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CEREBRAL SCLEROSIS.

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With 19 *Figures.*

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INTRODUCTION.

DERIVED from the Greek word $\sigma\kappa\lambda\eta\rho\acute{o}s$, the equivalent of the Latin *durus*, the term sclerosis denotes induration. It has been applied, perhaps too freely and with inadequate regard to pathogenesis, to a number of conditions of the brain having increased firmness, local or general, as a common character.

In this paper I propose to consider all the known forms of sclerosis, touching lightly on varieties familiarised to us by frequent occurrence, and giving details of rarer kinds.

Cerebral sclerosis is nearly always a secondary condition, reparatory or hyperplastic, and following some disturbance or destruction of normal constituents. Only in rare instances is it a pure katabiotic product, and even then suspicion of the operation of a primary factor cannot be wholly suppressed.

Viewed from the standpoint of histology, sclerosis is almost invariably synonymous with gliosis; also, it is almost of necessity associated with alterations in the more fundamental constituents of the central nervous apparatus, the nerve cells and their appurtenances, the stations and conductors of nervous impulses. It is seen in its simplest and purest form as an outcome of secondary degeneration of one of the known tracts of medullated nerve fibres, and is then reparatory. It will be well here to glance at the sequence of events which leads up to this particular form of sclerosis. The process begins in necrotic swelling and disintegration of the myelin and possibly of other constituents of the medullated nerve fibres. Then ensue important secondary changes in the nutritive apparatus and supporting tissue of the part. As a mechanical result of the swelling of the fibres, the vascular and lymphatic channels are interfered with and conditions favourable to the emigration of lymphocytes and leucocytes set up; with this is associated an enlargement[1] of the supposed fixed neuroglia residents, brought about by one or both of two causes, defective metabolism from impeded blood and lymph circulation, and irritation by or reaction to the toxic products of myelinic decay (cholin and allied substances). The next stage is one of absorption of the diseased and disintegrated nerve fibres. What the agents are here it is impossible to say, but some would give force to the supposed scavenger function of enlarged neuroglia cells, while others would credit the phagocytic capacity of

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[1] It is a moot point whether the enlarged neuroglia cells we see in such cases are changed residents or formative cells recently derived from the blood-vessels or lymphatics. In my opinion the latter is the case.

altered leucocytes and lymphocytes, and probably both are subservient, co-operating in the absorption of diseased products, and in the connection of such products to the lymph and blood channels now relieved of their primary embarrassment. In the final stage the place of the medullated nerve fibres is taken by a poorly vascularised mass of neuroglia or connective tissue cells and their processes, in the midst of which thick-walled vessels, some of them newly formed, ramify. I have seen it stated that cerebral sclerosis is not accompanied by shrinkage, but this does not apply to all forms, and certainly not to the simple form of sclerosis just used as an example. If proof on the point be needed, it is afforded by the alterations in form of the spinal cord seen in cases of tabes dorsalis and in cases of descending degeneration affecting the motor tract.

The principles seen in this simple instance of the manner in which sclerosis plays a reparatory *rôle*, apply to many varieties of cerebral induration ; that which we find so often around old-standing foci of softening and of hæmorrhage, that which is the outcome of impaired nutrition and which affects individual gyri (local microgyria), that resulting from agenesia and affecting whole lobes or even hemispheres, and many other forms, can be grouped as essentially of the same nature. In all an overgrowth of neuroglial constituents is a common character representing Nature's effort to make complementary amends for a deficiency, destructive or developmental, of nerve cells and nerve fibres.

Other forms of sclerosis have a mixed pathogenesis. In causing the initial necrosis of fundamental constituents and the superimposed reparative or repellent proliferation of neuroglia, *an irritant is the primary factor*. This may act locally or generally. The induration observed in general paralysis of the insane, a disease in which we assume for granted the circulation of noxious blood, instances the general condition, the sclerosis round an imprisoned foreign body the local.

Lastly, there are rare forms of sclerosis in which the principal constituent is not neuroglia, but some other element or structure. Thus, I shall have occasion to describe a

condition in which hyperplasia of ganglionic nerve cells has
been found accountable for the induration, and in this class
"colloid sclerosis," with its vascular alteration, must needs
be included.   These, however, are borderland cases, and it
is an open question whether they should not be called
outright tumours or new formations.

CHAPTER 1.—GENERAL REMARKS ON THE NEUROGLIA.

Some observations on the neuroglia must be introduced
here, because it is the most prominent tissue in nearly all
the conditions of which I shall write.   Since, however, it is
a tissue whose attributes have been discussed at length by
many able writers, of whom the late Professor Weigert,
von Lenhossek, and Storch, in Germany, and Dr. Ford
Robertson in our own country, may be specially mentioned,
it is proper that my remarks shall be shorn of detail and,
though flavoured with criticism, made pertinent to the
histogenesis and pathology of the condition in hand.

First, in order that the tissue may be considered in its
relation to sclerosis, we must look at the varieties of neuroglia
which have been recognised in the central nervous system.

While others have generally classified varieties of glial
elements according to their morphological and structural
peculiarities, I have always found it more convenient, paying
regard to their chemical affinities, to arrange them according
to their behaviour in the presence of different dyes and
histological reagents.   In doing this, I have avoided pitfalls
into which others seemed to have plunged.

§ 1.—*The Neuroglia in Sections Stained by the Method of
Bevan Lewis.*

As my earliest acquaintance with the neuroglia was
formed from an examination of sections prepared by the
fresh method of Dr. Bevan Lewis, I will begin by com-
menting on the revelations of this process.   And I will here
take the opportunity of expressing the belief that if others,
in particular continental workers, had been more generous
in their recognition of this method, past controversies re-

garding the structure of the neuroglia might have been considerably abbreviated.

So many years have elapsed since Dr. Bevan Lewis gave us his earlier publications, that many others in this country have made themselves familiar with his process and confirmed his observation that, in frozen sections of the fresh brain stained with "blue black" and some other aniline dyes, two kinds of glia cell are displayed, one small, the other large.

The smaller elements vary from 6 to 9 μ in diameter, and have a spheroidal, intensely-stained nucleus, surrounded by an extremely delicate protoplasmic investment apparently devoid of processes. They appear in three situations, irregularly distributed throughout the nerve fibre framework, in regular series around nerve cells, and in more or less regular succession along the course of the blood-vessels.

The larger elements are usually 13 μ in diameter, and are further distinguishable from the smaller by a preponderance of protoplasm over nucleus, by relatively pallid staining of the nucleus, by their flask-like form, and by showing numerous delicate radiating processes, one of which, stouter than the rest and attached to the wall of a neighbouring capillary, is known as the vascular process. In the normal brain such cells occur chiefly in the outermost layer of the cortex and in the white or medullary projection of a convolution. They bear a constant relation to the blood-vessels of the cortex. These are the cells described by Deiters in the year 1865; by many they are called after him "Deiters' cells"; but "scavenger cells," on account of their supposed phagocytic function, and "large spider cells," are other names which have been applied. We shall have frequent occasion to return to these cells, because as a factor in the production of cerebral sclerosis and as a feature in other morbid conditions of the cortex they possess great importance.

§ 2.—*The Neuroglia in Sections Impregnated with Salts of Silver.*

The service rendered to the neuro-histologist by Golgi when he elaborated his well-known process cannot be over-

estimated.   For the embryologist the method has no equal ;
with its aid all the beautiful work of Golgi, His, Capobianco,
and Fragnito, and others, on the development of the neuroglia
has been performed.   Similarly, the ordinary histologist will
vouch that with this process, or one of the many modifica-
tions which have been recommended, a clearer demonstration
of, at any rate, the external form of the neuroglial element is
obtained than by any other method.

The display in a silvered preparation of the normal cortex
is very different from that in a fresh section stained with
aniline blue black; in fact, there is some difficulty in cor-
relating the appearances.   The elements seen may be briefly
described as follows : (1) Cells with short (hence the German
name " Kurzstrahler "), thick, mossy, or feathery branching
processes roughly coated with the deposit of the silver
derivative, one of which is a vascular process.   These cells,
admirably fitting the designation "spider cell," have the
same distribution as the larger elements to be seen in fresh
sections, and, although the silver coat alters their general
appearance, there is no doubt that the two are identical.
(2) Cells with a smaller body, from which numerous delicate,
long (hence the German name " Langstrahler "), and clearly-
defined processes radiate.   A vascular attachment can be
found sometimes, but not always.   The term "stellate"
applies well to the shape of these cells.   The white matter
is again their elective site, and they are never far removed
from a blood-vessel.   (3) The third variety of cell was, I
think, first described by Retzius, and occurs only in the
plexiform layer (Ramón y Cajal) of the cortex, immediately
beneath the pia mater.   They seem to hang down from
vessels in the pia mater, to which they are attached by
several processes, including the vascular process; and from
the opposite or central end of the body there springs a
pencil of branching, delicate, and occasionally moniliform
processes.

It is commonly stated that the three varieties of cells
whose characters I have just described are all transition
forms of one element.   This is a statement to which I am
inclined to subscribe my belief.   In this connection the

character they have in common of growing in direct contact with a blood-vessel is most important. For, when we take notice of the point that they all have a different environment, one deposited in the loose substance of the cortex, another in the dense plexus of fibres in the white substance, and the third next the surface of the brain; when, also, we recollect how variable in its chemical reaction to silver salts is protoplasm in general, the statement gains additional justification.

Unfortunately, I cannot leave the silver method without expressing a word of regret. Excellent as the methods of Golgi, Cox, and Ramón y Cajal are as aids to the embryologist and the normal histologist, their fickleness of action condemns them in the eyes of the histopathologist, and I have found them of little value in my examination of sclerosed tissues.

§ 3.—*The Neuroglia in Sections Stained by the Methyl Violet Method of Weigert.*

We appeal next to a method which has received a high measure of praise, because of all methods it alone can pretend to be selective in action. Much faulty reasoning, however, seems attributable to overdriving this selective virtue. Simple constitutional principles appear to have been neglected. It has been forgotten that almost all tissues are chemically and structurally complex, and that to meet this combination there necessarily must be selection within selection. Take the nerve cell as an instance. Step by step we have perfected our knowledge of its structure by discovering that one dye or one means of impregnation selects and displays the cell envelope, another the tigroid bodies, another the neurofibrils, and so on. Accordingly, we find in practice that not one but many methods of staining have to be gone through before we obtain a satisfactory demonstration of the structure and condition of any nerve cells. And surely the same applies to the neuroglia.

I have made this explanation preparatory to saying that I share the opinion of those who refuse to entertain the statement of the late Professor Weigert that the nucleus and the fibrils in the neuroglia cell are chemically different

and morphologically separate. The statement is one which has been much discussed, and, although the preponderance of authority is unfavourable, it still finds many adherents. Those, however, who have stained and studied the neuroglia by various methods, and in conditions of health and disease, are forced to conclude that the supposition of the late Frankfort professor rested on a faulty basis. Without denying that the fibrils and the nucleus of the neuroglia cell differ chemically, they will rest their argument on the point that the neuroglia cell, like many other cells, is composed of envelope, nucleus, hyaloplasm, and spongioplasm. Each constituent requires special treatment for its display, and the last is peculiar in that it harbours fibrils, which extend along the processes and have a special affinity for methyl violet. The case, therefore, is one of limited selection. The method affords an exquisite display of the framework of the cell, but fails to show the covering; and I think that this may explain why Weigert held that the neuroglia cell had no vascular attachment, for we have reasons for assuming that this particular process is composed of non-fibrillar protoplasm.

And now a word on a question which has arisen out of the controversy to which I have just alluded. Can the neuroglia fibre live independently of the cell body? Possibly, but that existence is qualified by certain conditions. It appears that the neuroglia cell in the fully-developed form has a definite period of life, that there is a cycle in its history, that in its earliest form it is a nucleated mass of structureless protoplasm, that the formation of its contained fibres is a comparatively late phase, and that in the stage of devolution the nucleus and investing protoplasm disappears, leaving nothing but the fibrils behind. Unless some transition of this nature takes place, it is impossible to explain many forms of sclerosis in which the method of Weigert, and several other methods, display a dense fretwork free from nuclei of any description and composed exclusively of delicate fibrils.

As with the method of Golgi, so with the method of Weigert; as it stands at present it does not commend itself

to those investigating the condition of diseased tissues, because, for some unknown reason, it is uncertain in its results, and the risk of spoiling tissue when the supply is limited is a deterrent to its employment; but, as we all know, these imperfections were an admitted source of regret to the illustrious professor at the time of his death.

§ 4.—*The Neuroglia Cell in Sections Stained by the Platinum Method of Ford Robertson.*

Dr. Ford Robertson insists strongly that the neuroglia is not composed of one element, as is generally believed, but of two kinds of cells, of which " the origin, morphology, and behaviour in morbid conditions are entirely distinct." This hypothesis is based on the revelations of a specially-devised method of impregnation with platinum. The elements which Dr. Ford Robertson has discovered, and for which he proposes the name " mesoglia," are blackened by platinum, while the ordinary neuroglia cell is only darkened. They are small cells, with scanty perinuclear protoplasm and three to six delicate processes which tend to branch dichotomously. These processes, compared with those of the ordinary neuroglia cell, are short and sometimes varicose; they form no vascular attachment, indeed, special relation with any other structure has not been determined. Though first observed in the brain of the dog, such cells have been found in man also, and they are said to occur throughout the central nervous system. Some may think that Dr. Ford Robertson's evidence is scarcely strong enough to clinch the supposed mesoblastic origin of these cells; even so, and granted that more information is required, their discovery alone is an important addition to our knowledge of the glia.

I have now exhausted the list of stock methods for the display of glial elements, though in practice other stains and reagents are of contributory service; for instance, I have frequently obtained a beautiful view of the neuroglia as it appears in the white substance of the brain in sections primarily stained for neurofibrils by the method of Bielschowsky; and rubin, as recommended by Kultschitzky,

Mallory's hæmatoxylin, and several of the carmine preparations now falling into disuse, may prove convenient in helping us out of difficulties, but none of these stains reveals any elements not demonstrable by the principal methods, and therefore may be dismissed.

§ 5.—*Summary Enumeration of Neuroglial Elements.*

(1) The large neuroglia cells of the fresh method of Dr. Bevan Lewis, corresponding to the spider cells of the method of Golgi, and also revealed by the method of Weigert. Synonyms : large spider cell, scavenger cell (Bevan Lewis), Kurzstrahler (Lenhossek and other German authorities).

(2) The stellate cell of the method of Golgi, also revealed by the method of Weigert, and possibly representing a phase in the development of No. 1. Synonyms : small spider cell, Langstrahler.

(3) The cell next the surface of the cortex, displayed by the method of Golgi, possibly representing a form taken by No..1 in an unusual environment. Synonym : glia cell of Retzius.

(4) The smaller cell of the fresh method of Dr. Bevan Lewis, sometimes spoken of as a nucleus of the neuroglia.

(5) The mesoglia cell of Dr. Ford Robertson.

CHAPTER 2.—DEVELOPMENT AND GROWTH OF THE NEUROGLIA.

In the year 1885 Golgi told us that he had seen epithelial cells in the chick's spinal cord which he thought gave origin to the neuroglia ; these cells lined the neural canal, and from processes which they sent out to the pia mater the neuroglial element seemed to grow.

Since this opening speculation, many others have devoted attention to the subject, and, extending Golgi's observations, they have obtained evidence which suggests that other neuroglial elements may spring from the primitive epithelial cells of the central canal as well as from cells of the neural canal, and others, again, from mesodermic elements, penetrating the nervous system along with the embryonic blood-

vessels. In short, our information leads us to suppose that the neuroglia is descended from both epiblast and mesoblast.

And now, referring the reader desirous of further details on the early development of the neuroglia to the monographs of Golgi, His, Capobianco and Fragnito, and Ford Robertson, we can pass to a matter of more immediate interest, the history of the neuroglia in the later periods of life.

In this connection we seek information more precise and comprehensive than that already supplied on the series of tissue changes in the developed brain which end in sclerosis. And when we analyse our requirements we find that they nearly all revolve round one question, whether this sclerosis is brought about by a proliferation and hyperplasia of pre-existing elements or by the formation of new elements? This question I shall try and answer.

Thinking that profit might accrue from closely watching the sequence of events in the tissues surrounding cerebral lesions, both those arising in nature and those of artificial production, I carried out a special series of observations. For the artificial lesion I took a number of white rats, plunged a red-hot needle into the brain of each, and then killed the animals and examined the lesion after periods varying between one and twenty-one days. The brains of a series of cases of cerebral softening in the human subject, which I have collected and placed in the museum at Rainhill Asylum, afforded rich material for examining the changes in a natural lesion; more than this, the latter study safeguarded me against the objection that my results might have been invalidated by structural differences between the human brain and the brain of the rat.

In narrating the conclusions drawn from this examination, it will be convenient to take up in turn the varieties of cells met with and trace their life history. This will embrace an account of cells which I will classify as follows :—

(1) Large mononuclear phagocytes.

(2) Polymorphonuclear leucocytes and compound granular cells.

(3) Eosinophile cells.

(4) Lymphocytes or lymphoid cells.

§ 1.—*The Large Mononuclear Phagocytes.*

By the large mononucleated phagocytes (the designation is borrowed from Beattie) I mean cells which are, without doubt, the most important constituents in the conditions with which I am dealing. They are considerably larger than a leucocyte; their nucleus is large, crescentric, or reniform, and usually eccentric; it often touches the margin of the cell, and is supplied with chromatin, scanty and sometimes knobbed beneath the nuclear membrane. A nucleolus is almost always recognisable; the body protoplasm is scanty, with most dyes it remains homogeneous, but with Unna's alkaline methylene blue it stains darkly and shows some fine granules. These are the characters in the first stage of development, and I think it will not be denied that such cells are identical with cells described by many other observers in different inflammatory conditions, and called variously *large mononucleated leucocytes* (Metchnikoff), *infiltration cells* (von Marschalko), *pseudo-plasma cells* (Hodara), &c. Let us follow the history of these cells. In the early stage of a lesion, be it a hæmorrhage, a softening, or an artificial destruction, they are not at all prominent; if, however, we search along the vessel walls, particularly along the walls of vessels lying just without the focus of destruction, we may find what I take to be the originals of these cells. In the first state they appear to consist of nucleus alone; at any rate, the investing ring of protoplasm is extremely delicate, and it is at this stage that we get a hint as to their origin, for they are seen in such intimate connection with the walls of capillaries that it seems certain they are derived either from the endothelium lining these vessels or from contiguous lymphatics. It is not clear how they multiply, but, although I have not seen mitosis, I believe they divide by this method. Detached from the vessel wall, I imagine they next migrate to surrounding tissues, and their further development belongs to another stage.

In a similar lesion about six days old the conditions are changed; difficult to find previously, the cells in question now seem abundant, but this apparent increase in number is due in no small measure to an increase in size; they

approach the mature state. The nucleus remains as it was, but is so eccentric that it often looks as if it were on the point of breaking away from the cell. The scanty ring of body protoplasm is supplanted by a copious, pale-stained, homogeneous, or finely-stained mass, from the serrated edges of which many coarse processes extend, and it is significant that one of these processes establishes a direct connection with the nearest capillary or arteriole. Next, after a few days, the cell becomes reduced in size and the protoplasm of the processes condensed and converted into deeply-stained fibrils.[1]

Cells of this character may be recognised for weeks and even months after the preliminary disturbance, and may be studied conveniently in the tissues surrounding a patch of " yellow softening," where they are present in great abundance. In such material I have observed changes in these cells which have an important bearing on the histogenesis of sclerosis. Thus, as the cells grow older they lose their distended globose figure, and their processes become larger and more attenuated. And in this stage one is struck by the resemblance they bear to the larger neuroglia cells of the normal brain : indeed, the appearances afford proof, almost positive, that the commoner forms of sclerosis are brought about by the deposition and metamorphosis of new elements, and not by the proliferation of pre-existent cells ; also they strengthen our belief in the statement of Fragnito and Capobianco, that in the course of development the ingrowing blood-vessel is an important channel for the convection and introduction of the nuclei from which the neuroglia grows.

Passing on to the final stage in the history of these cells, displayed, for example, in the walls of an excavation resulting from old softening, the case is one of still further shrinkage. As an outcome of contraction and failure of nutrition from autochthonous vascular obliteration, the body

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[1] When making these observations I had forgotten for the time being that Dr. Watson had made a study, wanting nothing in exactitude, of the developing neuroglia in the brain of the juvenile general paralytic. It is satisfactory to find, however, that what is written above is quite in harmony with Dr. Watson's fuller and more precise account. (*Archives of Neurol. London County Asylums*, ii., 1903.)

and nucleus of the cell either disappear or become changed into small, round, deeply-stained nuclei ; the processes gain independence, but remain as attenuated and filamentous fibrils contributing to the formation of a network of great density.   Touching the nuclear remnants, it is possible that they represent what are often called the nuclei of the neuroglia, that is, deeply-stained, circular, or oval nuclei ; and, as it is absurd to think of a nucleus without function, it is possible that these bodies persist to exert some influence in the maintenance of adjacent neuroglia fibres.

Concerning the function of the cells, the life history of which has just been given, I have no hesitation in agreeing with Beattie and others in saying that they possess phagocytic properties, because in the swollen state it is common to see particles of blood pigment, the products of myelinic disintegration, and even nucleated bodies (leucocytes or lymphocytes) included in the cell body.   I do not think, however, that they play such an important *rôle* in the absorption and removal of diseased and foreign matter as do the leucocytes ; the part they fill in a later phase, that of binding and strengthening the zone of substance bordering the destroyed area, is of greater importance.   Then, speaking of the function of neuroglia cells in general, it is in accordance with these data to suppose that in certain phases a cell may act, as Bevan Lewis suggests, as a scavenger, while in others it may serve as connective tissue, and in the latter capacity coincidently it might fulfil the part of an isolator (Eurich, &c.).   That these cells are directly connected with the lymphatic system is for me difficult to believe, but that in an indirect manner they serve as drains for lymphatic fluid is readily credible, and in this capacity it seems of little moment that the vascular process should be solid instead of canaliculated, a point out of which some have made capital in criticising this hypothesis.   Here the siphonic action of a piece of string or worsted is a physical truth to be held in view.

Satisfied that the cell described is the most important element in the process of repair as it affects the brain substance, only a short account of other cells met with is called for.

§ 2.—*The Polymorphonuclear Leucocytes and Compound Granular Cells.*

In all artificially-produced and many natural lesions, in early and in late stages of the process, these cells, lying collected within and in the neighbourhood of obstructed blood-vessels, are prominent objects. So often are they choked with masses of blood pigment, altered proteids and detritus, that there can be no doubt they are more active agents in the removal of products of degeneration and disease than the large mononucleated cells; moreover, in this case they re-exhibit the phagocytic properties they are known to show in those conditions in which micro-organisms are the principal objects for removal.

The constant presence of these polymorphonuclear leucocytes in the cases of cerebral lesion in hand has naturally excited the suspicion that one might be a transition form of the other; more than this the frequent occurrence of collections of kindred leucocytes (compound granular cells, as they are sometimes called) along the blood-vessels in patches of disseminated sclerosis and slowly-progressing myelitis, appears to favour the possibility that these are the originals of glial or connective tissue cells. I have therefore taken considerable pains to arrive at the truth on these points, and I can say now that, while my specimens provide abundant illustrations of swelling, fragmentation, and dissolution of these elements, all proof of their persistence and metamorphosis into the large mononucleated astrocyte is absent.

§ 3.—*Eosinophile Cells.*

The coarsely-granular eosinophile cells of the blood seem to play no part of importance in the process of repair.

§ 4.—*Lymphocytes or Lymphoid Cells.*

The plasma cells of von Marschalko have been attracting attention lately, because it has been stated that they are pathognomonic of general paralysis of the insane, and, as they are present in some of the conditions of which I shall treat,

they must be noticed. According to von Marschalko, they are derived from the lymphocytes or, as he calls them, the lymphoid cells of the blood, and they are described as having scanty, non-granular protoplasm, and an eccentric oval nucleus showing several chromatin granules and a nucleolus.

These cells resemble in many particulars the large mono-nuclear phagocytes in their earliest state of development, and whether they are derived from the endothelium of blood-vessels or from lymphocytes, it is my belief that they are identical with these phagocytes.

CHAPTER 3.—TUBEROSE SCLEROSIS.

Synonyms. — Sclérose tubereuse ou hypertrophique du cerveau (Bourneville). Multiple tuberöse Sklerose des Gehirns. Hypertrophic nodular gliosis (Sailer). Neurogliosis ganglio-cellularis diffusa (Hartdegen and Neurath). Anoia (Sherlock).

First described by Bourneville in the year 1880, tuberose sclerosis is one of the most extraordinary diseases with which the neuro-pathologist has to deal. Not only are the potato-like (hence the name tuberose) masses of sclerosis in the brain unique in kind, but the accompanying affections of parts related neither to the brain nor to one another are as singular as they are difficult to explain.

Sailer found twenty-eight cases reported in medical literature. I have not been so fortunate; still, I have read accounts of twenty ; and on running over the salient clinical features, the first point which struck me, one which I desire specially to emphasise, is that no less than seventeen suffered from idiocy or imbecility, and that, even in the remaining three, congenital mental weakness could not be excluded. This complication, remarkable in itself, suggests an intrauterine origin for the cerebral disease which under-lies it.

Convulsions, identical with those of ordinary ideopathic epilepsy, form a second clinical manifestation, and although unmentioned in some reports, seem to have been invariably present in all the best recorded cases.

The frequent and, I believe, constant occurrence of the

peculiar and rare skin affection, adenoma sebaceum,[1] is a third sign, which, taken in conjunction with those just mentioned, as well as the youth of the patient, may lead to a diagnosis of the disease during life. The age limit for the occurrence of this disease is 25 years.

Great patches of indurated cortex, projecting nodules in the ventricles of the brain, and fibroid subcapsular tumours in the kidney, complete the extraordinary combination.

While most writers make no attempt to explain the remarkable complex of diseases, the pathology of the cerebral changes has been the subject of much speculation. Taking a retrospect we find that the view meeting most support—it is the only one which brings all the somatic changes into line—is that we have to deal with some obscure developmental anomaly of the nervous system. And touching the time of life at which this arises, it is probable that the process is in activity at birth, because Hartdegen has recorded a case in a newly-born infant. It appears also that although the germs may be sown earlier, they cannot be active before about the seventh month of intrauterine life, the month when the plan of the sulci and gyri is laid down. We are entitled to this assumption because we have learned from our studies of porencephaly that when the destructive lesion peculiar to that disease occurs prior to the seventh month, the effort on the part of the growing cerebrum to make good the deficiency results in distortion and a characteristic fan-shaped and bizarre arrangement of sulci and gyri around the lesion. When, on the other hand, the lesion occurs after the seventh month the gyri and sulci surrounding the destroyed part can all be identified and the arrangement is orderly. Now, in tuberose sclerosis, in spite of the deposit of great masses of fibroid

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[1] Adenoma sebaceum is a congenital affection having a predilection for the skin covering the bridge of the nose and the naso-labial folds; it is said to consist of hypertrophy of the sebaceous glands, which appear as minute, shotty nodules, lifting the epidermis and projecting above the general surface level. Pringle gives a good and succinct account of the disease in "Quain's Dictionary of Medicine" (3rd edition, London, 1902), and mentions the interesting facts that the observed cases have generally been afflicted with mental disease, and that other congenital diseases of the skin, such as warts, moles, nævi, and fibromata, have commonly co-existed.

material all over the brain, there is no disturbance of external morphology.   Therefore, knowing the distorting effects of cicatrisation, we cannot suppose that the sclerotic process assumes activity before the time I have mentioned.

Other views on the genesis of the condition can be soon dismissed.   Fürstner and Stühlinger, in assuming that a leptomeningitis arising in intrauterine life or early youth is the cause of a chronic gliosis, not only take an unwarranted liberty, but fail to account for the other somatic changes.

Koch's explanation seems to rest solely on a coincidence. In his case, thickening and adhesion of the pia mater beneath an old fracture of the parietal bone betrayed a difficult labour, and the application of forceps, which he was led to regard as a cause of the sclerosis; but we have had so many cases of tuberous sclerosis not so complicated that this suggestion cannot be entertained.

The fourth view, that of Scarpatetti, puts the onus of the disease on syphilis in the parents, " as a result of which multiple hæmorrhages affect the brain of the offspring at an important period of intrauterine development and call forth an extremely chronic form of reactive inflammation." This, again, fails to explain the invariable coexistence of the changes in the skin and kidneys; moreover, the constancy of the syphilitic taint has yet to be proved.

A microscopic examination seems to have been carried out in most of the recorded cases, and all observers agree in stating that the brain masses are composed of a dense network of proliferated neuroglia, choking and destroying the nerve-cell and nerve-fibre elements; only three writers, Sailer, Hartdegen and Neurath, mention the presence of scattered but exquisitely formed giant or ganglionic nerve cells.   Such cells are most interesting constituents of the masses; they occur in my specimen, and, since in a preliminary examination I overlooked them, I am inclined to think that others may have done the same.   More than this, I think that they are constantly present.   Accordingly, Hartdegen and Neurath are misleading when they call the disease " glioma gangliocellulare," for, although this name

correctly conveys the histology of the condition, when unqualified it creates the false impression that it is a disease distinct from tuberose sclerosis. Besides, we must not forget that there is another altogether different form of cerebral sclerosis associated with the presence of ganglionic nerve cells.

I will now proceed with the account of my case.

Clinical History.

The patient, a male, was admitted to Rainhill Asylum at the age of 6 years, and died therein at the age of 16. He came from a workhouse, and, unfortunately, no information regarding his family history could be obtained. Examination, on admission, revealed no sensory, motor or nutritional abnormality, but adenoma sebaceum was noticed affecting the skin covering the bridge of the nose and the naso-labial folds. Though congenital syphilis could not be excluded, the teeth were in good condition, and there were no outward indications of this disease. His mental state was one of idiocy. When spoken to he lifted his head, but his expression proved that he did not comprehend language; nor could he use it. He would pick up objects and handle them in an aimless way, but did not resent their removal, apparently forgetting that he had just had them in his possession. He was ill-tempered, restless, given to wandering about in an objectless manner, and to distorting his body and making grimaces.

He suffered from epilepsy, and this is the sequence of events observed in a fit occurring soon after admission. The opening cry was succeeded by conjugate deviation of the eyes to the right, and by dextriversion of the hand. The spasm was more marked in, and almost confined to, the muscles of the left side. When recovering, he placed his hands to his mouth and moved his jaws as if chewing at a bone. There was no expulsion of fæces or urine.

Beyond learning to understand and carry out simple instructions, the boy made no mental progress; physically, on the other hand, he developed normally, with this exception, his cranium failed to expand in proportion to his body growth, and left him distinctly microcephalic. He continued to suffer from epilepsy, averaging five fits a month, a number which dropped to one a month during the last year of life. Five months before death he was treated in the infirmary for an obscure attack of

pyrexia. This was transitory, and, at the time, regarded as trivial, but when he returned to the care of his usual attendant it was noticed not only that he was more apathetic and irritable than before, but that he was quite blind. (The necropsy proved that this attack was due to occlusion of both posterior cerebral arteries.) After this he gradually failed, and death was ascribed to exhaustion from epilepsy.

It is noteworthy that the record of the case contains no reference whatever to tremor, to paresis, or to any similar manifestation which we might expect to be associated with the cerebral sclerosis.

Anatomical Examination.

The Brain.—The brain was below the average in size and weight, the encephalon scaled 1,210 grammes, the right hemisphere 476 grammes, the left hemisphere 500 grammes, both unstripped, and the cerebellum with the pons and medulla 157 grammes. The occipital lobes were reduced in size by bilateral adventitious softening, to be described presently; but there was no lobar deformity or disparity which we could set down to defective development, and, in accordance with my introductory remarks, the disposition of gyri and sulci was free from striking peculiarity. (Fig. 1.)

The sclerosed masses characterising the disease did not obtrude, indeed, at first glance the surface appeared healthy; on closer inspection, however, numerous patches were observed, twelve or more in each hemisphere, some circular, others irregular in form, ranging between 1·5 and 5 cm. in diameter, and universally distributed, although chiefly occupying the frontal lobes of both sides, and the parieto-temporal region of the right side. These patches were characterised by an extraordinary firmness—they were little softer than costal cartilage—by a paler tint and a more granular aspect than surrounding parts, by projecting slightly above the surface level and by being coated with pia, not adherent, but poorer in vessels and more delicate than the rest. It was noticed, further, that some of these patches presented slight central umbilication, that the proximal wall or lip of bordering sulci was bulged so as to operculate the
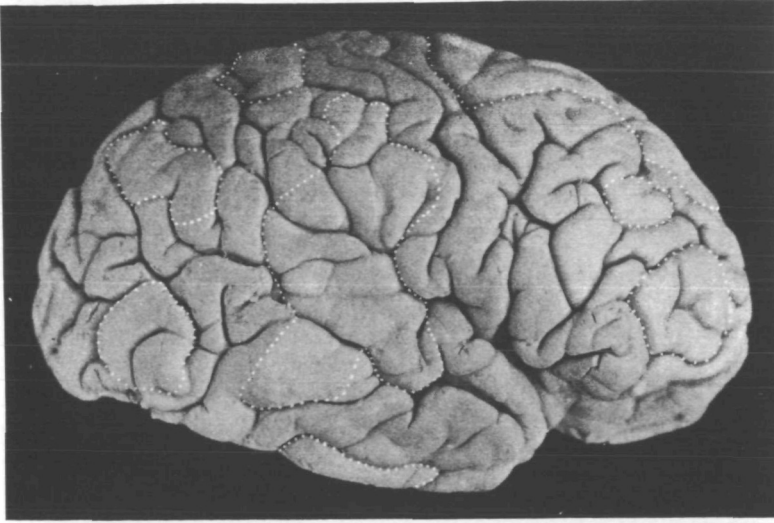
FIG. 1.

Photograph of the outer surface of the right cerebral hemisphere in the author's case of tuberose sclerosis. The distribution of the sclerosis is indicated by the dotted lines. The patches cause no disturbance in the plan of the convolutions.

FIG. 2.

Microphotograph of a giant nerve-cell from one of the sclerosed patches. × 400. In the original specimen, stained by Bielschowsky's method neuro-fibrils can be plainly seen.

opposite distal wall (a manifestation of cortical hypertrophy), and that in most cases the outline was sharp, though occasionally the passage from cartilaginous firmness to normal consistence was gradual. On section, the cortex was manifestly increased in depth, and the depth of invasion of the white substance was not in proportion to the surface extent; indeed, I think it may be correctly said that the sclerosis was mainly confined to the cortex and that only the immediately subjacent white substance was affected. This applied, at any rate, to most of the deposits; therefore, in regard to morphology, while the term "tuberose" aptly expressed the outward appearance of the masses it did not fit the sectional view.

So much for the cortical deposits. I have now to describe another variety of neoplasm seen on opening the lateral ventricles, which were dilated. These growths were of quite a different character, small (about the size of a split pea), white and very hard, they projected above the surface and were distributed along the lines of the venules, coursing over the basal nuclei and draining into the main vein of the corpus striatum. Others do not seem to have noticed this relation to the venules, but it is important and will be referred to again in discussing the histogenesis of the disease. One deposit, larger than the rest and situated beneath the ependyma lining the anterior horn of the lateral ventricle, appeared at first sight to be of different nature, but microscopic examination proved that this was not so. Subependymal growths of this description have been repeatedly observed in "tuberose sclerosis," and their occurrence quite away from the surface of the brain suggests that the original germs of the disease are sown elsewhere in addition to the cortex.

The occipital shrinkage previously alluded to was the result of bilateral occlusion by thrombosis of the posterior cerebral artery; the subsequent softening comprised the "area striata" (the area presenting the line of Gennari) and a portion of the subjacent lingual lobule. The affected parts were yellowish-brown and much contracted. Seeking a cause for the thrombosis, we found sclerosed masses

attacking the cortex in the stem of each calcarine fissure; they bulged into the fissures, and their pressure must have directly induced stasis and coagulation in the arteries. Such a bilateral softening is rare, and explained the patient's sudden blindness.

The cerebellum, pons, medulla, cranial nerves, spinal cord, and all remaining structures pertaining to the nervous system, appeared normal.

In the trunk the condition of the kidneys attracted attention. In each quite a dozen firm, round, white growths, 1 to 5 mm. in diameter, were seen projecting above the surface level; they were implanted in the cortex, but not deeply, as some came away with the capsule when it was stripped; they did not occur in the medullary substance, and otherwise the kidneys were healthy. Similar growths have been constantly found in the kidneys in other cases.[1]

In the left lung we found two wedge-shaped patches, solid and uniformly gray in colour, which we took for resolving infarcts, but there was no zone of congestion around and no heart disease[2] to account for them, so that our diagnosis may have been at fault.

The remaining organs were free from special disease.

Microscopic Examination.

(1) *Sclerosed Cortex.*

(a) *Nerve fibres.*—Sections which I have treated by the method of Wolters-Kulschitzky show profound want of fibres. There is no trace of a zonal layer, delicate fibrils are scattered about in the supraradiary layer, a line of Baillarger is barely discernible, the interradiary spaces are swept almost bare, only a few fibres remain to mark the position of the radiations of Meynert, and even these seem to be bereft of their myelinic investment. Such changes are more pronounced in the centre than at the periphery of the masses.

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[1] In Sailer's case a large "adeno-sarcoma" of the kidney was found, but I am inclined to doubt the correctness of the microscopic diagnosis.
[2] Ugolotti found a "fibro-myoma" in the heart muscle.

(b) *Nerve cells.*—It might be supposed that nerve cells could not exist in the presence of such profound tissue metamorphosis; they do, however, and their nature and condition demands careful consideration. There is, of course, a fall in numerical representation, and it varies in relation to the march of the sclerosis, being greatest in the most severely sclerosed parts, but nowhere is the cell destruction complete. It appears that the first cells to go are those of small size, namely, cells in the first, second, and fourth (stellate) layers. Some larger pyramids and some fusiform cells remain to the end, but while they retain their erect position and their apical and basal processes, their bodies become attenuated and their reaction to stains changes. With Nissl's method the protoplasm stains deeply and homogeneously, and Bielschowsky's process displays no neurofibrils.

Mention of neurofibrils leads on to another most extraordinary feature of this disease, one to which I have already briefly alluded; it is that the sclerosis is associated with the deposit or evolution of aberrant nerve cells, cells which in point of size and shape are akin to the large multipolar " motor " cells of the normal precentral cortex, and for which, therefore, the designation " giant " or " ganglion " cell is appropriate. (Fig. 2.) Such cells are not numerous, only one or two may be discovered in a section measuring two square centimetres; they affect no particular cortical level, at times being found near the surface, at others in the depths, and occasionally even in the subjacent white substance; they may occur in groups, but it is commoner to find them solitary. Structurally they are peculiar, inasmuch as the method of Nissl displays a protoplasm devoid of all chromophilic elements, non-pigmented, and practically homogeneous, while the method of Bielschowsky proves the persistence of neurofibrils.

It is a point of interest and importance that cells of this description have been recognised in all the masses examined, and, whether growing in the frontal, central, parietal, temporal, or occipital region, they have presented a uniform appearance.

(c) *Matrix.*—Examining a piece of tissue from the centre of one of these indurated areas, we find a matrix composed of a dense network of indefinite structure, a tissue showing neither nuclei nor distinct fibres, and one which is probably the outcome of a past neuroglial proliferation. Active neuroglia cells (methods of Weigert and Bielschowsky and staining with rubin) vary in abundance in different parts of the deposit and in different deposits; few are found in the central portions of the masses, nor are bodies which we can call nuclei of the neuroglia present in this situation. At the lateral edge of the masses, however, particularly around the gland-like structures to be described presently, and all along the surface of the cortex, I have found cells of glial nature in great abundance. Some of these are shown in the accompanying drawings (fig. 3), and attention is invited to their peculiar character, especially their great size, their succulent bodies, and their coarse processes.

(d) *Blood-vessels.*—Nowhere are the blood-vessels numerous, and those seen have normal, thin walls.

(e) *Other structures.*—I have now to describe some structures which have an important bearing on the histogenesis of the masses, structures so peculiar in themselves, and so foreign to the cortex cerebri, indeed, to any part of the nervous system, that I consider it necessary to illustrate one (fig. 3). They are found at the peripheral or growing edge of the deposit, and may be described as tubular glands, leading from the surface inwards for a distance of about 1 mm., and ending in blind alveolar expansions. Not having studied them in serial sections, I cannot tell definitely whether they branch, but I think they do. The lining cells are of columnar form, pallid, and finely granular, and they contain a well-stained nucleus. The basal membrane is indistinct, but " centro-acinar " cells (Langerhans) are present in the lumen of the tube from end to end. These " glands "—so I suppose we must call them—are not numerous, for although I saw one or more ducts cut transversely in almost every section, not often did I find the mouth and whole length of a gland as here represented. But while "glands," such as I have described, are only found
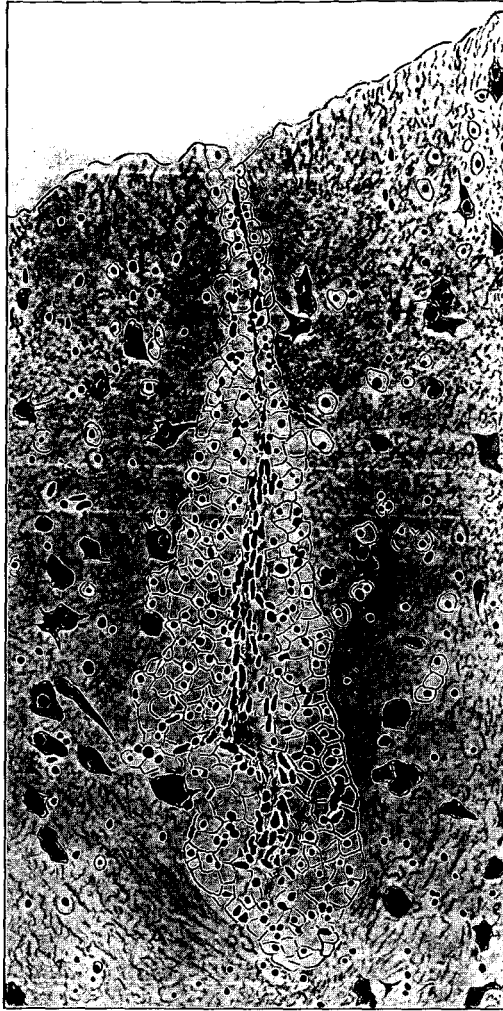
FIG. 3.

Tuberose Sclerosis.

A camera lucida drawing of one of the remarkable gland-like structures described in the text; it leads down from the surface, is tubular, ends in a blind alveolar expansion, and is lined with columnar cells.

Young neuroglia cells are to be observed in the neighbourhood. (Shaded in the figure.)

Beilschowsky's stain. Magnification × 200.

in what I take to be the growing part of the deposits, at the periphery, indications are not wanting that the remainder has been permeated at some time by similar structures, for dotted about in all situations are circular or oval cells 10 to 15 μ in diameter, without processes, finely granular, and with a deeply-stained nucleus 2 to 3 μ in diameter. These I take to be glandular vestigia, not only because they resemble gland epithelium cells more than anything else, but because their number and arrangement varies in different parts of each deposit; in parts where the cortex is of cartilaginous hardness, and the process apparently most advanced, such cells, though present, are not numerous; in other growths which are softer, and apparently of more recent origin, they occur in abundance; moreover, reminiscent of the tabular arrangement, several cells are occasionally seen in line and in apposition.

(2) *The Subependymal Growths.*

The subependymal tumours have not the same microscopic characters as those in the cortex. A single layer of ependymal epithelial cells coats the surface. Immediately below, separating the surface from the main growth, is a shallow layer, composed of densely interwoven delicate fibrils, and containing short lines and groups of ependymal cells. In this layer runs the vein which the growths follow; it looks distended, but the wall is healthy, and so likewise are the accompanying arteries.

The basis of the growth is composed of a more or less open network of coarse fibrous tissue (much too coarse to be called glial tissue), and a remarkable appearance is imparted by an abundance of corpora arenacea, like those seen in a choroid plexus which has undergone calcareous degeneration. Small vessels are numerous, and, since they nearly all have thick calcereous walls, and since where they are most numerous, so also are the corpora arenacea, I think there can be no doubt, as has been inferred by previous observers in other diseases, that there is a developmental relation between the two.

Of nerve cells there are none; indeed, in all the small

ependymal growths nucleated cells of any description are
scarce. The larger ependymal growth, however, which I
have especially referred to, contains, and in fact is almost
entirely composed, of cells so remarkable that I figure them
(fig. 4). They are elongated and fusiform, and have homo-
geneous protoplasm and one to three oval nuclei. It is
difficult to arrive at a conclusion concerning the nature of
these cells, but I hazard the opinion that they are of
endothelial origin, and this on account of their resemblance
to cells seen in growths regarded as endotheliomata. The
difference in appearance between this and the smaller
ependymal growths does not necessarily signify a different
origin. I take it that the smaller growths are the older, and
that they have undergone fibrous and calcareous degenerative
changes.

(3) *The Tumours in the Kidneys.*

On microscopic examination these tumours are found to
be sharply circumscribed, but not encapsulated. They retain
no renal structure, and are composed for the most part of
long nucleated cells, smaller, but otherwise not unlike those
seen in the larger subependymal cerebral growth. Blood-
vessels are numerous, and many show thickening of the
adventitia.

Reflecting on the remarkable complex of changes, naked
eye and microscopic, furnished by this disease, interest at
once turns on the question of histogenesis. And, in con-
sidering the origin of the various growths, weight attaches
to the determination of the nature and source of several
products revealed by the microscope ; first, the acinoid
structures, which I seem to have been the first to recognise,
in the masses of sclerosis on the surface of the brain ;
secondly, the giant nerve cells finding a place in the same
masses ; thirdly, the cells composing the intraventricular
and the renal growths ; and, lastly, the components of the
cutaneous deposits.

In taking a retrospect of the propositions which have
been advanced to account for the cerebral growths, I

FIG. 4.

Tuberose Sclerosis.

A drawing of some of the endothelioid cells in one of the subependymal ventricular growths.

Silver method of Bielschowsky.   × 500.

indicated the certainty that the morbid process, whatever it be, must be active during intrauterine life, although not before the seventh month. It is likely, therefore, that we have to deal with some aberration or disturbance of development, and along this line we will pursue our inquiry.

The preliminary point as to which of the three embryonic tissues, epiblast, mesoblast, or hypoblast, is selected for affection we can soon dismiss, not because the settlement of the point is unimportant, but because the tissue giving rise to one of the organs in which we are interested, the kidney, is undetermined. We know that the nervous system and the skin spring from epiblast, but which layer provides the kidney is still unsettled. Hence we cannot group the affected organs and parts into one category, stating that they are of common embryonic origin. Nor is it necessary, for, in describing the histology of the renal and the intraventricular growths, I insisted that the principal cell constitutents of both had characters reminiscent of cells occurring in endothelial neoplasms; likewise in the case of the growths lodged in the cerebral cortex, I pointed out that gland-like endothelial expansions were present, and were probably the cause of the neuroglial proliferation. This structural correlation is of great importance, in fact, it affords a clue to the solution of our problem, because if my primary assumption that all these growths have an endothelial basis is correct, it only remains to find the source of the endothelial elements. We are not without a guide. I think that the lining cells of blood vessels—probably veins—or of perivascular lymphatics will supply our wants, and such a source, in explaining the occurrence of kindred growths in various organs and parts, related to one another neither spacially nor developmentally, will overcome one serious difficulty.

While advancing my arguments for the vascular origin of these endothelial elements, it will be convenient to mention a few points which annul a possible alternative proposition, that they arise from endothelium-clad membranes. In the first place, a relation between the growths in the cortex cerebri and the arachnoid endothelium

might be suggested. Of this I will say merely, there is no evidence : there is no thickening, no adhesion, nothing to favour such a relation. On the other hand, the growths in question arise in a part which is particularly rich in arterioles, venules and perivascular lymph spaces; moreover, when the specific constituents to which I have drawn attention, the gland-like structures, are seen on longitudinal section, the arrangement of cells lining the mouth and the neck is singularly reminiscent of what one has often seen in cerebral perivascular channels.

Secondly, the intraventricular growths might be referred to a proliferation of cells of the ependymal lining, but, as I have shown, there is no indication of ependymal hyperplasia, and, on the other hand, there is clear and suggestive evidence of an intimate relation with subependymal venules.

Thirdly, the peritoneum might be thought to give rise to the renal growths, but this is in opposition to the observation that growths occur on the dorsal surface of the kidney, well away from the peritoneum, while, in support of my contention, the close relation of these growths with the venæ stellatæ cannot be gainsaid.

Lastly, in the case of the cutaneous tumours the endothelium of sebaceous glands is to be considered. At the same time, it must be remembered that these growths affect the most vascular part of the face, also, that in some histological reports written by dermatologists, the " nævoid " character of the growths is emphasised.

Therefore I feel justified in asserting that while the relation of the various growths to some endothelium-bearing structure is suggestive, that relation is neither so intimate nor so convincing as it is to the blood-vessels.

If, then, it be allowed that the endothelial cells forming the basis of these deposits is derived from blood or lymph channels, what is the process of evolution, and why should it be confined with such remarkable regularity to the same organs and parts ? These are questions which for the present must remain unanswered. We may surmise that the activity of the germinal elements giving rise to the growths has been deferred by some error in development, and that

they have continued to grow in an abortive and spurious fashion long after their appointed term of expansion and metamorphosis; and we may imagine that development has been disturbed by some unknown intrauterine, infective disorder, having, like scarlet fever and many other diseases and conditions which could be named, a predilection for unrelated organs and parts.

But apart from these speculations, I submit that the data I have set down favour my primary assumption that the complex of changes characterising this disease is the outcome of some evolutionary aberration or disturbance arising during the last few months of fœtal life, affecting the endothelium of blood-vessels or lymphatics, and resulting in a form of structural hyperplasia and heterotopism.

I have added the word heterotopism to this definition to cover the occurrence of giant nerve cells in the growths affecting the cerebral cortex, and my concluding remarks will be devoted to a consideration of these elements. To say the least, their presence is puzzling, and unfortunately our knowledge of the development of the nerve cell is not advanced sufficiently to admit of a definite explanation regarding their origin. I have noticed, however, in my studies of the neuroglia cell in the growing brain, that at a certain stage of development—prior to the formation of the processes—it is difficult to distinguish between the young neuroglia cell and the young nerve cell; and, although there is no developmental evidence to show that under normal conditions nerve cells, like neuroglia cells, are derived from elements pertaining to the vascular system, still the similarity in structure during development is suggestive, and I cannot help thinking that an embryonic disturbance might lead to an occasional exchange of form, to the aberration in development and the heterotopism of which this disease provides examples. Finally, although these nerve cells are most interesting constituents of the cortical masses, there is not the slightest evidence that they are active factors in the production of the gliosis; on the contrary, their presence favours the original assumption that tuberose sclerosis is the ultimate manifestation of some evolutionary aberration or disturbance.

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CHAPTER 4.—HYPERTROPHY OF THE CEREBRUM.

Synonyms.—Hypertrophic idiocy. Megalocephaly, macrocephaly.

Of these names hypertrophy of the cerebrum is in most common use, and, as I shall show presently, it fits histological findings : to the physiologist the name is not so apt, for whereas betterment of functional activity usually accompanies enlargement of an organ, the contrary is here the case.

It is wrong to describe tuberose sclerosis under the heading Hypertrophy of the Brain (*vide* "Quain's Dictionary of Medicine," last edition). By hypertrophy of the brain the majority of writers mean a specific disease in which simple, uniform enlargement of the organ, without definite lesion or cause, a state of cerebral gigantism, is the principal anatomical manifestation.

The correctness of including this condition in the category of sclerosis may be called in question. I do so, however, because certainly in the cases forming the basis of these remarks, induration was a pronounced feature, and I believe it has been so in all previously recorded cases. At the same time I recognise that the condition presents several important departures from the usual associations. In most forms of sclerosis shrinkage is an accompaniment, and for this shrinkage a proliferation of neuroglia or connective tissue is responsible; here, instead of shrinkage we meet expansion, and although, as I shall show, there is an undoubted proliferation of neuroglia, the disproportion between this and the induration is great. Further, the induration and the enlargement are general instead of local. And, touching causal factors, in the commoner forms of sclerosis an irritant, local or general, and a coincident destruction of nervous tissues have invariably been present, but in this disease we have no proof of the existence or action of an irritant and all the evidence is against any destruction of nerve tissue. It is evident, therefore, that we are face to face with an induration unique in kind, and obscure in origin.

Clinical Notes.

Case 1.—The first patient was a male, aged 29, who had been an inmate of Rainhill Asylum for fifteen years.

He was transferred from another asylum, and was without friends; hence no note concerning his family history or his childhood is recorded.

Being short in stature and having an immense head, a small trunk and delicate limbs poorly clad with muscles, he always presented a peculiar figure. All his movements were executed slowly, and he was readily fatigued, but there was no definite motor paralysis. So far as could be judged, cutaneous and special sensation were unimpaired. The commonly tested superficial and

deep reflexes were normal. No disease was detected in the organs of the trunk. He did not suffer from epilepsy, and there was no evidence of inherited syphilis.

Mentally he was an imbecile with a low degree of intellect; his vocabulary was so limited and his concepts so simple that he was quite unable to converse; he did not know his name or his age, and was rarely heard to say more than "give me a mug of tea." He smiled when taken notice of and evidently enjoyed some sense of conceit. A creature of spiteful impulses, he derived pleasure from attempting to injure aged and apparently feeble fellow-inmates, but, unable to discriminate between those who could retaliate and those who could not, and being weak himself, he received as much as he gave. He was unclean in his habits and addicted to self-abuse.

Necropsy.

As megalocephaly and hydrocephaly are sometimes confused during life, and I chanced to have at hand a hydrocephalic skull from a man of about the same age, I first made a series of comparative measurements. The figures are of sufficient interest to set down.

|	Megalocephaly.	Hydrocephaly.	Difference.
Circumference	59·5 cm.	64·3 cm.	− 48 mm.
Glabello-occipital length ..	19·6 ,,	20·8 ,,	− 12 ,,
Basi-bregmatic height	14·1 ,,	15·5 ,,	− 14 ,,
Vertical index	71·90 cm.	74·50 cm.	− 2·60 mm.
Cephalic index	77·1 cm.	82·6 cm.	− 5·5 mm.
Minimum frontal diameter ..	11·2 ,,	11·6 ,,	− 4 ,,
Stephanic diameter	14 ,,	14·5 ,,	− 5 ,,
Asterionic diameter	12·5 ,,	11 ,,	+ 15 ,,
Maximum transverse diameter ..	15·2 ,,	17·2 ,,	− 20 ,,
Frontal longitudinal arc.. ..	14·6 ,,	19 ,,	− 44 ,,
Parietal arc	16·4 ,,	20·5 ,,	− 41 ,,
Occipital arc	12·4 ,,	6·7 ,,	+ 57 ,,
Total arc	43·4 ,,	46·2 ,,	− 2·4 mm.
Vertical transverse arc, right ..	19·4 ,,	20 ,,	− 6 mm.
Vertical transverse arc, left ..	18·7 ,,	21 ,,	− 13 ,,
Total transverse arc	38·1 ,,	41 ,,	− 20 ,,
Basi—nasal length	10·1 ,,	10 ,,	+ 1 ,,
,, —alveolar length	9·4 ,,	9·4 ,,	0
Gnathic index	93·06 cm.	94 ,,	− 1·04 mm.
Asymmetry, frontal	R. + 4 mm.	0	
,, stephanic ..	R. + 10 mm.	0	
,, parietal	R. + 7 mm.	L. + 8 mm.	
,, asterionic ..	0	0	
Thickness of skull, frontal ..	10 mm.	3 mm.	+ 7 mm.
,, ,, occipital ..	12 ,,	5 ,,	+ 7 ,,
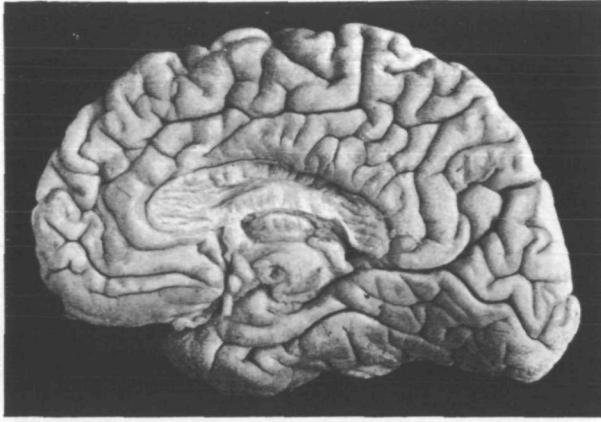
Fig. 5.

Hypertrophy of the Brain.

The inner surface of the right hemisphere from Case 1. In addition to the great size, the wealth of secondary sulci and the unusual distribution of parts in the region of the parieto-occipital fossa are noticeable.

Fig. 6.

The inner surface of the right hemisphere of the brain (weight 1,350 gms.) from a normal female, for comparison with fig. 5.

These measurements do not diverge from what might have been expected, and they definitely prove that the brain enlargement in the disease we are considering is not associated with faulty growth of the cranial bones, as in hydrocephaly. The principal discrepancy affects the longitudinal arc; thus, although the frontal and parietal arcs were much greater in the hydrocephalic specimen, the collapse of the occipital bone, in the same skull, so reduced the occipital arc that the total measurements came to be approximately equal.

Passing to the cranial contents, the dura mater was normal, and there was no excess of cerebro-spinal fluid. The soft meninges were slightly increased in thickness and easy to strip, but free from opacity. The basilar artery appeared small, but the remaining trunks, and likewise the main veins, were normal in size and distribution, and I may mention here that microscopic examination disclosed no changes in them.

The brain was universally enlarged and scaled as follows :—

Encephalon	1,775 grms.
Right cerebral hemisphere (unstripped) ...	816 ,,
,, ,, ,, (stripped) ...	775 ,,
Left ,, ,, (unstripped) ...	768 ,,
Cerebellum, pons and medulla	180 ,,

The inequality in weight between the two cerebral hemispheres was not associated with any obvious asymmetry, the various lobes were well represented, in fact, the appearances of a large and uncommonly well-developed brain were offered. The surface colour was healthy, but handling proclaimed an abnormal and pronounced increase in consistence.

The form of the individual gyri was normal, and there was a complete absence of local atrophy on the one hand, and local hypertrophy on the other. On attempting to define the various named gyri and sulci, an arrangement of extraordinary complexity was found; indeed, in the whole of my experience, embracing a study of the morphology of several hundreds of brains intimately, and of several thousands casually, I have never seen one which presented such

a wealth of secondary sulci, nor one in which guesswork had to be relied on so much in defining even the constant and better known sulci. But, since a full gyrological account will be of more interest to the anatomist than the pathologist, and will overburden the present article, I reserve details for a future anatomical paper. Here, in connection with the photographs reproduced, I will merely indicate that the fissure of Rolando has a remarkable course, and that the usual guide to its identification, the cingular incisure, is misplaced ; that the arrangement of parts in the quadrate and cuneate lobules is much disturbed by an abnormal disposition of elements constituting the parieto-occipital fissure or fossa; and that many fissures usually represented by simple lines are extensively ramified.

In my first notes of this case I find the statement, " wherever a sulcal annectant gyrus can come to the surface it has done so, hence the complexity of gyral arrangement." This, however, is not correct, because although, for example, it is true that the great arcus intercuneatus and much of the superior Rolandic annectant are exposed, the cuneo-lingual annectants in the posterior calcarine fissure and many others remain submerged. Therefore that assumption has been abandoned, and now, after more careful inspection, I favour the belief that the remarkable sulcal complexity has developed on common mechanical lines ; I would insist, however, on one fundamental difference between this and the normal brain, namely, that while the richly convoluted brain of the sane individual results from the restricted expansion of healthy substance containing a normal admixture of constituents, we deal here with the expansion of matter having qualitative defects, defects to be described presently under the heading " Microscopic Examination."

The cortex generally was increased in depth, but it is interesting that several of the usual naked eye, topical variations in depth and appearance were noticed ; for instance, the precentral cortex was appreciably deeper than the postcentral; of the frontal cortex the prefrontal was shallower than the rest, and in the visual area the line of Gennari was plainly visible.
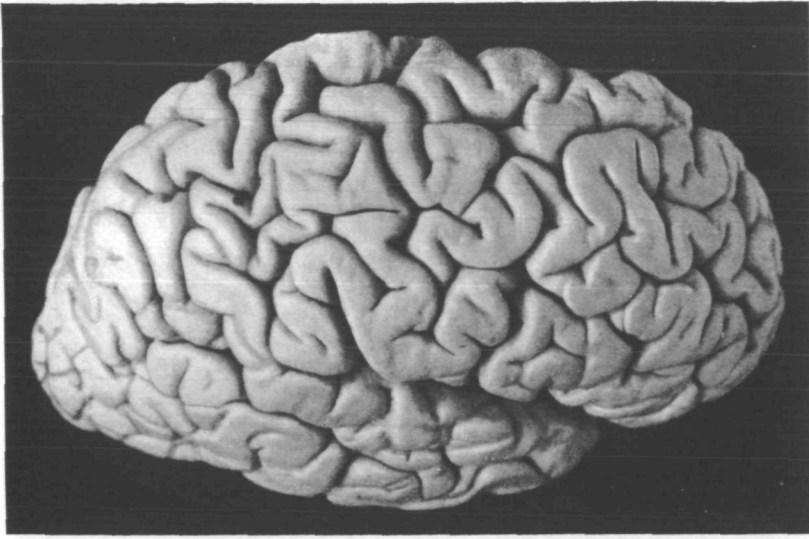
FIG. 7.

Hypertrophy of the Brain.

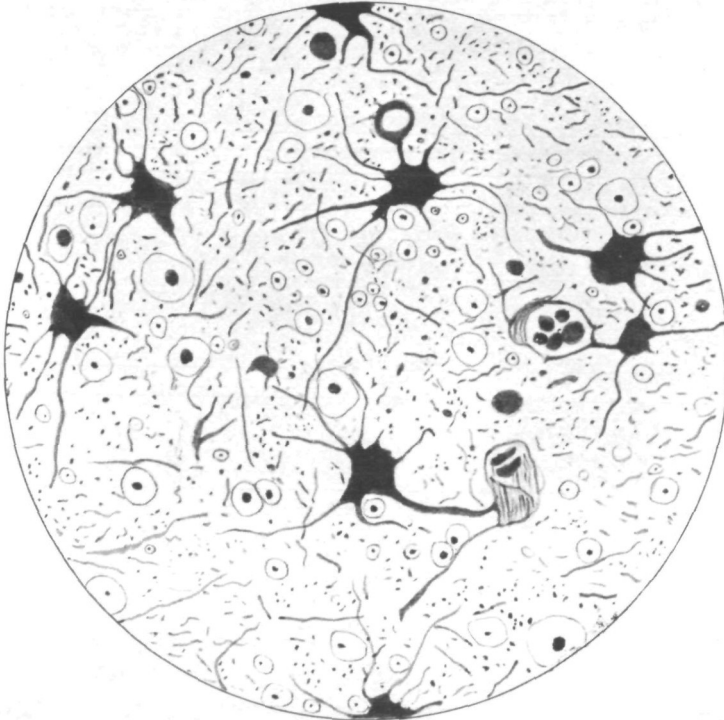The outer surface of the right hemisphere, from Case 1.

FIG. 8.

A reproduction of some of the large neuroglia cells present in the white substance of both cases of cerebral hypertrophy.

The white substance shared the general increase in bulk and looked healthy.

The lateral ventricles were not at all dilated; on the contrary, they were small in proportion to the size of the hemispheres; the ependyma was smooth. No abnormality of the basal nuclei could be seen. The corpus callosum was short, but stout. The anterior commissure was normal, the grey commissure smaller than usual. The septum lucidum, velum interpositum, choroid plexuses, and ventricular veins looked healthy.

The cerebellum, pons, medulla and spinal cord, were small in proportion to the cerebrum, but otherwise normal.

Examination of the trunk disclosed only the following points worth noting: a congenital malformation of the costal cartilage on the right side, the third and fourth being fused; universal plural adhesions, without thickening; œdema, congestion and some small gangrenous cavities in the lungs; old-standing mitral stenosis with much fibrous thickening of the cusps but little hypertrophy or dilation of the left ventricle or auricle; a small liver (945 grammes), congested and slightly cirrhosed, and congested spleen and kidneys.

Clinical Notes.

Case 2.—H. J. C., a male, aged 16, came from a private asylum, and again our record contains no reference to family or personal history.

Physically, no disability was apparent, and he was active in his movements.

A large but well-formed head and a bright expression suggested intelligence; on attempting to open a conversation, however, it was immediately discovered that he could neither speak nor understand the use of language; also, his general behaviour proclaimed a state of idiocy. He was mischievous; among other misdeeds he sometimes caused trouble by turning on gas and water taps, a product of imitation. When his wishes were not gratified, he displayed a vicious temper, and he was depraved in his habits.

It is remarkable that during the whole of his stay at Rainhill (five years) he did not have one epileptic fit, and yet status epilepticus—a series of forty-one seizures—was the cause of

death. The convulsions took the following form : during the
first ten seconds, drawing up of the legs, clenching of the fists,
half flexion of the arms and twitching of the facial muscles, all
bilateral, occurred in succession ; then followed snapping move-
ments and biting of the tongue. The concluding clonic stage was
prolonged and the apnœic exhaustion severe, so much so, that at
the end of the sixth fit the lungs were already œdematous. The
usual remedies were administered without benefit.

Necropsy.

The state of nutrition and the muscular and osseous
development were normal.

The head measured 22 inches in circumference, 8 inches
in the greatest sagittal diameter and 6½ inches in the
greatest bitemporal diameter. The forehead was high and
the parietal bones expansive, suggestive of hydrocephalus.
Placed anterior and internal to the parietal eminences were
two additional symmetrical elevations as large as the parietal
eminences. The interfrontal suture persisted. The calvarium
was of normal thickness and the dura mater healthy. The
pia arachnoid was opaque generally and thick, but not
adherent. There was obvious congestion, but the vessels
were normally distributed and had healthy walls.

For a boy of 16 years the brain was of great size. The
encephalon weighed 1,515 grammes ; the right hemisphere,
unstripped, 672 grammes ; stripped, 639 grammes ; the left
hemisphere, unstripped, 662 grammes ; the cerebullum, pons
and medulla, 145 grammes. The cerebral hemispheres were
equal, and the representation of the lobes symmetrical and
normal. The convolutions were perfectly formed, but the
sulcal plan, without being abnormal, was complicated by
many secondary ramifications, and various annectant gyri
usually submerged appeared on the surface. The cortex and
the white substance appeared to be healthy, but were dis-
tinctly increased in firmness. The ventricles were of normal
size and the ependyma smooth. No fault was discovered in
the commissures, basal nuclei, or remaining cerebral struc-
tures, and the same applies to the cerebellum, pons, medulla
and spinal cord, though they were perhaps small in propor-
tion to the cerebrum.

No change worthy of mention was found in the trunk.

Microscopic Examination.

The following account applies to both cases :—

(a) *Nerve Cells.*

Studying first the general lamination in sections taken from different parts and stained by the method of Nissl, it was astonishing not to find any positive abnormality. Whether taken from the frontal, parietal, temporal or occipital lobe, the sections showed an orderly columnar arrangement of cells, and both that disposition in layers and that representation of elements in the different layers known to characterise defined cerebral areas in the normal subject.

Going more into details I observed that the sectional outline of the cells, whether displayed by the method of Nissl, Golgi or Bielschowsky, was free from peculiarity, that the dendrons were normal in number and length, that in those cells which usually harbour chromophilic elements (Nissl bodies) such were visible, that when sections were silvered by the method of Bielschowsky neurofibrils appeared where they were expected, that there was no excess of pigment, and that none of those processless, pear-shaped, underdeveloped elements which we have seen in cases of idiocy were present.

Case of Macrocephalus.

			MM.				MM.
Layer 1	...	...	·278	...	...	...	·278
,, 2	...	...	·663	...	...	...	663
,, 3	...	...	·212				
,, 4	...	...	·236	...	...	...	·743
,, 5	...	...	·295				
		Total	...	...	1·684 mm.		

An Average Normal Case in Paraffin.

			MM.			MM.
Layer 1	...	...	·27713	...	...	·27713
,, 2	...	...	·83616	...	...	·83616
,, 3	...	...	·24117			
,, 4	...	...	·23592	...	...	·77875
,, 5	...	...	·30166			
		Total	...	1·89204 mm.		

(b) Nerve Fibres.

In sections stained by the method of Wolters-Kulschitzky I again saw nothing to associate with the defective mental state ; indeed, had I been uninformed on the history of the sections and had I judged by the normal standard, I would have said that both the general supply and the arrangement of nerve fibres were those of an uncommonly well-developed brain.

(c) Neuroglia.

With the neuroglia it was otherwise, and yet the proliferation did not equal what reporters of other cases led me to expect. Nor, although the increase in glial elements no doubt contributed to the firmness of the cerebral substance, would I describe the condition as a gliosis. The microscopic picture was as follows :—

In the first or plexiform layer, a part wherein we find a decided excess of glial cells in another disease characterised by neuroglial proliferation, general paralysis of the insane, there was, it is true, some increase in the number of these elements, but it was not pronounced, nor did one see those great succulent cells so common in the disease named.

As is usual in other diseases, even in general paralysis, glial cells were not found in any number in the remaining cortical layers. In the white substance, however, it was different ; here I have little hesitation in saying there was a true proliferation ; moreover, on comparing the cells in these sections with the cells in sections from cases of advanced general paralysis, I observed very slight differences, structural or numerical. It did not matter how the sections were stained, whether by the method of Weigert, Bevan Lewis, Golgi or Bielschowsky, the cells stood out plainly, and I immediately classified them as homologous with the larger neuroglia cells of Bevan Lewis. As may be judged from the accompanying drawing the cells were of great size ; they had many long, occasionally branched processes, and a stout vascular process ending in a sucker-like expansion on the vessel wall, and though the course pursued by the contained delicate, fibrillary elements seemed as usual to negative this,

there could be no question that the processes were attached to and formed integral parts of the cell ; the body protoplasm was granular and relatively copious, and enclosed a large, round or oval, deeply-stained nucleus.   (Fig. 8.)

Such, then, was the prevalent type of neuroglia cell ; in addition to these, cells of smaller size were noticed, but I am uncertain whether they were not large cells which had undergone retrograde changes ; also, there was an abundance of what are called nuclei of the neuroglia.

(d) Blood-Vessels.

In certain parts, for instance, the occipital region, the blood-vessels stood out prominently because they were congested, but nowhere were vessels seen with thickened or diseased walls—another difference from the condition found in general paralysis.

REVIEW OF THE MANIFESTATIONS OF HYPERTROPHY OF THE CEREBRUM.

Although megalocephaly must be reckoned a rare disease, the number of cases recorded from time to time has now reached well over double figures.   I do not pretend to have read all the reports, but I will insert a list here showing the weights of some of the brains described ; it will serve a purpose in demonstrating that while the brains in my cases do not approach the record they are still of extraordinary weight.

Reporter.			Sex and Age of Patient.			Weight of Encephalon.	
Walsem	..	..	..	Male, aged 21	..	..	2,850 grammes.
Simms	..	..	..	Male, aged (?)	..	..	2,400 ,,
Anton	..	..	..	Male, aged 20	..	..	2,055 ,,
Obersteiner	..	..	Male, aged 8	..	..	1,920 ,,
Brunet	..	..	..	Male, aged 18	..	..	1,780 ,,
Grant	..	..	..	Male, aged 43	..	..	1,869 ,,
Campbell	..	..	..	Male, aged 29	..	..	1,775 ,,
Bernardini	..	..	..	Female, aged (?)	..	..	1,755 ,,
Fletcher Beach	..	..	Male, aged 15	..	..	1,754 ,,
Brunet	..	..	..	Male, aged 17	..	..	1,632 ,,
Campbell	..	..	..	Male, aged 16	..	..	1,515 ,,
Fletcher Beach	..	..	Male, aged 16	..	..	1,500 ,,
				Average	..	1,892	

Running over the clinical manifestations we find that males are more disposed to the disease than females, that most cases die before reaching the age of twenty-one years, that a condition of idiocy or imbecility is invariable, and that when the latter is the case, although something of what is said to them may be understood, the receptive process is greatly delayed, while if they have learned the use of language their vocabulary is restricted and their words uttered slowly, without emphasis and in a low tone.   In about fifty per cent. of cases epilepsy is a complication, and that disease is a common cause of death ; indeed, it may be correct to say that after passing a number of years free, or almost free, from epileptic attacks, life is terminated by a series of convulsions (cf. my second case).   Although this observation has not always been made, the head seems to be enlarged at birth, and during childhood dulness, drowsiness and headache are suffered from.   Further, such children exhibit that inability to keep the head erect which results from inefficiency of the cervical musculature ; and in this connection let it be noted, that not only may the head be too heavy to balance, but the neck muscles may be abnormally weak, for in other directions there is proof of muscular in-activity ; thus, many of these cases are reported to have been as slow in learning to walk as they have been imperfect in muscular development and incapable of enduring fatigue.

Turning now to the pathology of the condition, it seems that not unfrequently these cases are tainted with an heredi-tary neurosis, and have brothers or sisters afflicted with idiocy or some other form of mental weakness.   There is also abundant proof that the morbid process is active during intra-uterine life ; the large size of the head at birth, the presence of accessory parietal eminences and the persistence of the interfrontal suture which have been noticed, all signify abnormal cerebral growth at an early stage of development. Yet in searching for the cause further than this we cannot go.   It is possible that the disease may rest on syphilis in the parents, but there is no certain evidence to that effect ; indeed, it seems to me that not until a great many more observations are made and attention specially directed to

obtaining correct family histories, shall we light on the right cause of this disease.

Next, regarding histogenesis, in few cases has a microscopic examination been carried out, and in fewer cases still has the brain passed through the hands of a competent microscopist, hence the histology of the condition is imperfectly reported. In particular, I notice a tendency to write loosely of the presence of inflammatory sequelæ in the brain and meninges; thus one observer makes capital of a superficial encephalitis (whatever that may mean) of the anterior third of the brain; another, recording a case in which death occurred in status epilepticus, apparently is unaware that capillary congestion and " myelocytosis " are simply characteristic of the disease which proved fatal; again, some thickening of the cranial bones and firm union of the sutures have been wrongly given as evidence of chronic inflammation of the brain. But, in my opinion, the case for the inflammatory process has been greatly overstated. To begin with, it is a fundamental truth that we do not get inflammation without vascular affection, and yet to the best of my judgment the blood-vessels in the brains I have examined have been remarkably free from disease; as blood-vessels are particularly numerous in the pia mater, therefore chronic inflammation always manifests itself in the soft meninges, but the thickening, opacity and adhesion of these membranes, which we regard as post-inflammatory signs, have not been present in my cases· Again, inflammation necessarily brings in its train malnutrition, destruction and decay, and yet here we find the principal and the most unstable elements actually represented in increased numbers. Lastly, while neuroglial proliferation is a product of both inflammation and decay, and it cannot be denied that this tissue is unduly abundant in megalocephaly, still, as I have pointed out, there is a great disproportion between the degree of the proliferation and the size and induration of the brain; moreover, neuroglia is a supporting element, and it is significant that it is excessive in the white substance only.

To me it seems that much more importance attaches to

the proof we have that the enlargement of the brain is uniform and unattended by morphological imperfection. The architectural plan of the gyri and sulci may be unusual, but it is not bizarre; it is what we look for in the case of a person of high intellectual attainments, in accordance with the view that intellectual superiority runs hand in hand with advantage in cortical expansion. Inspection of known functional areas reveals nothing unexpected; for instance, on making a series of sections through the occipital lobe I observed that the area striata—visuo-sensory cortex—has a normal distribution; looking for giant "motor" cells, I find them where previous experience tells me they normally lie, and there only; indeed, the microscopic architecture shows no inconsistency in any part of the brain; in short, we have to deal with what seems to be a genuine cerebral hypertrophy.

In face of all these facts, the thought is forced upon us that this remarkable development of nerve cells, of nerve-fibres, and of cerebral nervous tissue in general, must be referred back to embryonic life, and tentatively I would suggest the influence of a developmental error. I would submit that there has been a deposit in excess of those embryonic elements which normally go to form the great system of cerebral neurones, a deposit quite out of proportion to standard requirements. Each primary specific centre (those for sight, smell, taste, touch and movement), each higher functional area, in fact the whole cerebral cortex, has been endowed with a wealth of fundamental elements far in excess of what is usual, and each element following a natural process has developed morphologically; but while development seems to have been good in so far as the central portion of the neurone is concerned, the same does not apply to the peripheral portion. To instance my meaning, let us take the motor area: for the perfect conveyance of impulses arising in the superabundant cortical motor elements, there should be a corresponding addition to the number of motor fibres in the motor tract; to the naked eye, however, the size of this tract in the medulla and in the spinal cord appears normal, and if, as is possible, there is an increase in

number of the individual fibres without an increase in volume of the tract, a point which I have not attempted to prove, plainly there must be an insufficiency of investing myelin on each fibre, hence insulation must be imperfect. Of necessity, the same defect must obtain in the case of fibres for the conveyance of special sensory impressions; while among the multiplied neurones pertaining to higher functional areas, that coupling together, that association essential to the smooth working of the cerebral machine, as a whole has remained imperfect. The apparatus has been unwieldy, too complex to assume normal functional activity and impossible to educate. Although, to continue my instance, the cortex is endowed with good motor cells, their perfect excitation has been impossible, and the resulting movements sluggish; similarly, the process of education leading to the execution of skilled movements, an example of the use of higher function, has been out of the question, while in higher spheres still, complications and counteractions, clogging mental processes, have produced the clinical picture of idiocy or imbecility.

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CHAPTER 5.—CEREBRAL HEMIAGENESIS OR HEMISCLEROSIS.

A diminution in size affecting one hemisphere alone, equally distributed, associated with sclerosis but unaccompanied by disarrangement of the gyral and sulcal architecture, outlines the anatomical picture in the condition now to be considered.

It is not uncommon to meet with brains on the *post-mortem* table in which there is a disparity of more than 100 grammes between the weight of the two hemispheres, and in which the asymmetry is sufficiently decided to be noticeable with the eye; but in the disease before us the disparity in weight and the asymmetry are profound.

The condition is rare; I have seen it once only, and the records contain accounts of few cases which I would place in the same category. The Index Medicus mentions several papers entitled "Cerebral Hematrophy," but on reading these I have discovered that the "hemiatrophy" was a reduction in size due to some local defect, a restricted area of microgyria, sclerosis and contraction round an area of destruction consequent on arterial embolism or occlusion occurring in early life, and so on—not hemiatrophy strictly speaking, and a state quite distinct from that with which we are concerned. Finding that the name "hemiatrophy" had been loosely attached to various diseases, it became necessary to employ a term which would distinguish the present condition, hence the name "hemisclerosis"; this, though physically proper, may not meet the approval of the pathologist, who, as I shall indicate in commenting on the condition, may prefer the term "hemiagenesis."

The case which I shall relate has already formed the subject of a note by Dr. J. Wiglesworth in the *Liverpool Medical Chronicle;* I have restudied the brain from the histological aspect.

Clinical Notes.

The patient was a female, aged 16 years, an idiot and a sufferer from epilepsy.

The clinical report gives no information touching the family history and is very imperfect It is stated, however, that the
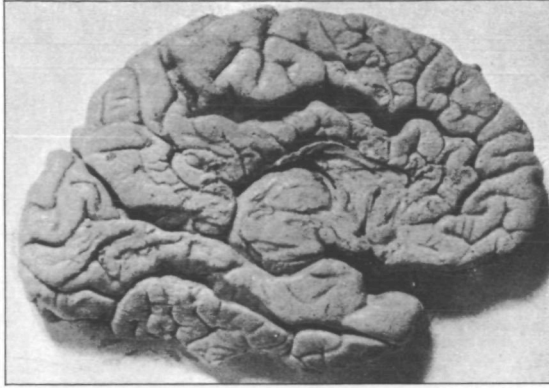
FIG. 9.

Cerebral Hemisclerosis.

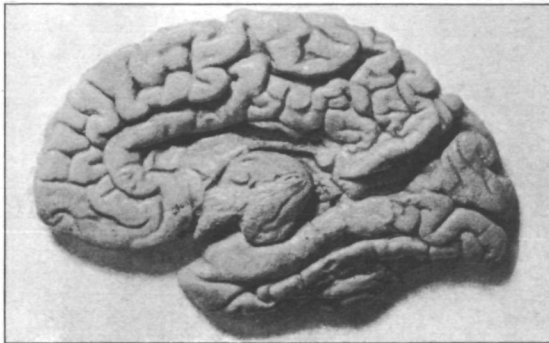Photograph of the inner surface of the left hemisphere.

FIG. 10.

Photograph of the inner surface of the right hemisphere illustrating the asymmetry in the author's case. Although the sclerosed right hemisphere is so much the smaller it has preserved its form.

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extremities of the left side were small and " shrivelled," and that talipes varus on the left side, and genu valgum on the right, made walking impossible, although the patient could stand. What power of movement she had in the wasted limbs is not mentioned, nor do the cutaneous and special senses seem to have been tested.

Necropsy.

The brain scaled as follows : Encephalon, 800 grammes ; right cerebral hemisphere, unstripped, 218 grammes ; stripped, 198 grammes ; left cerebral hemisphere, unstripped, 417 grammes ; stripped, 405 grammes ; cerebellum, pons and medulla, 112 grammes.

The disparity in size and in weight between the cerebral hemispheres were features of dominant interest in the case. They were accompanied by many secondary changes in the cranium, but I need mention only that the right half of the head was obviously smaller than the left, and that this applied to the bones of the vault as well as to those forming the basal fossæ. In thickness and in density and as regards sutures, the bones were normal. So was the dura mater, save that a pale pink film,[1] composed of migratory and red blood cells, lined the vault on the right side. There were no abnormal adhesions between brain and dura. The cerebro-spinal fluid was not markedly excessive. The pia-arachnoid membrane covering the right hemisphere was thick and opaque, and stripped in one sheet; that covering the left hemisphere was normal. The main arteries of the right side were smaller than those of the left. Anæmia was general.

Comparing the cerebral hemispheres (*vide* figs. 9 and 10), it was remarked that although the right was so greatly deficient in size it was not strikingly altered in form ; every convolution was attenuated, every sulcus gaped and was shallow, all the basal nuclei were small, the white substance was wasted and the lateral ventricle dilated, but the general architecture was undisturbed, and it could not be said that any lobe or part in particular had suffered more than the rest. There was a striking difference in consistence, the

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[1] This had no bearing on the principal change ; such films are common in phthisis, the disease which caused death

lesser hemisphere throughout was greatly increased in firm-ness, cutting almost like costal cartilage; the same hemi-sphere was pale and pearly in appearance, and its cortex shallow and indistinctly striated.   In all these respects the opposite hemisphere was approximately normal.

Consequent   on   this   cerebral   asymmetry   and   the deficiency of cortical nerve cells and central nerve fibres, there were changes in related parts.   The contralateral cerebellar hemisphere was distinctly reduced in size; the corresponding motor tract throughout the mesencephalon and spinal cord was wasted, and the lemniscus presented the attenuation of retrograde atrophy.[1]

The changes in the trunk included severe chronic tuber-culosis of the lungs, secondary tuberculous ulceration of the intestine, and lardaceous degeneration of the liver, spleen and kidneys.

Microscopic Examination of Cerebral Cortex.   (Fig. 11).
(a) Nerve Cells.

A careful examination of many pieces taken from cor-responding parts of both hemispheres revealed uniform changes throughout the affected half. On the whole the cells preserved their columnar arrangement and the individual members their erect attitude, but the cortex was reduced in depth by quite two-fifths, and the lamination altered in the following manner.

The plexiform layer (1) was very thin.

The small pyramidal cells (2) were deficient in number.

The numerical deficiency fell even more heavily on the medium-sized and large external pyramidal cells (3 and 4), and the shallowness of the combined layers struck the eye immediately; moreover, few elements persisted here which might be described as normal; the majority were small and round, or oval, instead of pyramidal, their processes were stunted, they lacked spongioplasm and were achromophilous. Such cells recalled alike the neuroblasts seen in the deve-

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[1] I investigated the changes in these parts very carefully, but do not describe them at length because they were an exact replica of what we have often seen in other cases of unilateral cerebral defect.

loping brain, the stunted elements in cases of idiocy, and the atrophied cells in specific centres altered by interruption of incoming stimuli (cases of old-standing deafness or blindness, of tabes dorsalis, &c.).

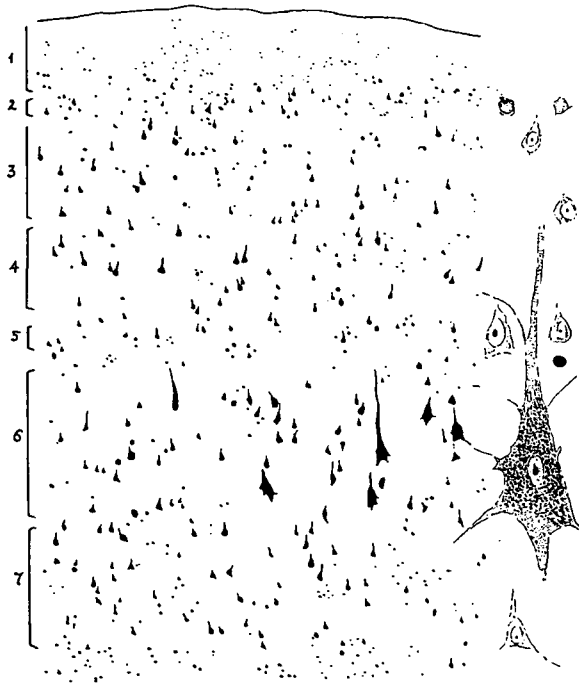A few small cells remained to mark the position of the stellate layer (5).

FIG. 11.

Camera lucida drawing of the cell lamination in the cortical motor centre for the leg in the diseased hemisphere.   The cortex is shallow, the reduction in depth mainly affecting the suprastellate layers.

It is a remarkable and important feature that in cortex where the cells of the next layer—the internal layer of large pyramidal cells—are specialised, such cells persisted and showed but minor alterations.   For instance, in the motor cortex, which I illustrate, the preservation of the giant cells was astonishing ; their figure was attenuated, but their number good ; the method of Nissl showed chromophilic elements diminished in size, but not true chromotolysis, and
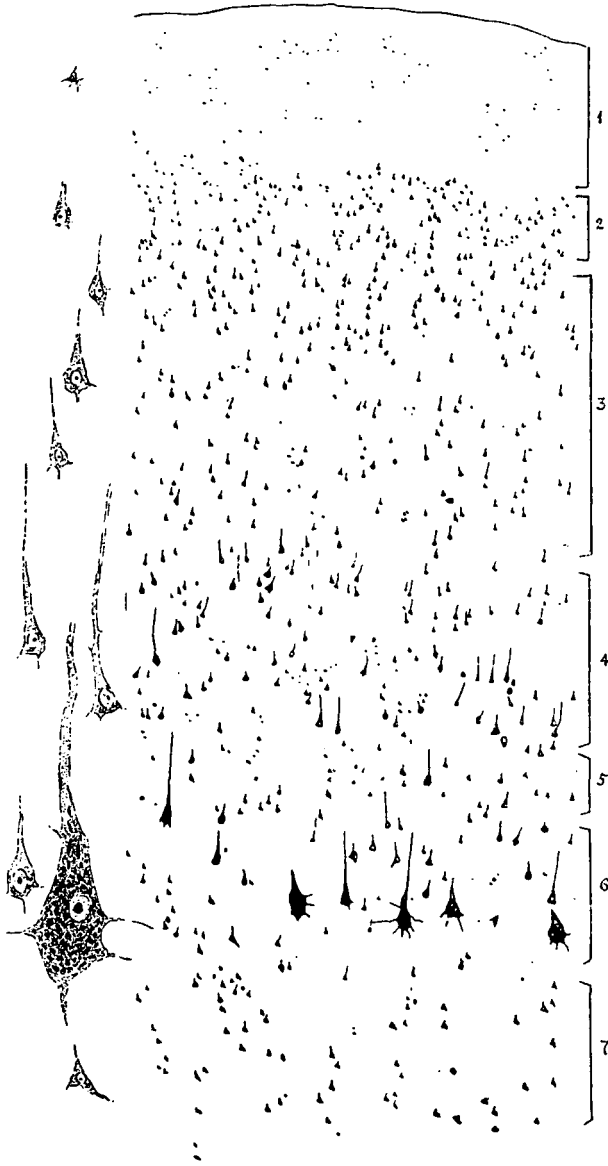
FIG. 12.

Camera lucida drawing of the cell lamination in the cortical motor centre for the leg in the normal hemisphere of the author's case of Hemisclerosis for comparison with Fig. 11.

the method of Bielschowsky revealed both a wealth of neuro-fibrils[1] and normal processes. Similarly in the visuo-sensory, in the postcentral and in the olfactory areas, areas wherein homonymous specialised cells are found, these among the cells of all other luminæ, save the fusiform layer, showed the best state of preservation.

The last layer, that of the fusiform cells, could be included with the layer just considered as preserving its constituents fairly intact.

Most of the points regarding cell lamination that I have mentioned are illustrated in the accompanying figures. The significance of the changes will be discussed in a later section.

(b) The Blood-vessels.

I searched many blood-vessels for signs of past inflammation, but the quest was negative. The vessels were not more numerous than usual, nor did thickening or over-cellularity of their walls cause them to stand prominent; also, signs of syphilitic endarteritis and of hyaline and other forms of degeneration were not in evidence.

(c) The Nerve Fibres.

Examining the nerve fibres as carefully as I examined the nerve cells, I again found changes in the lesser hemisphere as pronounced as they were universal.

The zonal layer in all regions, even in the motor area, where it is so prominent in the normal brain, was reduced to the palest of bands, made up solely of a few varicose fibrils. The supraradiary layer was correspondingly poor. A line of Baillarger was scarcely visible.[2] The radiations of Meynert, instead of being stout and composed of many large medullated fibres (I refer to the motor cortex) were

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[1] The persistence of the neurofibrils is not easy to explain. In other conditions I have displayed them in cells quite denuded of Nissl granules. Evidently more information is needed regarding their nature and significance.

[2] In my "Histological Studies on the Localisation of Cerebral Function," I pointed out that the line of Baillarger lay on a level with the external large pyramidal cells, and that its representation varied proportionately to the representation of these cells. The condition of the line in this brain accords with that observation.

attenuated, made up of coarse varicose fibres, and seldom strengthened by a normal evenly-medullated fibre.[1]

The interradiary spaces were almost empty, even in parts like the motor area, where in the normal state they are packed with fibres.

In short, a general loss of fibres was apparent, and I think it correct to summarise with the statement that the deficiency fell most gravely on the various systems of association fibres.

(d) The Neuroglia.

Large active neuroglia cells like those seen in the white substance of the normal brain were scarce; in all parts, how-ever, there were numbers of the smaller variety of cell, as well as an abundance of so-called nuclei of the neuroglia, also the glial feltwork was uncommonly dense.   The condi-tion suggested a past glial proliferation to compensate the cell and fibre deficiency.

The origin of this condition is not easy to discover, and several speculations have been urged concerning its pathology; these we will briefly consider.

The weak suggestion has been advanced by one writer that it may be the outcome of unilateral narrowing of the carotid canal. No doubt narrowing of this canal will reduce the flow of blood along the middle and anterior cerebral arteries, and if it occur early in life may well interfere with the development of the parts of the brain nourished by these vessels; but surely coincident obstruction of the homolateral vertebral artery by narrowing of the foramen in the atlas, and over and above these constrictions, anastomotic im-perfections, such as inelasticity of the Willisian arteries of

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[1] It may seem incongruous that in the motor area, where the giant cells were preserved, the radiations of Meynert were attenuated. It will be remem-bered, however, that while these cells retained their shape they were reduced in size and showed internal alterations. And I have little doubt that if it had been possible to trace the axon of one of these cells, it would have been found attenuated and wanting in myelin. This supposition is consonant with an observation I made to the effect that the wasted pyramidal tract leading from the affected hemisphere retained a blue tint, instead of being decolorised, in Weigert-Pal specimens, and that on microscopic inspection the contained fibres, though not wholly amyelinic, were mainly composed of axis cylinder.

communication, would be necessary to make the wasting of the hemisphere complete. There is no proof of any such obstructions, so that the suggestion need not be further pursued.

Of unilateral synostosis of the cranial bones preventing cerebral expansion there is likewise no evidence.

Injuries at birth are fruitful sources of brain lesions, and syphilis in parents or child are disease-producing factors always to be kept in view; here, however, we have no trace of the operation of either agent.

An attack of meningitis during infancy is more deserving of consideration, because we can readily believe that such an inflammation will not pass away without affecting the calibre, the elasticity, and the carrying capacity in general of the main arteries. This, notwithstanding there are several objections to meningitis as a cause of the condition of the case before us. In the first place, meningitis is not a disease which confines its attack to one hemisphere, and touching its effect on the main arteries, although in the majority of cases it attacks the base of the brain and involves the arterial trunks, it is as difficult to believe that it can confine its operations to the arteries proceeding to one hemisphere as it is to think of it spreading over one hemisphere and leaving the other intact. And yet other writers, particularly those of the German school, who lay stress on antecedent meningitis as a source of various changes which we see in the brains of idiots, might give causal importance to the thickening and opacity of the meninges noted in this case. To this I can only reply that the condition of the membranes did not suggest past acute inflammation; it reminded me of what I have observed repeatedly in the brains of the chronic insane, especially those afflicted with severe dementia, a condition of obscure origin, but certainly not the product of acute meningitis. The microscopic appearances, also, did not favour meningitis; in the cortex of this hemisphere we saw that, while cells and fibres were deficient, they were not arranged in a disorderly manner; the radiary fasciculi of fibres pointed straight towards the surface, and the cells stood erect and in column formation. This would not

have been the case had meningitis pre-existed ; in that event it would have been in accordance with our experience to have found the uppermost laminæ swept bare of cells and fibres, contracted and converted into connective tissue ; moreover, from unequally distributed obliteration of cortical arterioles, patches of cortical. destruction surrounded by contraction changes would have been seen in the deeper parts.

Having disposed of these preliminary speculations, we can now pass to the consideration of a problem which, in my opinion, it is of fundamental importance to solve. Did the condition exemplify atrophy of a part previously well developed, or was it the outcome of arrested growth ? In my opinion it was the latter, and the following observations strengthened my belief. In form and in size the hemisphere resembled that of a full-term fœtus, but it was from the microscopic rather than the naked-eye appearances that I derived chief support for my contention. When studying the cell lamination we were struck with the fact that cells beneath the stellate layer, namely, the polymorphic and the internal large pyramidal cells, were preserved, where-as the cells above the stellate layer, in particular the medium-sized and large pyramidal cells, were very weakly represented, and to deficiencies in these layers we thought that the shallowness of the cortex was mainly due. Let us compare this with the state in the fœtal brain. As Dr. Bolton has proved, if the cortex of a fœtus be measured beside that of an adult, exactly those layers in the former will be shallow which were found to be so in this case ; the corollary follows that the suprastellate pyramidal cells are the last to develop. Turning to deeper cells, it is well known that comparatively early in intrauterine life the specialised large pyramidal cells peculiar to certain areas— the cells, be it noted, which persisted in this case—may be recognised, and that the fusiform cells, likewise persisting in this case, are not much later in making their appearance. The resemblance, so striking from this standpoint, does not end here. From the writings of Flechsig, Kaes, Vulpius and others, who have studied the myelinisation of the cortex

of the growing brain, we learn that the tangentially-directed fibres, the supposed association fibres, become invested with myelin considerably later than the vertically-placed projection fibres. A replica of this stage of development was seen in this brain; the radiary fasciculi, though deficient in myelin, were fairly prominent; the zonal layer, the line of Baillarger, and the association fibres, on the contrary, were barely recognisable, and this even in parts where normally they stand out with the greatest plainness. Furthermore, the amyelinic condition of the fibres composing the pyramidal tracts was a reproduction of the fœtal state.

While maintaining that all these microscopic revelations favour my thesis that the defect in this instance is ascribable to arrest of development, it does not escape my mind that some of these data may be seized upon by those who favour the view that the condition is the outcome of atrophy. In particular I recognise that an attempt may be made to explain the deficiency of stellate cells on the ground that, being highly organised elements and the last to develop, so they are the first to disappear in processes of degeneration. This is an axiom the truth of which cannot be gainsaid. Also, I will not deny that in cases of atrophy the change is dominant at the level in question; but in all my experience of cortical wasting, I have not yet met with a case in which other layers besides the suprastellate have not shared the change, in which, to be more precise, the specialised substellate pyramidal cells, the fusiform cells and other elements, have not exhibited pigmentation, swelling, disintegration, numerical deficiency, and many other signs of degeneration. In this manner, therefore, wasting differs from the condition in hand. Further, and this is an important point, the profound asymmetry of the cranium contraindicated atrophy of its contents as strongly as it suggested their restricted growth.

Accordingly, I submit that we have to deal here with a true case of arrest of development, that the original deposit of elements going to form the nerve cells and nerve fibres was not deficient, and that growth proceeded normally until just before, at, or soon after birth (the conformation of the hemi-

sphere is preserved), but then ceased ; that the elements subserving primary essential functions, being developed already, persisted ; that the elements subserving higher evolutionary functions, being only partially developed, and therefore unstable, to a large extent, but not wholly, suffered decay, and that coincident with this decay the neuroglia proliferated, hence the sclerosis.

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<div align="center">CHAPTER 6.—LOBAR AGENESIS WITH SCLEROSIS AND MICROGYRIA.</div>

I will now pass on to another remarkable condition, which from the standpoint of pathogeny I would classify with cerebral hemiagenesis, because, in my opinion, it is likewise a manifestation of arrested development. Anatomically it differs from hemiagenesis in being bilaterally distributed ; but it bears a resemblance to this condition inasmuch as the gyri of the affected lobes, though attenuated and sclerosed, are not puckered, and the plan of the sulci is not disarranged.

Lobar sclerosis and lobar microgyia may be suggested as better names for the condition. I must point out, however, that these names have been affixed indiscriminately to cases of lobar sclerosis resulting from intrauterine destructive lesions (really cases of porencephaly), to the contraction and induration occurring round an old and extensive patch of cerebral softening, to postmeningitic atrophy and sclerosis, always without regard to the exciting factor, where the sclerosis or microgyria is but a sequel of the primary disease. This is surely wrong, and, in my opinion, now

that our knowledge of the anatomy of the brain in idiocy is becoming more stable, it will be better either to abandon the titular use of these names, or to reserve them for conditions (they must be very rare) in which the sclerosis or the microgyria, being the primary and essential feature, is deserving of capital mention.

I am fortunate in having three specimens with which to illustrate my remarks. Of the subjects two were females, aged 17 and 32 years at death respectively, and one a male aged 35 years at death. All suffered from epilepsy, and though their mental state, as observed in Rainhill Asylum, suggested idiocy, a history of the display of a certain amount of intelligence during childhood proves that they were not cases of congenital amentia. Since the anatomical picture in all the specimens is alike, it will not be necessary to describe more than one in detail. I choose that from the female, aged 32 years, because it was the last observed.

Clinical Notes.

The patient was admitted to Rainhill Asylum at the age of 16. The mother informed us that there were four other children in the family, all healthy, and that this girl had attended school and been apparently normal until the age of 12, when she began to suffer from epilepsy. This was the signal for a mental deterioration so rapid that three years later she was completely demented and in need of asylum restraint.

On admission to Rainhill she would have been classed as a case of congenital amentia had no details concerning her earlier life been forthcoming. She seemed to understand nothing of what was said to her, she took no interest in her surroundings, and either would not or could not speak. No physical defect was discovered except some weakness of the left arm, and this proved to be transitory.

The further course of the case was devoid of interest. In summary form the notes state that she was a petulant, degraded, coprophagic ament, and a sufferer from frequent and severe epileptic fits.

Necropsy.

Though short in stature the limbs and trunk were duly proportioned, well clothed with muscles and free from

deformity. The fat covering was normal and the mammæ
were fairly developed. There were no traces of congenital
syphilis. The scalp was thickly covered with coarse, black,
curly hair. In the shape of the head and face there was
nothing peculiar, and in regard to cranial size the following
measurements are illustrative :—

Circumference of head	55 cm.
Arc measurement from glabellum to occipital protuberance ..	33 ,,
Arc measurement from ear to ear	30 ,,
Greatest transverse diameter	14·3 cm.
Greatest antero-posterior diameter	18·5 ,,
Cephalic index	77 cm.

The calvarium was very thick, yielding average frontal
and occipital measurements of 12 mm. and 11 mm. respec-
tively; the increase in thickness mainly affected the inner
table; the structure of the bone was fairly open, and the
thickening seemed to be compensatory. The lines of the
meningeal arteries, strange to remark, were not deep. A
groove of normal depth and breadth accommodated the
superior longitudinal sinus. The sutures were close, but
not obliterated. Broad furrows, following the lines of the
sutures, which we have learned to associate with syphilis,
were not present.

The dura mater and its sinuses were normal. A slight
excess of subdural fluid was noticed. The main arteries,
carefully inspected, were only a little more delicate than
usual. The pia covering those gyri to be noted presently as
attenuated, was somewhat thickened and easily stripped,
elsewhere it was normal.

The cerebrum exhibited remarkable bilateral alterations
affecting the frontal and parietal lobes.

The Frontal Lobes.

The frontal lobes in each hemisphere and almost sym-
metrically were greatly diminished in size; viewed from
above they stood apart from one another; from the side
they looked pointed and the orbital face was tilted outwards.
Excepting the precentral or ascending frontal gyrus, which
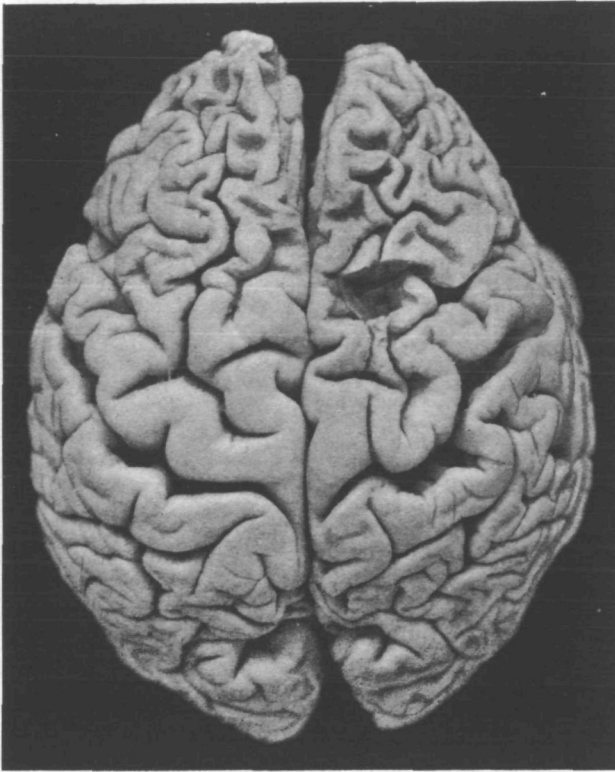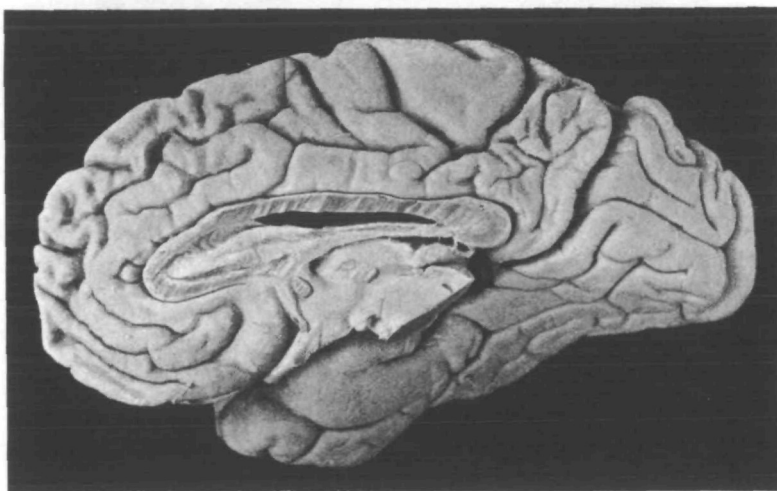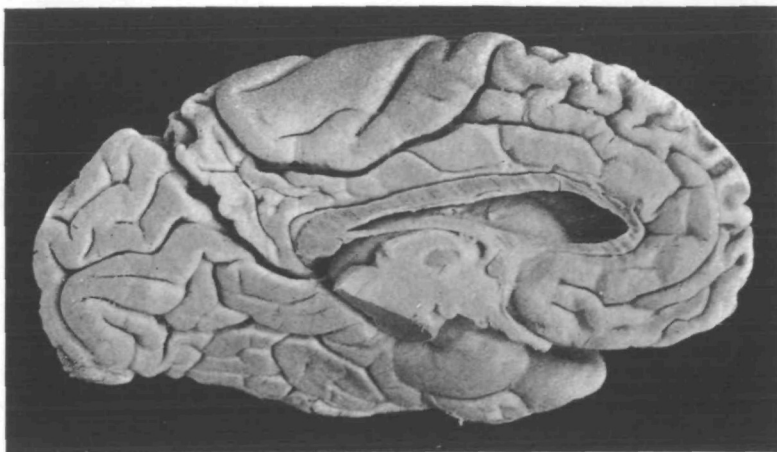was normal in each hemisphere, not one convolution on the

FIG. 13.

Lobar Agenesis with Sclerosis and Microgyria.

A view of the upper surface of the hemispheres in Case 1, showing the wasted frontal and parietal lobes.

FIGS. 14 AND 15.

Lobar Agenesis with Sclerosis and Microgyria.

The inner surface of the hemispheres in Case 1. Observe the bilateral and symmetrical attenuation of the gyrus marginalis and the precuneus; also, the large relative size of the oval lobule.

convex surface had escaped attenuation ; the degree varied ;
those most changed were wormlike, pale brown and tough.
those less affected, white and not so tough. On the mesial
surface the marginal gyrus alone suffered, the oval lobule
and the gyrus cinguli being normal. On the orbital surface
all gyri, excepting those bounding the sulcus olfactorius,
shared the change.

The Parietal Lobe.

Save the postcentral gyrus and its paracentral annexe
which, like the precentral gyrus, were normal, the whole
lobe was diminished in size and microgyrous. On the mesial
surface the withering was very pronounced, but restricted
in a most extraordinary manner to the precuneus and to that
portion of the postcingular gyrus with which it stands
connected. On the convex surface the wasting was less,
and yet the superior parietal gyrus and the upper parts of
the supramarginal, angular and posterior parietal gyri, were
much below the normal size.

The Occipital Lobe.

The external occipital gyri were slightly attenuated, but
those on the minor surface healthy.

The Temporal Lobe.

The temporal lobe stood out in that it was unaffected.
The insular likewise remained untouched.

The Limbic Lobe.

The lobus pyriformis and all parts in the regio olfactiva
were normal.

The corpus callosum, the fornix and the anterior and
posterior commissures, were all slightly attenuated. The
anterior horns of the lateral ventricles were dilated. The
crura cerebri were small, but equal.

In the cerebellum some folia of the lobus clivi and others
along the great horizontal fissure were wasted and unduly
firm, apparently having undergone changes not unlike those
in the cerebrum.

The heart was the only diseased organ in the trunk; it presented mitral stenosis (·45 inch), but evidently this was very old and had been naturally compensated, for the heart weighed only 243 grammes, and the size of the chambers relative to one another and the thickness of the walls was not greatly altered.

Microscopic Examination.

(a) Nerve Cells.

Portions of different gyri were examined, but to instance the changes I will take the condition of the cortex at the base of the superior frontal gyrus (regio precentralis intermedia of the author).

We have seen in our study of other brains that the cell laminæ most prone to decay are those which are the last to appear in embryonic growth, namely, the small, the middle sized, and the external large pyramidal cells (layers 2, 3 and 4). Exactly these laminæ were most deficient in this brain, and their weakness accounted for some thinning of the supraradiary plexus and the line of Baillarger to be noted presently. Of the internal large pyramidal cells many persisted, but they were all much reduced in size, and in addition so intensely chromophilous that even the nucleus was barely visible. The layer of fusiform cells, which is early to develop, which is constant throughout the animal series, and which is very resistive to decay, was the best preserved of all the layers. Lastly, the cell changes were evenly distributed, that is to say, the disorder and the patchy affection seen in inflammatory and vascular lesions were absent.

(b) Nerve Fibres.

The general fibre wealth of the cortex and of the medullary projection was greatly diminished, but of chief interest was the finding that the association system of fibres had suffered much more that the projection system. Thus, even in gyri which were most wasted, the radiations of Meynert, although attenuated to a considerable extent, were still prominent objects in the field, and they were

strengthened by a few large medullated fibres, doubtless the axons of the remaining large pyramidal cells, and some large varicose fibres. The interradiary spaces, on the other hand, were comparatively empty; in particular they were quite bereft of those long, oblique or horizontal, large medullated fibres, which we look upon as associational or internuncial in function, and which are usually present in abundance in this situation.

As a feature of minor interest, the absence of a zonal layer, a wasted supraradiary layer, and a scarcely recognisable line of Baillarger were noticed, and, lastly, I will again emphasise the points that the radiary fasciculi stood erect, and that the signs of architectural disturbance were wanting.

(c) Neuroglia.

Neuroglia fibrils and so-called nuclei of the neuroglia were abundant in the diseased parts, and explain their firmness; but there were no large active neuroglia cells.

(d) The Blood-vessels.

The blood-vessels as seen in these sections showed no change calling for special remark.

Commentary.

In our search for enlightenment concerning the origin of the changes illustrated by these three brains, the first, indeed, the fundamental, point for consideration concerns distribution. In each specimen, with remarkable symmetry, precision and uniformity, the process is distributed over and restricted to the frontal and parietal lobes; in the former all gyri suffer, excepting the gyrus precentralis and some on the orbital surface; in the latter the postcentral gyrus alone escaped, and the precuneus is singled out for specially severe affection. To explain this distribution the series of causal factors from which we may choose includes vascular obstruction of different kinds, trauma, specific forms of inflammation and anomalies of growth and development.

The first factor, vascular obstruction, deserves careful consideration, because to the morbid anatomist the naked-eye appearance of the altered gyri at once suggests nutri-

tional disturbance. Regarding this suggestion it is obvious that if there had been a reduced supply of nutriment, it must have been due to an affection of either arteries or veins, and if the former the cerebral changes should present an arterial distribution. But here at the very outset we meet an insuperable obstacle, the required agreement in not forthcoming. The atrophied gyri in the frontal lobe derive their blood supply partly from the anterior cerebral and partly from the middle cerebral artery, but not once in an examination of several hundred cases of softening from embolism and thrombosis of varying origin which have passed through my hands, have I seen a lesion having this distribution, even in one hemisphere, much less bilateral. Not only does it so happen that this part is one which is seldom the seat of a localised softening (a widespread softening from plugging of the anterior or the middle cerebral artery is of course not uncommon), but it is impossible to believe that the twigs to this field should be selected for occlusion and other branches of the same arteries left open.

Under the same premise the parietal defect is still more difficult to explain, because a part is wasted which draws its blood from all three cerebral arteries.

The microscopic appearances still further negative this suggestion. I have stated that there was no distortion of the general cortical architecture, that the cells preserved their columnar arrangement, and that the projection bundles of fibres stood erect, and, in my experience, gyri attenuated and sclerosed as a result of deficient blood supply, for instance, those on the borders of an old patch of softening, are never free from this distortion. For these reasons I regard arterial obstruction as an untenable hypothesis.

Turning to venous obstruction, there is one condition worth more than passing notice, thrombosis of the superior longitudinal sinus. In several cases of thrombosis of this sinus which have come under my observation, I have noticed that the congestion and the resulting multiple capillary hæmorrhage have favoured special situations, namely, the parietal and the frontal lobes on the convexity, and it has

been interesting to see, presumably on account of the cross anastomosis along the veins of Trolard, that the two central gyri, just as in the cases under notice, escaped. Bearing these observations in mind, I can imagine that if a thrombosis of the superior longitudinal sinus were recovered from —it is usually fatal—and the obstruction persisted, or only imperfect recanalisation of the thrombus took place, it would exert an atrophic influence on the parts in which we are interested. But, unfortunately, I have no evidence to put forward to prove the occurrence of this thrombosis, my suggestion is purely speculative. The condition of the superior longitudinal sinus is not always noted at an autopsy, and it was overlooked in one of my cases; in the other two, however, I satisfied myself that the channel was apparently normal at death, whatever it may have been previously.

Touching trauma as an agent, all our evidence is negative. I suppose we may take it for granted that the chief manifestation of an injury is a rupture or thrombosis of blood-vessels; here there are no hæmorrhagic residua, and reasons have been given which render antecedent rupture of arteries unlikely.

Meningitis, encephalitis, and other inflammatory conditions, as possible causes of altered nutrition and subsequent atrophy, are all similarly disqualified by the remarkable distribution of the change.

Having found none of these hypotheses sufficient to explain the condition, we will lastly discuss the possible influence of a developmental defect, and now several very interesting points will be presented for consideration. One feature of great importance meets the eye when we view these brains from the aspects of physiology and comparative anatomy; selecting first the negative side of the picture, the side showing the parts which are preserved as against those diseased, we observe that the intact areas are precisely those we have recognised as designed for the control of movement and for the reception of the different sense impressions, in other words, for the government of those simple functions common to and used as a means to survival by all animals; thus, the visual area in the occipital lobe, the lobus

pyriformis, representing the chief known centre for smell; the central gyri for the control of movement and for the registration of cutaneous sensations; the gyri of Heschl and the temporal gyri concerned with hearing, are all plump and healthy. Turning to the positive side, we notice that the parts destroyed are those which have been the last to appear in the progress of phylogenetic development, and which are elaborated for the government of those higher psychic functions and faculties possessed by man alone, and making him pre-eminent among terrestrial animals. In other words the specimens afford a pregnant illustration of a reduction towards the elementary state obtaining in the lower mammals.

This view of the brain is full of instruction. It seems to be a general physiological truth that structures and parts whose development, alike in the ontogenetic and in the phylogenetic sense, is deferred, are designed and specialised to subserve high evolutionary functions; likewise we may regard it as a natural law that the same structures and parts are penalised for their greatness by being the first to deteriorate, both in the normal process of dissolution and decay, and when the organism is subjected to an adverse and devitalising environment. In the case of the brain the frontal lobes, excluding the motor area, and the parietal lobes may be pointed to as being the last phylogenetic addition to the central nervous apparatus, and it is an established truth of ontogeny that they are the latest to acquire their fundamental nerve cell and nerve fibre constituents. On these grounds I maintain that the withering of these very parts in the specimens before us must be more than a coincidence. I submit that the wasting is not the product of any of the ordinary locally-acting morbid factors, but the manifestation of an unnaturally premature decay of parts constitutionally disposed to early dissolution, and at the same time specially susceptible to the effects of evil hereditary influence or any other adverse agent which may proclaim itself during the progress of either pre- or post-natal development. On this and no other ground that I can think of can we explain those features which puzzled us before, the bilateral, symmetrical and altogether remarkable distribution of the change,
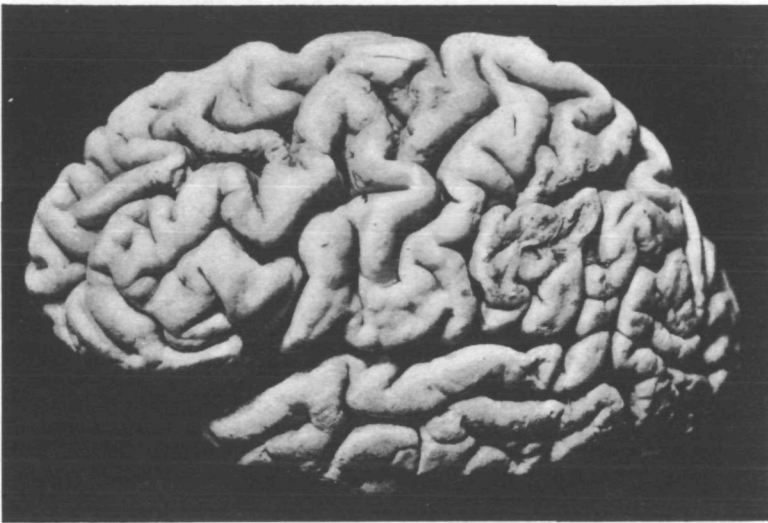
FIG. 16.

Cerebral Arterio-Sclerosis.

A photograph of a cerebral hemisphere, showing puckered gyri in the frontal and parietal lobes.

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the perfectly preserved architectural plan of the affected gyri and the well-ordered arrangement of cortical elements as seen through the microscope.

CHAPTER 7.—CEREBRAL ARTERIO-SCLEROSIS.

The morbid process now to be considered is chiefly of interest to the anatomist and histologist. In all parts of the brain, but especially on the outer surface, convolutions, or portions thereof, are irregularly picked out for attenuation and sclerosis; at the same time the surface is puckered by many minute pits and linear or radiate cicatrices, and withal the form of the gyri is not wholly lost.

As gyri in a similar state may be observed around patches of softening from arterial embolism and thrombosis, it must be explicitly stated that the present cases were independent of any gross lesion.

The condition is not common; although my experience has been among the insane, in whom cerebral lesions of all kinds are more frequent than in the sane, in a sequence of more than two thousand autopsies I have obtained only four specimens.

I will now enumerate briefly the leading features in each case.

Case 1.—A male, aged 24 years, who suffered from dementia with epilepsy. Both hemispheres were affected, the right more than the left. Analysing the distribution of the shrunken gyri, it was noticed that most lay within the area of supply of the middle cerebral artery, exceptions being some in the retrocalcarine region, pertaining to the posterior cerebral artery. The changes had not altered the plan of the fissures, and yet they must have been of old standing, because the cerebral disparity was accompanied by corresponding cranial asymmetery. The distribution suggested that the condition might have resulted from partial arterial occlusion such as arises in syphilis, notwithstanding that we could produce no evidence of syphilitic infection. Death was ascribed to phthisis.

Case 2.—A female, aged 80 years, who suffered from dementia with epilepsy. The withered gyri were scattered over the posterior and upper parts of the frontal lobes, the parietal lobes and precunei, and along the external parieto-occipital boundary. The

arteries of the brain, indeed, of the whole body, were exceedingly atheromatous and calcareous, the basal nuclei showed *état criblé*, and there were a few small scars in the centrum ovale.

Case 3.—An obese woman, aged 64 years, who died of strangulated umbilical hernia. There was scarcely a convolution in either hemisphere which did not at some point show foci of cicatricial puckering. The associated reduction in size of the brain was so great that the weights are worth recording, encephalon, 970 grammes; right hemisphere, 402 grammes; left hemisphere, 402 grammes; cerebellum with pons and medulla, 138 grammes. The skull was very thick and the frontal bones rough internally. Calcification of arteries was general and extreme.

Case 4.—A female, aged 65 years, suffering from dementia. The brain was small (1,070 grammes), and, in addition to senile changes, presented withering of the gyri bordering the horizontal limb of the intraparietal sulcus and the second frontal sulcus in the right hemisphere. The case was unusual in that the change was unilateral. The subject was stout and well-nourished, the larger arteries were very calcareous, and the kidneys in a state of senile arterio-sclerotic fibrosis.

Commentary.

As three of these subjects were women, we may say that the female sex is disposed to the disease more than the male. Age also seems to bear an influence, because, although the man was but 24 years old, all the women had reached senility. The relation between the disease and an affection of the arteries is of greater importance. In the young subject the influence of syphilis could not be excluded, and in the remaining cases the arteries exhibited a degree of atheroma and calcification such as is not often seen even in cases of advanced senility; and, as I have already indicated, the distribution of the cerebral disfigurement favours the suggested relation to syphilis. At the same time, when we remember that rupture and thrombosis of such vessels are frequent in the aged, and particularly in the aged insane, it is singular that there was no gross lesion in any of these cases; and equally strange that in one case alone we found that dilation of the perivascular channels and those small scars in the central nuclei and white substance which we associate with degenerated vessels.

We will now enquire into the nature of the process, and here we shall be helped by the microscopic appearances.

Microscopic Examination.

Having made horizontal as well as transverse sections of many affected gyri, I have come to the conclusion that the change is attributable to a discrete occlusion of numerous
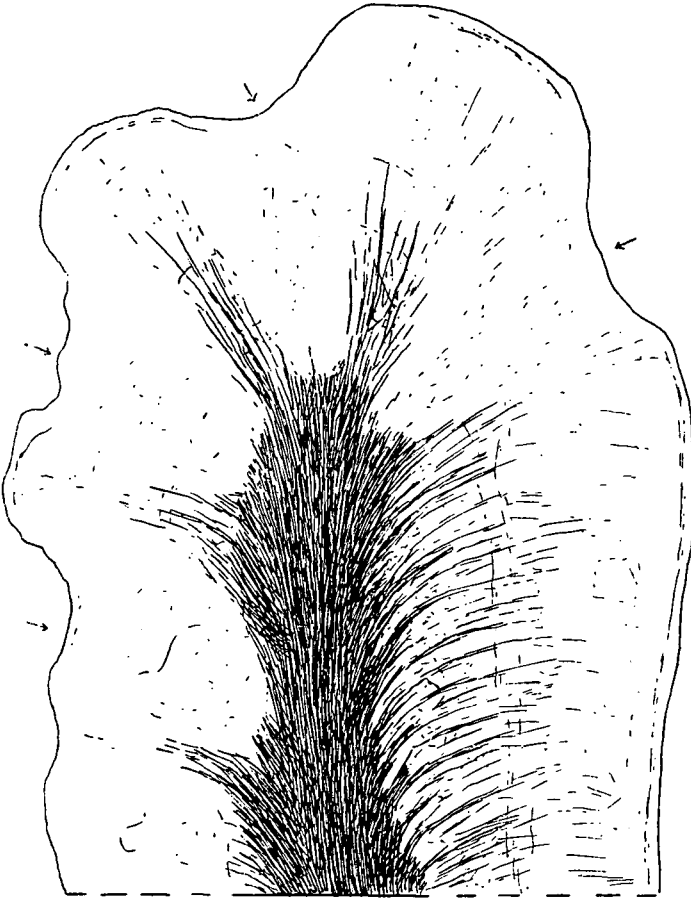

FIG. 17.

Cerebral Arterio-Sclerosis.

A semi-diagrammatic representation of a transverse section of one of the affected gyri, stained for nerve fibres. Along the margin are indentations which correspond with the pits seen before section. Beneath these the cortex is wholly denuded of nerve fibres and nerve cells and converted into glial tissue: elsewhere it is healthy. × 80.

cortical arterioles.   First taking the appearances on trans-
verse section, the cortex is divided into a series of healthy
and diseased compartments; strips of substance entirely
bereft of nerve fibres and cells, and composed of glial tissue
only, alternate with strips wherein the nerve cells and fibres,
although distorted by cicatrisation, are preserved; and it is
interesting that each sclerosed strip lies immediately below
one of the surface pits.   Turning to the horizontal sections,
the fields of sclerosis seen before as strips now appear as
islets occupying about half a low power field of the micro-
scope, most of them isolated and circular, but some oval and
joined to neighbouring islets by a linear band of glial tissue.
These islets are composed solely of fine glial fibres, and
appear to be non-vascular; evidently by contraction they
have drawn on the surface and caused the pitting which is
a feature of the lesion.   At the edge o. each islet, in the
adjoining healthy substance, one or more blood-vessels run,
and also as a result of cicatrisation these are dilated.   Else-
where the vessels show hyaline degeneration and general
senile changes.   There is no indication of cyst formation,
nor can hæmoglobin crystals be found.

To explain these microscopic appearances, we can only
suppose that each strip or islet of sclerosis represents a field
of substance originally supplied by a cortical arteriole now
for many years occluded.   Not to discover the occluded artery
running down the centre of each strip is no proof against
this origin, because time has converted the vessel into con-
nective tissue, but it is hard to understand why some arteries
should be selected for stoppage and others left patent.

In conclusion, gyral arterio-sclerosis with atrophy and
pitting is a disease chiefly confined to aged dements with
diseased arteries, it attacks the cortex in patches, and
apparently is the outcome of a discrete occlusion of cortical
arterioles.

CHAPTER 8.—COLLOID SCLEROSIS.

An affection of the blood-vessels is the principal factor
in this form of sclerosis; glia-cell proliferation participates
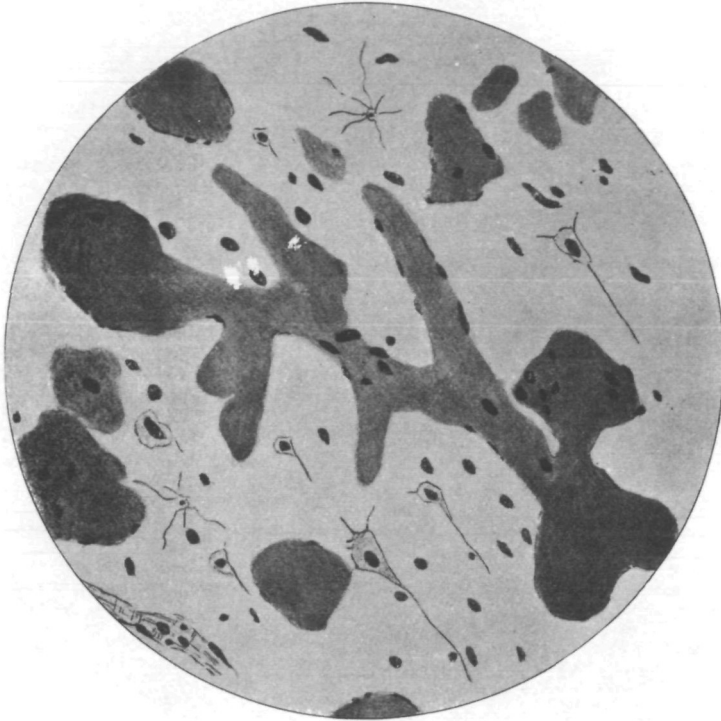only to a minor extent.   The condition is rare; for several

FIG. 18.

Colloid Sclerosis.

A microscopic drawing to indicate the size and shape of the colloid masses. The form of the main mass proclaims that it is an altered vessel. The drawing is taken from the level of the large external pyramidal cells. × 250.

years it was our routine practice at Rainhill to examine microscopically some part of the cerebral cortex in the case of every patient who died, and, with my later experience added, I have now notes of the inspection of more than 500 brains. In one case alone have the appearances I am about to describe been observed.

The subject was a man, aged 38 years. He presented the classical signs of general paralysis, and this combined with tuberculosis of the lungs to cause his death. As indicating general paralysis the brain was greatly wasted (weight of encephalon 1,162 grammes), the pia-arachnoid membrane was thick and opaque, the ventricles were dilated, and the ependyma was granular; and as the feature of special interest we found all the gray matter of the brain, including the cortex of both cerebrum and cerebellum, and the substance of the basal nuclei, greatly increased in firmness and abnormally yellow. Of course, it is the rule in general paralysis for the cortex to be unduly firm, but in this case the induration was profound, declaring itself not only to the fingers but to the knife.

The lungs provided examples of acute "pneumonic" phthisis, and, as proving the rapidity of its progression, there was no ulceration of the intestines.

The remaining organs were free from gross disease, and I must note specially that they were not lardaceous.

Microscopic Examination. (Fig. 18.)

In sections of the cortex and basal nuclei an abundance of large, semi-transparent, almost homogeneous masses immediately arrests attention; a few of these are cylindrical, but the majority are round, and for the latter 35 μ is an average diameter. Occasionally what appear to be concrete masses, giving a transverse measurement of about 180 μ, are seen. Many of the masses contain a few nuclei like those in vessel walls, but in other respects they are structureless. They present no concentric markings. They are almost transparent, and in the presence of most dyes retain their natural yellow tint; with methyl violet, however (in Weigert's stain for neuroglia), with hæmatoxylin,

and with carmine, they stain intensely.   With ordinary solutions of methyl violet a faint pink tint suffuses the intense violet colour, but, as proving that the reaction is not that of amyloid tissue, the masses neither turn brown with iodine nor blue with iodine and sulphuric acid.   In the case of the basal nuclei the masses are more numerous in the caudate and lenticular bodies than in the optic thalami, and in the cortex they distinctly favour the walls and floors of sulci.   The white matter is not deeply invaded.

Notwithstanding that this change cannot be shown in every section, there is no doubt that the masses are directly related to, indeed, represent, blood-vessels.   On the question whether the process is a degeneration or an infiltration it is hard to pronounce an opinion, but, judging from general appearances, and particularly from the way in which the material follows each vessel in the form of a confluent mass, I prefer to think that we have to deal with an infiltration or a precipitation in and around the tissue elements rather than a degeneration.   The change produces great thickening of the vessel wall, and here and there remarkable bulgings or buds (*vide* fig. 18), which are further curious in staining more intensely than the rest of the vessel.   The isolated masses represented in the drawing are similarly thickened portions of surrounding vessels on partial section.

As to the nature of the material, I have little hesitation in declaring it to be colloid ; it could only be confused with hyaline matter, but not if it be remembered that tissues altered by hyaline degeneration do not stain with methyl violet.   Also I believe that the change is identical with that seen by Alzheimer in one case of general paralysis and in one of epilepsy.

<div align="center">REFERENCE.</div>

ALZHEIMER.   "Die Colloidenentartung des Gehirns."   *Archiv. f. Psychiatrie*, 1898, p. 18.

<div align="center">CHAPTER 9.—GIANT CELL SCLEROSIS.</div>

Perhaps more commonly than we imagine sclerosis manifests itself in a heterotopic anomaly of the nervous system in which a collection of giant nerve cells is an important
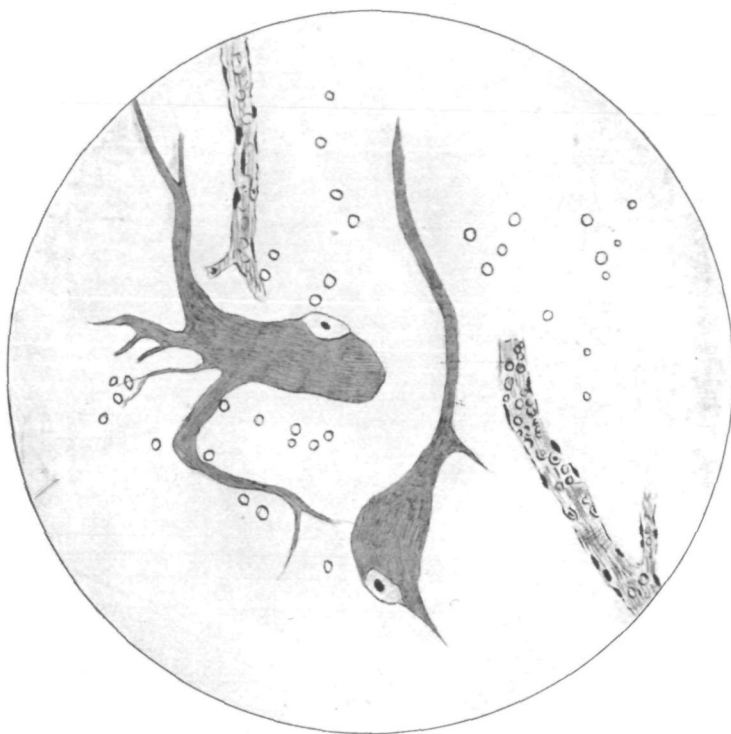
FIG. 19.

Giant Cell Sclerosis.

A camera lucida drawing showing two of the pallid giant nerve cells, with eccentric nuclei, which occupy the mass. Two capillaries and some nuclei of the neuroglia are included in the figure.

Stain, Thionin. Magnification × 300.

constituent. I have seen one case, an epileptic woman, aged 23 years, with various physical stigmata of degeneration, and a family history disposing to nervous disease and insanity.

In the second temporal convolution of the left hemisphere, four centimetres behind the tip of the lobe, imbedded in the white substance immediately below the cortex, was an indurated mass of the same colour as surrounding parts, and about the size of a hazel nut.

The microscopic sections I have prepared are occupied by numbers of giant multipolar cells, similar in shape and equal in size to those in the precentral gyrus (motor area), but their processes, which are long, point in all directions; their protoplasm is pallid, contains no Nissl bodies and is sometimes vacuolated, and the nucleus, small in proportion to the size of the cell, is frequently eccentric. Other nerve cells dotted about are small and polymorphous. The field is rich in nuclei of the neuroglia, and is interlaced by abundant fine capillaries. The overlying cortex appears to be healthy. (Fig. 19.)

I am conscious of transgression in including this condition in the category of sclerosis; still the giant cells are reminiscent of those seen in cases of tuberose sclerosis, and it was by the induration alone that the growth was detected. If it should not be accepted as a form of sclerosis, the name "glioma gangliocellulare," not so aptly applied to tuberose sclerosis, might meet the case.

CHAPTER 10.—OTHER FORMS OF SCLEROSIS.

There are several other forms of cerebral sclerosis, but being of common occurrence and having a known pathology they require only brief mention.

(a) Sclerosis in General Paralysis of the Insane.

We are familiar with the cerebral induration of general paralysis, and in the majority of cases do not err in ascribing it to the proliferation of glial tissue, and the universal thickening of vessel walls running in company with the neuronic degeneration characteristic of this disease.

(b) *Cerebral Sclerosis in Senility.*

As in general paralysis, so in senility, neuronic decay, vascular disease and glial proliferation combine to cause a general increase in the firmness of the brain.

In special cases, localised induration attended by extreme wasting of gyri occurs, and may be explained by atheromatous narrowing of the lumen of special arteries to the parts, whereby the blood supply, without being quite cut off, is much diminished, so aggravating the ordinary process of senile decay.

I have seen several cases in which the tips of the temporal lobes and the gyri on the convex face of the frontal lobe have been selected for affection in this manner.

(c) *Sclerosis of the Cornu Ammonis in Epilepsy.*

Although I have examined a number of brains from cases of epilepsy, I have found no support for the statement of early writers that sclerosis of the cornu ammonis is a common feature in this disease. Clothed by a dense, felted lamina medullaris externa, or zonal layer, and strengthened by radiating fasciculi of long and stout medullated nerve fibres, the cortex of the cornu ammonis, or gyrus dentatus, indeed, of the whole hippocampus, including the lobus pyriformis, is structurally firmer than other parts of the brain, and often feels much indurated, but not more often in epilepsy than in other diseases.

(d) *The Effects of Cerebral Softening and Hæmorrhage on Surrounding Parts.*

There is no doubt that the puckering and induration affecting gyri along the borders of a patch of ordinary embolic or thrombotic softening, or the parts around a hæmorrhage, are due to the severance and decay of internuncial neurons and the subsequent proliferation of neuroglia brought about by the arterial disturbance.

I have already mentioned that such cases have proved of great use to me in studying morbid conditions of the neuroglia, and there is no occasion to enter further into their histology.

(e) *Microgyria in Idiocy*.

In addition to the microgyrous conditions affecting idiots, described in foregoing sections, there is one which is very common, and though more frequent in the parietal and occipital lobes than elsewhere, it is not restricted to any particular part of the brain. The diseased area varies in extent, and is represented by a small nucleus of puckered and contracted, or wholly-destroyed, gyri, surrounded by others which are attenuated and sclerosed, but not deformed. There may be more than one lesion, and in any case considerable cerebral deformity and asymmetry results.

I refer specially to this condition in order that I may protest against the view that such areas are manifestations of some developmental error. I have seen many cases, and in all the distribution of the lesion and the constant signs of post-necrotic destruction in the centre of the area suggested a vascular origin, namely, embolism or thrombosis, at birth or soon after, of the artery leading to the part.

(f) *Cerebral Sclerosis in Syphilis*.

More or less widespread sclerosis of the brain has been reported in cases of congenital syphilis, but I myself have not seen an instance of the affection. In cases of gummatous subdural growths, however, arising in adults, I have observed infiltration and induration of the subjacent brain substance to a depth of several millimetres; and in other cases of syphilis, also in adults, I have noticed sclerosis and attenuation of gyri, particularly those of the frontal and temporal lobes, which I have ascribed to partial closure by syphilitic endarteritis of the supplying arteries, a condition which I have considered as akin to that sometimes seen in the brains of aged individuals with atheromatous vessels. Clinically, in such cases, the diagnosis of syphilitic pseudo-general paralysis has been sometimes made.

(g) *Disseminated Sclerosis*.

To complete the list of forms of sclerosis I have only to name disseminated sclerosis (sclérose en plaques) and military sclerosis, and mention that I have nothing to add to the descriptions of these conditions given by others.