in the adult the large fibres are from 10 to 15 μ in diameter. From the third to the sixth week the myelin becomes more abundant and the fibres double in diameter. In the eighth month there are still some unmedullated portions in the nerves, but these gradually disappear.

There is no fixed relation between the *volumes* of the cell bodies and the *length* of the axones which they produce.

In the frog Dr. Dunn [22] has shown that the fibres of greatest diameter in the sciatic nerve pass to innervate the muscles and skin of the thigh, while those going to the parts of the frog's leg below the thigh have a smaller average diameter, as well as being individually of less calibre. In this instance, therefore, the fibres of larger calibre tend to run the shorter course.

Looking upon the three groups of neurones as elements modified to receive stimulation, and to transmit impulses, it is found that the afferent neurones (Group I.) increase on the receptive side mainly by the expansion of their peripheral axones in the skin and muscles; that the cell body is practically devoid of dendrites receiving but few stimuli, and that their field of influence is determined by the extension of the proximal axone within the central system. The central neurones (Group II.) extend their receptive side by the multiplication of the dendrites, and their discharging side by the extension and ramification of their axones; while the efferent neurones (Group III.) extend their receptive side by the multiplication of their dendrites within the central system, and on their discharging side influence a greater or less mass of muscle or of sympathetic neurones according to the ramifications of their axones.

From this it will be seen that the complexity of the central nervous system depends first on the ramification of the proximal axones of Group I., second on the ramifications of both the dendrites and axones of Group II., and finally on the ramifications of dendrites alone in Group III. It is to this complexity that the growth changes in the neurones ultimately contribute, and there already exist very suggestive observations by Athias [23] showing how the growth of the dendrites of the Purkinje cells and of the terminals of the "climbing fibres" are correlated. During growth the cell bodies may also change in shape apparently under mechanical stress. In those parts of the spinal cord like the cervical and thoracic regions, where the segments of the cord lengthen with the growth of the vertebræ, the axes of the mature cell bodies tend to be drawn out parallel to the long axis of the cord; whereas in the lumbar region of the spinal cord, where the segments remain short, the bodies of the efferent neurones are more nearly equiaxial.

As the spinal cord increases in weight, the central canal also becomes larger. This involves (in the case of the white rat) a large extension of the wall of the canal, formed by the ependyma cells. Measurement of the ependyma cells shows that the individual elements increase but very slightly in their diameters, and hence the great increase in the wall must be due to the insertion of new cells. It seems probable, moreover, that the ependyma lining the other cavities of the neuraxis is extended by a similar process.

Neurones in Old Age.—As a rule the life of the neurone is coterminous with that of the individual. There is, however, evidence that some neurones die before the individual dies, but no evidence shows that new elements take the place of those which thus perish.

Old age in man is accompanied by a loss in the gross weight of the encephalon. This has not yet been demonstrated in animals. In the white rat, however, old age is correlated with the smallest percentage of water found. Systematic studies on the white rat show that in old animals (three or more years) the cell bodies in every division of the neuraxis are shrunken when compared with the corresponding elements during the prime of life. Casual observations on man suggest the same changes, though they are well demonstrated only in the spinal cord. Hodge [24] found in a man of ninety-two years a diminished number of Purkinje cells in the cerebellar cortex, and in the spinal ganglia the cell bodies and nuclei were shrunken, the nucleoli absent from all but a few cells, and the cytoplasm was loaded with pigment. The coarse changes in old age appear, therefore, in the cell bodies and their parts—while the finer changes will be brought out when the alterations in the cytoplasm with age are described. We should further expect in old age a loss of physiological connections between the separate neurones, but this has not been demonstrated.

Changes in the Cytoplasm of the Cell Bodies during Growth.—The studies of Marinesco [19] and Biervliet [25] show that in the large cell bodies of the efferent group in the ventral horns of the spinal cord the "stainable substance" of Nissl is fully formed at birth — the other portions of the cytoplasm being correspondingly well differentiated. This does not mean that this stainable substance is formed in *all* these cells at this time, but only that those neurones which have first developed have already attained this differentiation. The process repeats itself as the neuroblasts, with longer latent periods, gradually enlarge. The neurone in its first embryonic stages stains by the Nissl method so as to reveal a faint blue tint evenly distributed in the cytoplasm. As the element grows, the blue tint becomes denser at the periphery of the cell body. Here discrete particles, stained intensely, appear, and these, increasing individually in size, also form a wider band which spreads toward the nucleus. As the features of the mature cell become more evident the diffuse blue tint disappears, as though the constituent capable of that reaction had by degrees become concentrated in the masses of stainable substance. This process of the formation of stainable masses is carried farthest in the largest cell bodies—for example, in the large cells of the spinal ganglia; those of the ventral horns of the cord and the large pyramids of the cerebral cortex. The smaller cells of the neuraxis exhibit varying degrees of a less complete formation of the stainable substance, representing in their final condition phases through which the largest cells have already passed. In old age the neurones undergo involutionary changes one at a time. The masses of stainable substance become disorganized; the changes progressing from the centre or nucleus toward the periphery. When this occurs, a black or yellow pigment-like substance, often in very fine grains, appears to take the place of the masses destroyed. In the ventral-horn cells true pigment is to be found about the twentieth year, though it comes much earlier in other portions of the neuraxis. With the destruction of the stainable substance, the cell body, as well as the nucleus and its contents, tends to shrink and to stain less strongly.

In correlating growth with function, it is often stated that a neurone which is destined to become medullated does not become functional until its medullary sheath has been acquired. The young white rat, in the nervous system of which there is at birth not a medullated fibre, is a sufficient contradiction to this dictum. It is admitted, nevertheless, that in general the appearance of functional adjustments runs parallel with the medullation of the neurones by which those adjustments are mediated; but the two events do not stand in a strict causal relation. The same is true of the stainable substance of Nissl in the cell body, where the formation of well-marked masses is characteristic of full development and full functional power, without being absolutely necessary. By prematurely exposing to light the eyes of young rabbits, the optic nerves of which were unmedullated, Held [26] was able to hasten the formation of the medullary sheath in the stimulated animals. Just how this experiment should be interpreted is not perfectly clear; but if we consider it as due to exercise, then the unmedullated fibres must, in spite of statements to the contrary, have been capable of being exercised even before they acquired their sheaths. Beyond this experiment there are no data on the effect of activity on the growth processes in the central nervous system. In this connection we recall that the encephalon has attained very nearly its full weight at seven years, that is, at a time before any formal school training has begun. If this is granted, then the subsequent functional powers which the child may attain are correlated with a very small addition of substance to the encephalon. This seeming paradox disappears, I think, when the very small volume of the cell bodies in the central system is considered (27.2 gm.), and when it is remembered how a very slight additional weight of material could be so disposed as to add greatly to the physiological complexity of the system.

Judging by every-day experience, it appears that favorable growth conditions have their effect more in prolonging the growth changes that have once been initiated than in hastening prematurely the onset of any given set of changes, and that when growth is hindered, there often appears in the individual a "prematureness," which we might call precocity, if it did not tend to become permanent in spite of increasing age, and thus in later years show itself in its real form as an arrest of development.

C. Growth of the Cerebral Cortex.—Despite the great interest which attaches to changes in the cerebral cortex, our information is very imperfect. In one locality in the white rat, on the lateral aspect of the hemisphere at the level of the optic chiasma, the thickness of the cell layer increased as follows between birth and maturity:

Table XIII.—White Rat—Thickness of Cell Layer of Cortex in Millimetres.

Weight of rat in grams.	Age.	Thickness of cell layer.
4.6	Birth	.40
10.4	Ten days	.82
25.7	Twenty days	1.32
68.5	Fifty days	1.37
159.2	Maturity	1.49
242	Old age	1.36

The data on the change in the thickness of the human cortex are contradictory, some observers claiming that it actually becomes thinner with age. For this reason we omit a discussion of this point and pass to the determination of the increase in the medullated fibres, which all investigators have found.

The general course of the development of the fibre systems of the human cerebral cortex is described in the following way by Kaes,[27] and we here quote from a summary of his observations given by Miss Thompson.[31] For the stages earlier than one and one-quarter years, Kaes relies on the observations of Vulpius,[28] but the subsequent history is based on his own investigations. The first group of fibres to become medullated are the cortical projection fibres. At birth these appear raying out almost as far as the cortex. At about four months the fibræ propriæ, the first of the cortical association fibres, become medullated (Fig. 904). At about eight months the first of the intracortical fibres begin to be medullated in those regions which are most advanced. The description of the further development cannot be accurately assigned to definite ages, partly because some regions of the cortex develop so much more rapidly than others, and partly because Kaes examined no brains between the ages of one and one-quarter and eighteen years. A general description of the course of events can, however, be easily derived from a comparison of the different stages of advancement within the same brain. The first cortical fibres which develop shortly after the fibræ propriæ are a few scattered fibres running parallel to the layer of the fibræ propriæ on its ectal border. Gradually these latter increase in number, spread for a short distance toward the surface of the cortex and assume a stratified appearance. These form the beginning of the "outer association layer" of Kaes. Before the formation of the outer association layer is completed two other sets of fibres appear; one of these surrounds the outer limit of the projection fibres, which by this time have completed their normal growth into the cortex. This is the Baillarger or Gennari layer. It marks the ectal border of the outer association layer, but is composed of fibres of larger calibre than the remainder of that layer. The second set of fibres which appears at this period is the zonal layer, at the ectal border of the cortex and immediately beneath the pia. It also is composed of fibres of large calibre. The stage of development just described is characteristic of the advanced portions of the cortex in a child of one and one-quarter years. Its distinctive features are, in brief, a partly formed outer association layer, consisting of some stratified fibres lying next the fibræ propriæ, and the Baillarger layer at its ectal border. At this stage these two portions of the outer association layer are separated by a region free from medullated fibres. On its ectal side

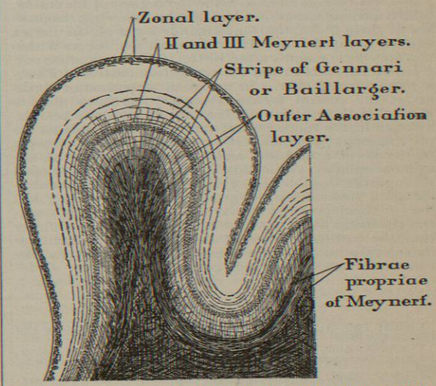

Fig. 904.—Semidiagrammatic Representation of the Cortical Fibres in a Section of the Occipital Cortex of a Male Child of One and One-Fourth Years. (From Theodore Kaes, 1894. The designations are the same as those used in Kaes' papers.)

the Baillarger layer is separated from the zonal layer by a second region free from medullated fibres, the region corresponding to the "II. and III. cell layers" of Meynert.

As development continues, the layer formed by the outer association fibres spreads gradually toward the Baillarger layer until it reaches the latter. At the same time the Baillarger and zonal layers grow broader and richer in fibres. The next stage is marked by the appearance of the inner Baillarger layer, and of the first fibres of the II. and III. Meynert layers. The inner Baillarger layer appears as a narrower line of coarser fibres among the fine fibres of the outer association layer, just ental to the outer Baillarger layer.

The fibres in the II. and III. Meynert layers are the finest of the cortex. The first of these to become medullated are those lying nearest the outer Baillarger layer. From the region of its first appearance, this layer (II. and III. Meynert layers) gradually extends ectad, and this process continues until these fibres meet those of the zonal layer. The final stage in the development of the cortex is the addition of a secondary system of coarse fibres to those which have been already described. The fibres of this secondary system are first seen in the outer association layer. Shortly afterward fibres of the same sort are found scattered through the II. and III. Meynert layers. At first these appear singly, but later are organized into a stratum which Kaes identifies with "Bechterew's streak." Still later, similar fibres appear in the Baillarger layer, and in the most highly developed cortex

known they appear as a secondary system of coarse fibres generally distributed through its entire thickness. Very few regions of the cortex reach this highest stage, however, even in the fully grown adult. The period from youth (eighteen years) to maturity is in general characterized by the gradual appearance of the fine fibres in the II. and III. Meynert layers, and the formation of the secondary fibre system of coarse fibres; but in the fully grown cerebrum there are regions which do not reach even the stage at which the fibres of the II. and III. Meynert layers become medullated.

The central gyri exhibit the most highly developed fibre systems. The addition of new medullated fibres may continue, according to Kaes, up to the fiftieth year of life, though this limit must certainly be subject to wide individual variations.

Flechsig[29] has shown that the cortico-petal projection fibres first became medullated in the regions of the cortex, which mediate sensations, and thus by following the process in these fibres, the sensorimotor areas of the cortex can be mapped out. Their demarcation occurs within the first three months after birth. The intervening portions of the cortex form the association centres of Flechsig and develop later. In the great sensorimotor region about the central fissure Passow[30] has been able to show that the association fibres are at maturity best developed in the more ventral portion which contains the (discharging) pyramidal cells controlling the movements of the lower arm, hand, and face. In the child at one and one-quarter years this layer is equally developed through the length of the gyri, that is, there is no differentiation between the cell groups controlling the leg and the proximal portions of the arm and those which control the distal portions of the arm, and from this we infer that the cortical control of the finer muscles and finer movements increases for some time after that for the coarser movements has been completed.

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BRAIN, HISTOLOGY OF.—METHODS.—The nerve tissues of the brain may be studied fresh or in frozen section, by maceration and isolation, or after hardening by various methods.

Fresh Tissues.—Nervous tissues from animals can be obtained immediately after death. In human beings a certain number of hours practically always elapse before the material can be removed from the body. Certain post-mortem alterations occur early, particularly in the most labile constituents of the nerve-cell protoplasm. But for ordinary histological purposes tissue obtained from the central or peripheral nervous system within twelve hours after death, provided the body has been kept cool, is sufficiently fresh for minute microscopic examination. For many studies, too, tissue removed as late as twenty-four hours after death, provided the body has been kept cool, is quite satisfactory, though one should be sceptical in such tissue in drawing conclusions from the condition of certain of the microscopic pictures, for example, those of the Nissl bodies, and the so-called fibrillary structures.

In examining fresh tissues either teased particles or sections made by the double knife of Valentine may be employed. The teasing method is particularly applicable to the study of the peripheral nerves. These may be observed in an indifferent fluid like physiological salt solution or blood serum, or after the addition of some reagent (acetic acid, osmic acid, caustic potash). Sections of entirely fresh tissue made with the double knife of Valentine are very fragile, besides being extremely difficult to prepare. They may be examined in physiological salt solution, care being taken that the cover slip is not pressed upon. Ehrlich's method of staining fresh masses of tissue will be referred to later.

Maceration and Isolation.—For the isolation of histological elements, especially in the central nervous system, the use of some macerating fluid is desirable. A large number of these have been employed, but only the more important ones need be mentioned. Osmic-acid solutions (one-tenth of one per cent.) work well, any fatty structures, including of course the myeline sheaths, being stained of a dark color. Müller's fluid and dilute chromic-acid solutions (one-one-hundredth of one per cent. to four-one-hundredths of one per cent.) are useful macerating reagents provided the fluids are not allowed to act too long. Tissues macerated in these solutions should be teased and examined at the end of twenty-four hours. Ranvier's alcohol (thirty-three and one-third per cent.) yields very good results.

The tissues intended for maceration should be divided into small pieces before being placed in the macerating fluid. At the end of the period of maceration gentle shaking in a test tube often facilitates the isolation of elements. A pipette may be used for transferring minute particles suspended in the fluid to the microscopic slide for examination. Coarser particles may be teased upon the slide or squeezed between the cover slip and the slide.

The fluid used for maceration may be employed as a mounting medium for the microscopic observations, but as a rule it is better to render the tissues somewhat transparent. For this purpose dilute solutions of acetic acid (one per cent.), saturated aqueous solution of potassium acetate, diluted glycerin, or salty glycerin may be used.

Hardened Tissues.—The three fluids most frequently employed at present for the hardening of nerve tissues are: (1) Müller's fluid, (2) alcohol, and (3) formol.

Müller's Fluid. This hardening reagent consists of potassium bichromate, 2.5; sodium sulphate, 1; distilled water, 100. If desired the sodium sulphate may be omitted, simple solutions of bichromate of potash appearing to act as well as the fluid prepared according to the original formula. Müller's fluid should be changed frequently during the hardening process. Hardening in this fluid requires from several weeks to several months at the ordinary temperature, though if the tissues be kept in the fluid in a thermostat at the body temperature the process may be much shortened. In summer the fluid is particularly prone to become contaminated with growths of fungi. This may be prevented by the addition of a small quantity of camphor. After Müller's fluid hardening, the tissues are best prepared for embedding by dehydration in alcohol, as a rule without previous washing out in water. Tissues hardened in Müller's fluid stain well in carmine and with Weigert's myeline stain. They are not suitable, however, for the application of finer histological methods, such as that of Nissl.

Alcohol. This reagent should be employed when the original Nissl procedure is to be applied, small pieces of the tissue being left in ninety-five-per-cent. alcohol for about three days (see Nissl's method). Alcohol hardening is also desirable if Weigert's fibrin stain or Gram's method of staining bacteria is to be utilized. The periphery of bits of tissue hardened in strong alcohol is likely to undergo marked contraction and distortion. The blood at the periphery of such tissue is also much altered. Artefacts in various parts of the tissue may result from the action of the alcohol.

Formol. At present solutions of this substance are much employed in neurological technique since tissues fixed in them can be stained by several different methods. Formol, or formalin, is a forty-per-cent. aqueous solution of formaldehyde. As a rule, ten-per-cent. solutions of formol are used for hardening pieces of the central nervous system. This corresponds to a four-per-cent. aqueous solution of the gaseous formaldehyde. The whole brain may be hardened more or less satisfactorily in such a solution, but it is better, as a rule, to more or less subdivide the organ. Formol does not contract the tissues hardened in it, but fixes them rapidly in their original form, thus differing markedly from many other hardening fluids. The fluid has a characteristic odor and gives off irritating fumes. Injury to the eyes must be carefully avoided when using it, and it is also well to keep the hands as much out of the fluid as possible, as sometimes a troublesome form of dermatitis is set up by it. After hardening in formalin for a few days the tissue is ready for further manipulation. If Weigert's myeline stain is to be employed the tissue may be placed in Müller's fluid or his chromic acid mordant. The latter also suffices for the application of Weigert's neuroglia stain. Formalin tissues can also be used for studies by Marchi's method; the ordinary Marchi procedure is gone through with after the formalin hardening. Tissues prepared in formalin do not warp so much as those simply hardened in Müller's fluid. Very good Nissl preparations can also be made from formalin tissues provided they have been gotten fresh and cut into small pieces. The results are not equal, however, to those obtained after fixation in alcohol or sublimate. Marini's modification of the formalin hardening is especially recommended when it is desired to examine tissue by several different methods. This investigator recommends a fluid consisting of five per cent. formol with one-tenth of one per cent. chromic acid in ninety per cent. alcohol. Large pieces of the tissue put into this fluid for twenty-four hours are then removed and divided into small pieces. The latter are placed in more of the fluid freshly prepared, which is changed every day for from three to five days. The blocks of tissue are then fastened upon cork (without any other preparation), and kept in ninety-per-cent. alcohol or in a one-per-cent. solution of chromic acid in ninety-per-cent. alcohol. Sections for staining with methylene blue or thionin are placed in ninety-per-cent. alcohol; those for Weigert's myeline stain in Müller's fluid or in a three-per-cent. solution of potassium bichromate, while sections to which Weigert's method for studying neuroglia is to be applied are placed in a solution of chromogen.

When the material to be studied is not limited in amount it is preferable to use at least three hardening fluids: (1) alcohol for Nissl's method; (2) formol for Weigert's myeline stain, for Marchi's and for Golgi's methods; and (3) Weigert's formol-chrome-alum mordant for the neuroglia stain.

Sublimate solutions, Orth's fluid, Erlitzki's fluid, Flemming's mixture, Van Gehuchten's fluid are all recommended for special purposes. The formulæ for these fluids are to be found in the text books of histological technique. (See also article: *Histological Technique.*)

Embedding.—Three methods are ordinarily employed for embedding neurological tissues: (1) embedding in pith or gum; (2) celloidin embedding; and (3) paraffin embedding.

Pith or gum embedding may be dispensed with. Nissl, for his method, insists upon the avoidance of embedding entirely. He simply fastens the mass of tissue to the block by a solution of gum arabic. He fears that celloidin or paraffin embedding will interfere with the structure of the protoplasm of the nerve cells. He is here in error. Careful embedding in celloidin or paraffin, especially the latter, preserves beautifully the structure of the protoplasm.

Celloidin embedding is carried out as follows: After dehydration in absolute alcohol the tissues are left for twenty-four hours in equal parts of absolute alcohol and ether. They are then transferred to a very thin solution of celloidin dissolved in alcohol and ether. Here they remain until the thin fluid has penetrated the tissue. Small blocks are sufficiently penetrated if they remain for from two to five days. Large pieces, however, as, for example, a whole hemisphere of a baby's brain, must remain in a thin celloidin for a much longer time. The tissues are next transferred to a solution of celloidin which has the consistency of thick syrup. They need not remain in this fluid long; twenty-four to forty-eight hours suffice. There is a widespread idea that the longer tissues stay in thick celloidin the better are the sections obtained. The reverse rather is true, especially when we have to deal with large pieces. The penetration by the thin celloidin should, however, be complete. The thick celloidin may be allowed to stiffen very gradually through evaporation of the alcohol and ether, and a block of it containing the tissue be fastened by means of celloidin on a piece of cork or wood. Or it may be placed directly, without previous stiffening of the celloidin, on a block, allowed to stand in the air for a few minutes until the surface of the celloidin has hardened, after which it may be immersed in eighty-per-cent. alcohol. The blocks may be kept in eighty-per-cent. alcohol until the sectioning is carried out. Instead of celloidin, photoxylin may be employed if desired; it is more transparent than celloidin.

Celloidin embedding is to be preferred when large pieces of tissues are handled, when the tissue is friable, or when the staining method to be employed is one involving considerable manipulation. It is always to be used when Weigert's myeline stain is to be applied.

For embedding in paraffin small pieces should be taken, thoroughly dehydrated in absolute alcohol (twenty-four hours), cleared in xylol or chloroform, and then passed through equal parts of the clearing reagent and soft paraffin, thence into melted paraffin (melting point of 52° C.) for two to eight hours, the paraffin being changed twice during this period. After complete penetration by the paraffin, best in the thermostat kept at the melting point of the substance, the piece of tissue is placed in a shallow dish and covered with paraffin. This is rapidly cooled with cold water until the paraffin stiffens, after which the paraffin block, properly trimmed, can be fastened on the platform of a microtome, when it is ready for cutting.

In warm weather it may be necessary to use a paraffin of higher melting point (60° to 65° C.); in cool weather, a paraffin of low melting point will be found useful (45° to 50° C.). If two kinds of paraffin, very soft and very hard, be kept in stock, it is easy, by mixing them in variable proportions, to make a paraffin of any desired melting point.

Paraffin is to be preferred when very thin sections are desired, or when staining *in toto*, before embedding, is possible. It is especially useful, therefore, in the study of the embryology of the nervous system, and also in the investigation of the finest histological details of the neural elements. It is one of the best methods which can be used when Nissl's method is to be applied.

A combination of the celloidin and paraffin methods may sometimes be used with advantage. The tissue after