anatomy, Physiology, and Pathology of the higher nerve centres are of extreme complexity, and their solution is attended with special difficulties. Fortunately, however, these problems have during the last 50 years engaged the attention of a large army of able investigators, and the successes they have gained and the scientific interest and the practical importance of the subject are still attracting workers in every civilized country.

In the course of one brief address I cannot hope to do more than deal with a few of the many interesting points connected with the cortex; I shall

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therefore, confine my remarks to some features in its structure and connections which have recently engaged the attention of various anatomists and which seem destined to extend our knowledge of cerebral physiology and pathology.

The key to a correct appreciation of the action of the cerebral cortex lies in a knowledge of the relations of its nerve cells with one another and with other parts of the body. Within the last few years numerous important contributions have appeared on this subject in the departments of pure histology, embryology, and comparative morphology. To properly appreciate the value of much of the recent work, let us briefly review some of the earlier observations. It is obvious that one of the first points in cortical anatomy that had to be determined was whether or not the numerous and complicated cerebral fissures and convolutions of the adult human brain were arranged in any regular manner; yet it was not until some time after the beginning of the present century that anatomists set themselves seriously to the study of this question. Until then the general neglect of the use of hardening reagents and the ignorance both of the development of the brain in the human foetus and of the comparative anatomy of the primate brain had caused anatomists to look upon the cerebral convolutions as quite destitute of any regular order or arrangement. Time will not permit even a brief review of the gradual discovery of the morphological significance of the various fissures and convolutions. Suffice it to say that the knowledge we now possess was gained, not merely by the examination of the surface of the adult human cortex, but very largely by a study of the gradual evolution of its complicated form from a primitive smooth surface as seen in the developing human foetus and in a comparative study of the primate brain. By these means, not only were the convolutions shown to possess a remarkably regular arrangement, but the relative importance of the numerous sulci and gyri was determined. These researches rendered possible the brilliant discoveries of the localization of motor functions in definite regions of the cortex with which the names of Broca, Hitzig and Fritsch, Ferrier, and numerous other investigators are associated. The practical application of the knowledge gained by these morphological studies and physiological experiments to the accurate diagnosis and successful treatment of cortical lesions is one of many debts that suffering humanity owes to science. It must be confessed that while the knowledge gained by the careful and elaborate study of the development and comparative anatomy of the surface form of the

cerebral cortex has laid a solid foundation for future work, and has been of the highest practical utility, yet it has not directly thrown that amount of light on its functions that might have been anticipated.

It is true that an extended series of observations of the cerebrum in the mammalia generally has led anatomists to recognise certain fissures as separating an area devoted to the reception of olfactory stimuli from the rest of the cortex, so that the terms rhinencephalon and pallium possess a certain physiological as well as a morphological significance. The morphological sub-divisions of the pallium generally accepted at present by anatomists do not, however, correspond to any known functional localisation. We admit that the centres in the pallium for common sensibility, sight and hearing, are related respectively to the central, calcarine, and sylvian fissures, but the connection between these sensory areas and fissures is too ill defined and indefinite to be of much significance. It must be acknowledged that the cerebral fissures do not bound definite physiological areas, nor do they constitute centres around which these areas are definitely grouped, although, speaking generally, the appearance of convolutions on a primitively smooth brain, or an increase in the complexity of convolutions already existing, must be regarded as an evidence of increase of function. In the small members of any particular class of animals the brain is usually smooth, but in those of larger size it is convoluted. It is evident that there must be a definite relation between the amount of superficial grey matter and the subjacent white matter, since the cells of the cortex are represented by their processes in the subcortical white mass. Baillarger and Jelgersma have explained the forces at work in producing a folding of the surface, when additional grey matter is developed by the well-known mathematical law that in the growth of a body the surface increases with the second, but the interior with the third power of the radius. This law does not explain the characteristic arrangement of the folds found in certain groups of animals. Numerous theories have been advanced to account for the position of the fissures and the direction of the convolutions in the various orders of the mammalia, but hitherto with only a limited amount of success. While much work still remains to be done before the morphological studies based on a comparison of the cerebral surface in the primates and the developing and adult human subject are completed, other methods of research are now being eagerly pursued with great success by a host of able investigators. I refer more particularly to the study of

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the structure and connections of the nerve cells by the chrome-silver method of Golgi, and the determination of the relation of the different parts of the cortex with one another, and with more distant parts by ascertaining the order of the medullation of the various strands of white matter by the method of Weigert and its modifications. If observers, confining their attention solely to the adult human brain, failed to recognise a definite order in the arrangement of the cerebral fissures and convolutions, how much less likely was its infinitely more complex internal structure to be unravelled without the aid of comparative and embryological studies. The evolution of the vertebrate brain is not a history of continuous and uninterrupted increase in complexity of all its parts. While certain portions are the centres of active growth, others retain their primitively simple condition; and structures after gaining a comparatively high position in the central nervous system may remain practically stationary, or even undergo marked atrophy. Hence comparative anatomy not only enables us to see, stage by stage, the formation of highly developed parts, but also to appreciate the significance of rudimentary and degenerated structures.

In one of the lowest vertebrata – the amphioxus lanceolatus, the brain can only with difficulty be differentiated from the spinal cord. In all other vertebrata, however, the developing brain is distinguished by the presence in the anterior part of the neural tube of three saccular dilatations termed the anterior, middle and posterior cerebral vesicles. Further the anterior of these vesicles develops at its fore part a process, which soon becomes divided by a medium infolding into two lateral halves, the cerebral hemispheres or prosencephalon. Each hemisphere may be regarded as a somewhat oval vesicle the ventral wall of which thickens posteriorly and becomes the corpus striatum and in front of this gives rise to the olfactory lobe, while the roof and lateral walls of the hemisphere form the pallium. This pallium, which in the human subject attains relatively such enormous dimensions extending forwards and backwards so as to cover on their dorsal aspect all the other parts of the brain, is composed in the bony fishes of a single layer of epithelial cells and is quite destitute of nervous elements.

As you may readily imagine the numerous stages by which this simple pallium has attained the size and complexity which it possesses in the higher mammalia are as yet only partially known, still many points of great interest have been discovered. In the Elasmobranch fishes the anterior part of the pallium

thickens and contains a few scattered nerve cells. In the Amphibia this thickening extends considerably farther back, but it is not until we come to the Reptilia that we meet with a well defined cortex, hence these animals form a group in which the comparative simplicity of cortical structure affords a favourable field for ascertaining the precise structure and relations of the cerebral hemispheres in an early stage of their evolution. Important contributions on this subject have been made by Edinger, Meyer, C. L. Herrick, Brill, Koppen, Rabl-Ruckhardt, and the brothers Pedro and Santiago Ramon y Cajal. Amongst these authors I must express my special indebtedness in the preparation of this address to my friend Prof. Ludwig Edinger not only for his various monographs on the reptilian brain, but also for his "Vorlesungen über den Bau der nervösen Centralorgane" the last (5th) edition of which contains a masterly review of the present state of our knowledge regarding the phylogeny of the vertebrate brain.

I cannot attempt even to summarize the numerous points that have been determined regarding the anatomy of the reptilian fore-brain, but there are a few features of outstanding importance to which I must briefly allude.

It has been clearly established that the fore-brain in the reptilia is almost entirely devoted to the sense of smell, and that this is the first of the special senses with which the cortex in its evolution becomes associated. Thus not only the olfactory bulb, but also a large surface (area olfactoria) at the base of the cerebral hemisphere are connected with olfactory fibres. Further, a large number of nerve fibres spring from the area olfactoria and end in the dorso-median part of the pallium. These form the principal connection between the cortex and other parts of the brain. There are also fibres passing from the olfactory lobe directly to the cortex. It is worthy of notice that every part of the fore-brain connected with the sense of smell is united with corresponding areas in the other hemisphere by the so-called commissural fibres. Edinger believes that he has detected a small bundle of fibres passing from the optic lobe to the pallium so that the reptilia probably possess a rudimentary cortical centre for sight. There is also a small tract connecting the frontal part of the pallium with the optic thalamus. This tract represents the highly developed thalamo cortical-radiation of mammals. Thus even the lowly organized reptilian brain shows a great wealth of possible association paths between the various parts of its cortex.

The method introduced by Golgi for staining nerve cells has revealed a complexity in the branching

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processes of the pyramidal nerve cells of the human cortex of which the older methods gave only a faint indication. Further, comparative researches by Ramon y Cajal, Edinger, and others have shown that these pyramidal cells possess a comparatively simple structure in those animals in which the pallium is rudimentary, and that with the growth of the cortex generally there has been a corresponding increase in the size and complexity of the individual nerve cells. This is very strikingly shown in the drawings that Ramon y Cajal has given of these pyramidal cells in the frog, lizard, mouse, and man.

If we examine one of these cells from the human adult brain we see that from the base of the cell there springs an axis-cylinder process, which passes into the subjacent white matter, and in its course through the grey matter gives off at irregular intervals fine collateral branches, and these, after branching two or three times, end in free processes. From the apex of the pyramid a long thick process extends to the free surface, near which it ends in numerous branches, which form, with neighbouring cells, a dense mass of fibres. From the sides of this apical process twigs pass off at right angles, and usually divide into two or three secondary processes. From near the base of the cell larger and more numerous processes arise, some of which incline obliquely downwards, while others extend horizontally outwards. These basal processes undergo repeated division before terminating. All observers are practically unanimous in asserting that all the processes of a given cell terminate in free extremities, so that there is, normally, no direct continuity between one cell and another. It must be obvious, however, that the pyramidal cells of the human cortex, by the large number of their processes, as well as their great length and frequent sub-divisions, are brought into close relation with numerous neighbouring nerve cells. In the rabbit these pyramidal cells resemble those of the human subject, except that the processes are fewer in number, shorter, and less branched. In the lizard the apical process is short, and soon breaks up into its terminal tuft, and there are only one or two rudimentary basal processes. In the frog the pyramidal cells have merely an axis-cylinder process at their base, and several branched apical processes.

I have ventured to lay before you this very imperfect sketch of some of the work that has been done within recent years on the anatomy of the lower vertebrate brain, because I believe it is along lines such as these that we must travel in order to gain a broad and philosophical view of brain structure and function in the higher vertebrata.

In the course of this address reference has been made to the importance of the study of developmental anatomy in the investigation of the structure of the brain. A series of observations on the development of the human cerebrum, which have recently been published by Professor Flechsig, of Leipzig, afford a striking illustration of the truth of this statement, and I trust you will excuse a somewhat detailed reference to these researches, as I believe the conclusions at which Flechsig has arrived are not only of great anatomical interest, but are also of special importance to the physiologist, pathologist, and psychologist. Flechsig is well known to us all for his discovery of the order of medullation of the nerve fibre tracts in the spinal cord and lower parts of the brain. His great work, "Die Leitungsbahnen im Gehirn und Rückenmark," which was published in 1876, constitutes an important landmark in the history of modern neurological progress, not merely by reason of the number and importance of the new facts it contained, but also because it revealed a new and most valuable method of ascertaining the course and connections of the enormous mass of nerve fibres found in the central nervous system.

This memoir dealt especially with the development of the nerve tracts in the spinal cord and lower parts of the brain, and for the last 20 years or more Flechsig has been engaged in a natural extension of his earlier work by endeavouring to ascertain the order of medullation of the nerve fibres in the higher parts of the brain. This task was attended with special difficulties, not only on account of the complicated structure of the cerebrum, but more particularly because this part of the brain attains a large size before its fibres begin to medullate, hence the laborious task had to be undertaken of cutting, staining, mounting and examining an enormous number of very large sections.

Professor Flechsig announced some of the main conclusions formed from these extensive and difficult investigations in an address which he delivered in October, 1894, as Rector of the University of Leipzig. This address was published under the title "Gehirn und Seele" and in the spring of this year a second edition appeared with copious notes and containing drawings of section of the brain of the human foetus near full time and of the young infant stained by a modification of Weigert's haematoxylin method, also diagrammatic representations of the cortical areas and the general distribution of the nerve fibres of the cerebrum. According to Flechsig certain regions of the cortex are in direct connection, through the

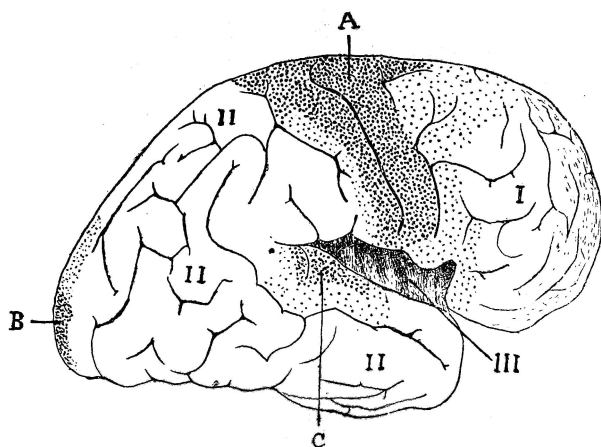


Fig. 1. — Outer aspect of right cerebral hemisphere showing sensory or senso-motor and association centres in the cortex (after Flechsig). Sensory centre dotted, association areas left white. The thickly dotted areas correspond to the termination of the majority of the sensory fibres, the more lightly dotted ones indicate where the fibres are sparingly distributed.

- |      |  |   |                   |
|------|--|---|-------------------|
| A    | Senso-motor centre for body.   | B | Visual centre.    |
| C    | Auditory centre.   | D | Olfactory centre. |
| I.   | Anterior or Frontal association centre.  |   |                   |
| II.  | Great posterior association centre, comprising parts of parietal, occipital, and temporal lobes. |   |                   |
| III. | Middle or Insular association centre.  |   |                   |

corona radiata, with the lower parts of the brain or the spinal cord, while a still larger portion consists of areas which are destitute of this connection, but are centres of associations between different parts of the cortex. Those areas which are connected with the corona radiata can be classified as follows:— 1 common sensory or senso-motor for the body generally, 2 visual, 3 auditory, 4. olfactory, and 5 gustatory.

The existence of these areas has of course been known for some time and much good work has already been done in determining their precise position. Flechsig, however, has demonstrated the important fact that the sensory fibres which terminate in these parts of the cortex are medullated before the motor ones which pass out from the same regions and also before the association fibres. By the careful study of the fields of distribution of these sensory fibres he has rendered more exact our knowledge of the topography of the sensory areas. It is now generally admitted that the so-called motor centres situated in front and behind the fissure of Rolando are not purely motor in function, but are also sensory. Flechsig holds this opinion very strongly and indeed maintains that there is no such thing as a purely motor or a purely sensory area in the cortex, but that these two functions are always combined in any given area. His observations on the medullation of

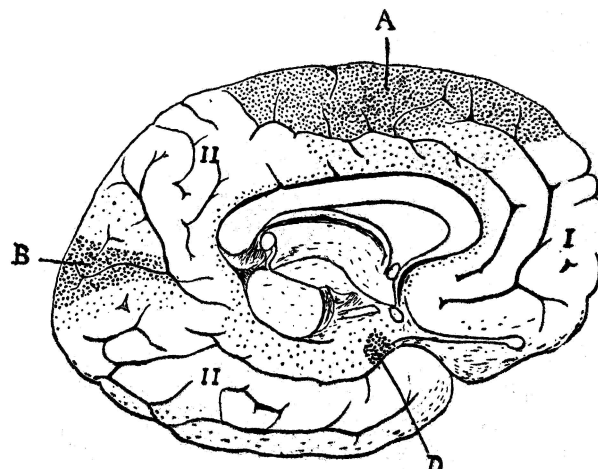


Fig. 2. — Inner aspect of left cerebral hemisphere. Lettering as Fig. 1.

the fibres in the Rolandic area show that fibres connecting this part of the cortex with the corona radiata become medullated before the fibres of the pyramidal tract acquire their medullary sheath. The senso-motor area for the body generally is bounded posteriorly by the vertical portions of the intra-parietal sulcus, anteriorly it is not so well defined as it extends forwards in front of the precentral sulcus on to the posterior parts of the superior middle and inferior frontal convolutions. On the inner aspect of the hemisphere it includes about the posterior half of the marginal convolution and probably involves also the portion of the gyrus fornicatus situated above the anterior half of the corpus callosum.

The visual centre is situated mainly on the inner aspect of the hemisphere in close relation with the calcarine fissure. This area includes the cuneate lobule and the gyrus lingualis and a small portion of the outer surface of the hemisphere at its posterior extremity. Horizontal sections of the brain of an infant a few months old which I have had the opportunity of examining and one of which Flechsig has figured in plate II., fig. 3 of his work, show beautifully the course and the distribution of the optic radiation in the areas above mentioned, but there are no indications of any fibres going to the angular gyrus which Ferrier considered to be the visual centre. The fibres from the macula lutea of the retina go to the external geniculate ganglion and from these to the walls of the calcarine fissure, so that they have no direct connection with the optic thalamus or anterior quadrigeminal body.

The cortical centre for hearing is generally stated to be placed in about the middle third of the outer surface of the superior temporal convolution, but

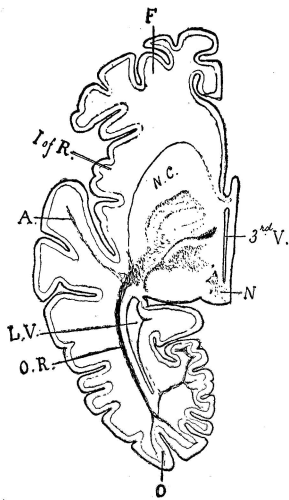


Fig. 3. — Horizontal section of one cerebral hemisphere of an infant, who died at the beginning of the second week after birth. Medullated fibres stained by Weigert's method.

F., Frontal lobe; O., Occipital lobe;  
 I.R., Island of Reil; L.V., Lateral Ventricle;  
 3rd V., 3rd Ventricle; N., Nates of Corpora Quadrigemina;  
 N.C., Putamen of Nucleus Caudatus.

Flechsig has shown that it also includes one or two convolutions which pass transversely inwards from this superficial area and form part of the lower boundary of the sylvian fissure.

The olfactory sense is feebly developed in man and the exact limits of its cortical centre are doubtful. The principal centre is in the uncinata convolution, but Flechsig is inclined to extend it into the hippocampal convolution and a narrow strip of the gyrus fornicatus close to the corpus callosum.

The cortical centre for taste is not definitely known.

The medullation of the fibres passing to these various sensory centres is practically completed by the end of the 3rd month after birth. A glance at Flechsig's diagrams shows that the ordinary sensory area for the body is very large in the human brain, indeed it greatly exceeds in size all the other sensory areas combined. It is worthy of note that the various sensory regions of the cortex are not continuous with one another, but are separated by distinct intervals except on the inner aspect of the hemisphere where the areas for common sensation and sense of smell are probably contiguous for a short distance (see Fig. 2).

We have already directed attention to the fact that, according to Flechsig, the portions of the cortex situated between the various senso-motor areas are association centres being connected by association fibres with other parts of the cortex, but having no direct connection with lower parts of the brain. These

association centres constitute fully two thirds of the cortex and may be divided into an anterior or frontal, a middle or insular, and a posterior or parieto-occipito-temporal, the last mentioned forming nearly one half of the whole cortex. According to Flechsig these association centres constitute the mental cortex proper, it is principally their diseases that give rise to disorders of the mind, and an analysis of their functions is the special object of psychology. Our knowledge of the relative development of the senso-motor and association centres in the cortex in the mammalia is as yet very imperfect, but Flechsig asserts that the association centres fail completely in the Rodentia, in the Carnivora they are small, and in the catarrhine monkeys equal in size to the senso-motor. Their great development in the human subject must be regarded as an indication of man's superior mental endowments.

It is well known that the cortex has not the same microscopic appearance throughout its entire extent, but that its nerve cells present some variety in their shape and arrangement in different regions. The functional significance of these variations has hitherto been very imperfectly understood, but the opinions and observations of Flechsig have invested the question with a new interest. He holds that all the association centres closely resemble one another in structure, belonging to the five laminated type of Meynert with very few large pyramidal cells. On the other hand, the senso-motor areas have each a characteristic structure. Thus in the visual area of the occipital lobe the layers are more numerous than in any other region, and here Meynert recognised no less than 8. The typical pyramidal cells are much less numerous than in various other parts of the cortex, while an abundance of small granule cells is very characteristic of this region, these cells being especially numerous in the walls of the calcarine fissure where the cortical centre for the macula lutea is situated. The lower border of the visual area in the gyrus lingualis contains a layer of large cells, and it should be noticed that similar cells are scattered throughout the visual area, but are few in number as compared with the rolandic areas. The cortex of the auditory area presents a considerable resemblance to that of the visual, but it only possesses a six-laminated formation. It contains, however, numerous large pyramidal cells. In the senso-motor area around the fissure of Rolando the pyramidal cells of the third layer are very large and numerous, while in the fourth layer occur the so called giant cells, these latter cells being mainly confined to the upper part of the area. The olfactory region is so well known

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to differ very greatly from any other part of the cortex that any detailed reference to it is unnecessary.

The determination of the connections of the enormous mass of nerve fibres situated in each cerebral hemisphere between the basal ganglia and the cortex is of necessity a very difficult task, and it must be admitted that the anatomy of this region is as yet very imperfectly known. More than 25 years ago, Theodore Meynert, in his work on the "Brain of Mammals" in Stricker's Histology, made a bold, and on the whole very successful attempt to formulate a general scheme for the classification of these fibres. He divided them into three main groups, viz. — projection fibres uniting the cortex with lower nerve centres, commissural fibres passing between corresponding parts of the two hemispheres, and association fibres which unite different parts of the cortex on the same side. Notwithstanding inevitable imperfections and errors in the details of the scheme its general principles have been accepted by anatomists up to the present and Meynert's diagrams are still copied into our text-books.

The recently published work of Flechsig deals especially with the projection and association fibres and the views advanced in it differ in various important particulars from those of Meynert. Meynert divided the projection system of fibres into two main groups, a crustal and a tegmental, the former being connected with the corpus striatum, and the latter with the optic thalamus. The fibres of projection were considered by him to connect all parts of the cortex with these ganglia, while, as we have seen, Flechsig maintains that only about one third of the cortex is provided with projection fibres. This discrepancy is partly to be explained by the fact that Flechsig regards the corpus striatum as a part of the cortex, which developmentally, and probably also functionally, it is, while Meynert considered it to be a ganglion of interruption between the first and second links of his crustal projection system. The latter observer described the tegmental fibres as passing to the occipital and temporal lobes of the brain, the crustal going to the frontal and parietal lobes. Schaefer, in the last edition of "Quain's Anatomy," describes the fibres, issuing from the outer side of the optic thalamus and entering the corona radiata, as going to almost every part of the hemisphere.

The view that the projecting system of fibres are connected with the senso-motor areas of the cortex only and the embryological evidence upon which this opinion is based must be placed to the credit of Flechsig. His embryological studies also afford valuable support to the belief, now generally

entertained, on experimental and clinical evidence, that sensory and motor functions are found in the same area.

While Flechsig's specimens demonstrate with great clearness the course of many of the fibres of the senso-motor areas (see Fig. 3), the distribution of the association fibres cannot be shown with the same precision owing to the fact that they become medullated at a later period when the extensive medullation of other tracts prevents their complete differentiation.

The diagram which Flechsig has prepared to illustrate the connections of the cerebral fibres shows several interesting points regarding the connections of the association fibres, although of course it is impossible in a diagram to convey any adequate idea of the wealth of these association fibres.

In the frontal lobe these fibres connect part of the anterior association centre with the senso-motor area for the body. It also contains numerous fibres connecting different convolutions of this association centre with one another and also through the knee of the corpus callosum, corresponding areas on the two sides. In the posterior association centre the cortex is connected more particularly with the visual and auditory centres. It is interesting to see that in this region Flechsig has traced fibres from both the visual and the auditory centres to the angular gyrus. The visual and auditory centres are united with the corresponding centres in the opposite hemisphere by fibres which go through the posterior part of the corpus callosum, and further, these centres on the one side are connected with that part of the posterior association centre of the opposite side which lies between these two sensory centres.

I will not weary you with a list of numerous other association fibres that undoubtedly exist, my object will have been attained if their great complexity is recognized.

The brain is the organ of the mind and although the most profound and accurate knowledge of cerebral anatomy will never enable us to fathom the mystery of the real relation between the activity of nerve cells and states of consciousness, yet the more we know of the anatomy of the brain the more accurately we shall be able to localize the exact seat of many mental processes and the less vague will be our classification of mental diseases. From our present knowledge of the symptoms and pathology of the various forms of aphasia it is clear that even the simpler mental processes require for their successful performance numerous complex nerve associations.

I trust I have satisfied you that we are now within

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measurable distance of gaining some clear conception of the structure of the material with which these mental processes are associated.

The history of medical science abounds with illustrations of the debt which practical medicine owes to scientific researches which apparently had but little or no direct bearing on the diagnosis and treatment of disease. In no department is this more striking than in connection with the nervous system, where the labours of the comparative anatomist and embryologist have been of immense value in the localization of nervous lesions in the human subject.