APR 2 - 1934

THE JOURNAL OF NEUROLOGY AND PSYCHOPATHOLOGY

Vol. XIV.

JANUARY, 1934

No. 55

Original Papers

MEGALENCEPHALY*

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THERE appears to be no pronounced exception to the general rule that any somatic tissue or organ is susceptible of undergoing a departure from its normal standard in the direction of either under- or overgrowth. But decision as to what constitutes definite distinction from the norm must always be somewhat difficult. A true mean has first to be calculated, and then, on either side, deviations have to be allowed ere the physiological can be said to have become the pathological. These things are from their very nature hard to establish. Current nomenclature is not perhaps at its best in this respect. In general, the term 'hypertrophy' is taken to denote increase in the bulk of a tissue or organ, and 'hyperplasia' increase in the numerical amount of its constituent elements; but hyperplasia of cells must lead to hypertrophy of the organ of which they are the components. 'Hypotrophy' is a word seldom used, perhaps for its cacophonous note, yet it is manifestly more correct than 'atrophy,' with which it is often confounded; but 'hypoplasia' is properly in vogue for something less than actual 'aplasia.'

The idea that the brain, as one of the organs of the human frame, is likewise susceptible to under- and overgrowth is old in the history of medicine. For fairly evident reasons, included among which is the fact of its being less rare, a small head, with its inevitably small brain, will perhaps engage attention more than a large head—in the sense, that is, of a large brain within it. Here again current nomenclature leaves something to be desired. The term 'microcephaly' refers indifferently to 'small-brainedness,' for which the word 'micrencephaly' is obviously preferable and should be in regular use, or to a small skull, for which 'microcrania' must commend itself. The former feature, indeed, is probably the cardinal one, since there is no evidence to show

* Presidential Address, Section of Neurology, Royal Society of Medicine, October 19, 1933. Published here by kind permission of the Council of the Society.

that a small skull retards brain development and restricts its evolution in volume. In respect of the converse anomaly, however, the correspondence is not quite the same. From a large head a large brain cannot immediately be inferred, seeing that the chief cause of cranial enlargement is hydrocephalus, and the hydrocephalic brain is distended but in no sense hypertrophied.

On theoretical grounds, 'big-brainedness' is a possible developmental anomaly, but the possessor of an unusually big and heavy brain whose functions are normal cannot be considered in any way pathological; he might, indeed, be remarkable for outstanding intellectual power (though, as we shall see, this is by no means always the case). Increase of bulk accompanied by superlative physiological activity is a departure from the norm, but not a morbid state.

Scattered sparsely through the literature, however, will be found records of cerebral hyperplasia accompanied by some degree of mental retardation or idiocy, by epilepsy, or by other abnormalities of function. The brain as a whole has undergone harmonious and well-proportioned enlargement in its general naked-eye dimensions; it fills the cranium completely, its surface is covered with plump convolutions, and its weight considerably exceeds the average for age and sex concerned. The brain *looks* normal, but yet is the seat of some dynamic defect. For such a genetic anomaly the term 'megalencephaly' was, so far as I can discover, first suggested by Andrews and adopted by Morley Fletcher¹ in 1900. Long before then, and occasionally since, brain 'hypertrophy' or 'hyperplasia' has sometimes been employed to denote the same condition, but neither perhaps quite conveys the idea of *pathological* overgrowth implicit in the word megalencephaly.

Before a diagnosis of megalencephaly can be made it is naturally essential to ascertain what may be regarded as normal limits in respect of age, sex, and race, and desirable also to know the normal relations of brain weight to cranial capacity and to body weight.

BRAIN WEIGHT FOR SEX, AGE, HEIGHT, BODY WEIGHT, AND RACE

1. Many compilations of *brain weight for sex* have been made, Taking first the adult, we have, among others, those of Bischoff,² Boyd,³ Marchand,⁴ and Retzius,⁵ expressed in grammes.

						Normal Adult Brain Weight.	
						Male.	Female.
Bischoff	.	.	.	.	.	1,362	1,219
Boyd	.	.	.	.	.	1,325	1,183
Marchand	.	.	.	.	.	1,399	1,248
Retzius	.	.	.	.	.	1,388	1,352

Adding these up and striking the average, we find it to be 1,368 and 1,250 grammes respectively for male and female adult brains.

Yet these means, based though they are on data obtained from examina-

tion of thousands of brains, are capable of conveying a wrong or, rather, misleading impression. Attempts have frequently been made to correlate brain weights with *different social and intellectual classes*, the inference generally turning out to be that intelligence and brain weight increase *pari passu*. For example, we may cite the figures furnished by Matiegka.⁶

Social and Intellectual Class.	Average Brain Weight in Grammes.
Navvies (14)	1,410
Workmen (34)	1,433
Minor Officials (14)	1,435
Tradespeople and Artisans (123)	1,449
Minor Officers, Teachers, Musicians, etc. (28)	1,468
Students, Officers, Doctors, etc.	1,500

(The numbers in brackets refer to the number of cases examined.)

It is perhaps not amiss to remark that the intellectual divisions conceived by Matiegka, however gratifying to members of our own profession, seem to have been fixed without reference to any standard of humour, and that if some reshuffling took place the statistics might be rather different. Be this as it may, their interest resides rather in the fact that the average of all groups combined is itself considerably higher than that which we have already quoted.

2. As regards *brain weight for age*, tabulations vary somewhat between themselves (cf. Pfister,⁷ Schwalbe,⁸ Boyd, Marchand, etc.), but the appended figures may be taken to represent the facts with fair accuracy.

Age.	Average Weight of Male Brain in Grammes.
Birth	370
Six months	730
One year	960
Two years	1,010
Three	1,080
Four to six	1,300
Six to fourteen	1,350

It is well recognized that the brain ceases to grow in weight after a certain period; according to Marchand, this occurs at some time between 15 and 20, according to Handmann,⁹ between 18 and 20. Growth thereafter is virtually nil, but even before that period increase for several years, viz. from about 8 or 10, has been slight indeed. Later in life, from the sixth decade onward, weight decreases—some believe this commences after the age of 40 (cf. Weigner,¹⁰ Matiegka, Fritze,¹¹ and others). The difficulty with all such compilations is, that they can never show how in one and the same person brain weight varies from one life-period to another, for the self-evident reason that a brain can only be weighed once.

3. Connexion between *brain weight and body height* is also troublesome to assess, except in a general and rather vague way. It is, for example, illegitimate to affirm that the bigger the body, the heavier is the brain, though in a general fashion such relationship holds during the early months and years of life. Statistics on this point vary rather widely among themselves; two sets may be cited, bearing on body heights between approximately 4 feet 7 inches and 6 feet 3 inches.

(Marchand)			(Handmann)		
Body Height.		Brain Weight.	Body Weight.		Brain Weight.
cm.		g.	cm.		g.
139-160	.	1,335	144-160	.	1,329
161-170	.	1,405	161-170	.	1,357
171-192	.	1,422	171-184	.	1,432

A relationship of another kind unites the data as follows: to each centimetre of body length corresponds a brain weight of 8 grammes (Bolk¹²), or 8.6 (Matiegka), or 8.3 (Handmann); Marchand gives a variation of from 7.7 to 8.8 for each centimetre. Here is evidently a fairly close agreement. None the less, tall people have sometimes rather a light brain weight, and little persons rather a heavy one, proportionately; in point of fact, the latter condition obtains with considerable frequency. No general rule can be laid down, for exceptions occur so often as to discount its worth.

4. Still more difficult is the establishing of any regular ratio between *brain weight and body weight*. Since the former can only be learned at autopsy, the condition of somatic nourishment must be borne in mind when comparisons are made, and here, evidently, the nature of the fatal illness has to be considered. A 'wasting' disease may have altered proportions ere the chance for comparison of the two weights occurs. According to von Bechterev,¹³ in states of starvation the brain wastes very much less than the body—insignificantly so; and I have the authority of the late Sir Frederick Mott for a similar assertion. If this be accepted, the statement becomes one of considerable importance, and will be referred to again later. In this connexion one naturally thinks of the cases of hunger or famine œdema which occurred during and after the War, and of other forms of inanition such as hypophyscal cachexia. Though in respect of the former most observers agree that pronounced reduction in size and weight of all the viscera and endocrine glands characterized the affection (cf. Bigland,¹⁴ Enright,¹⁵ etc.), it has proved regrettably difficult to obtain information as to the weight of the brain; nor does the literature on experimental starvation and avitaminosis, so far as I can discover, supply the needed data.

5. *Racial differences* in brain size and weight, well recognized though they are, do not directly concern our topic, for we are dealing with stocks in which these are not particularly noteworthy. The relation of brain weight to *cranial capacity*, also, may be briefly dismissed. According to Reichardt,¹⁶

the normal proportion is as 90 to 100, and he considers that when the margin is reduced to 5 per cent. or less, instead of this 10 per cent., a pathological condition of brain enlargement is present. In some examples of megalencephaly, as we shall see, the cranium is occupied 'to capacity' by the brain, bearing out Reichardt's conception. More generally, the greater the intelligence of the individual the larger is his cranial capacity likely to be—at least, such is the conventional view, based on numerous statistics. But exceptions are so frequent that Karl Pearson's ¹⁷ words must be taken to reflect the real state of affairs: 'it would be idle to endeavour to predict the intellectual ability of an individual from his or her head measurements.'

ABNORMAL BRAIN WEIGHTS

Dealing now more closely with brain hypertrophy, our first remark is that it occurs in association with very different levels of mental endowment and acquisition.

1. To link brains above the average in weight with the possession of outstanding mental abilities seems a natural tendency; at any rate it has been practised for generations. The measurements of these so-called 'élite brains' have often been recorded; yet while perhaps individually and superficially impressive, once a series of such measurements is compiled and contrasted the impressiveness vanishes. This will be appreciated by a glance at fig. 1, where a few selected instances are given. Clearly, we cannot suppose that the brain weight of the Russian novelist Tourgeniev, much greater than that of the English novelist Thackeray (both being élite brains) can be taken to mean a corresponding degree of literary superiority. The massive cranium of Bismarck, and his heavy brain, have often been set alongside his powerful intellect; yet the brain of the wayward poet Byron was actually heavier. The absurdity of such inferences is intensified by consideration of élite brains below the average weight, of which also examples are furnished in fig. 1. Thus the brain of the French novelist and satirist Anatole France weighed only 1,017 grammes—about the same as that of a two-year-old baby—or almost exactly half of the weight of Tourgeniev's, and indeed is not very far removed from the upper limit of so-called micrencephaly. Whatever be the anatomical or physical substratum of talent or genius, it has nothing to do with brain volume or mass.

2. Again, in a fair number of cases the owners of heavy brains have been considered mentally normal—i.e. undistinguished; they are the plain John Smiths of life, despite their possessing large and heavy brains. Several examples are noticed in fig. 1. Thus Gerlach's case ¹⁸ (2,140 g.) was that of a man who was 'geistig normal'; Fritze's (1,930 g.), that of a 'normal' soldier, in whom neither as boy nor man had any distinction from his fellows been remarked; similar comment applies to his other case, also that of a soldier (1,860 g.), and to Marchand's (1,790 g.).

3. In a third group come those exceptional cases where the owners of large and heavy brains have been much below the average in mental attainments, being classified as idiots or mental defectives, or as epileptics, or

FIG. 1.—Brain weights above and below the average, measured in grammes. The figures in brackets give the age at death of the subject concerned.

manifesting a combination of these states. To them, as a whole, the epithet 'megalecephalic' belongs, although pathological examination has not always been conducted with requisite fullness. For the sake of convenience adults and juveniles may be separated.

(1) The premier place is taken among the adults (fig. 1) by van Walsen's¹⁹ case, that of an epileptic idiot who died at the age of 21, and whose brain reached the well-nigh incredible figure of 2,850 g. Schmincke's²⁰ case was that of an epileptic dement aged 55, whose brain weighed 2,155 g.; Anton's,²¹ that of an epileptic, 23 years old, with a brain weight of 1,995 g. Volland's²² (1,874 g.) was also that of a feeble-minded epileptic, and Middlemass's²³ too (1,850 g.). Others might be quoted in this connexion, e.g., those of Grant,²⁴ Sims,²⁵ and Campbell²⁶; the last-named briefly

FIG. 2.—Brain weights of megalencephalic cases in children, measured in grammes. The figures at the foot indicate years of life. The upward curve gives the average weights for these respective years.

records 15 cases of brains weighing from 1,701 to 2,027 g. among 1,146 post-mortems performed at an asylum. One-third had suffered from epilepsy, and all but one were in males. Less striking, in a way, is Peter's²⁷ case of idiocy (age 22); the brain weighed 1,470 g., a figure above the average, but the cerebellum in particular was overgrown; its weight was 205 g., which corresponds to a brain of 2,210 g.

(2) Among the children's cases (fig. 2) we have that originally described as megalencephaly by Morley Fletcher.¹ The boy was mentally backward but not specially stupid, and had never suffered from fits.

Ever since birth he had been noticed to have a large head, and was known as 'big head' at school. He died at the age of 10, when his brain was found to weigh 2,065.9 g. and to be uniformly increased in bulk, with all relative proportions maintained. Another case we owe to Haberlin,²⁸ that of a male child of two, who died after a series of convulsions, and whose brain weighed 1,712 g. De Lange's²⁹ concerns a male infant of seven months, who probably did not see very well and who exhibited occasional convulsions. The weight of his brain was no less than 1,750 g., more than twice the average for seven months.

To this same class, scanty as it is, belong two personal cases now to be described.

PERSONAL CASES

Case I.—Ronald A., age two-and-a-half years.

Family History.—The patient was the youngest of four children; the first, a premature infant, died at birth. Two boys, ages seven and five, were normal in every respect. No history of familial or hereditary nervous affection could be obtained. Both parents were living and healthy.

Previous History.—The infant was born prematurely at the eighth month by instrumental delivery. At its birth apparently no comment was made on the size of its head, but when it was about three months old the mother called the doctor's attention to it: 'he did not think anything of it.' The child did not progress as the others had done; 'it was backward in everything.' Teething did not commence till the twelfth month, by which time, moreover, it had not yet begun to sit up. Taken to hospital, its case was dismissed with the remark that the baby was 'backward.' Circumcision and tonsillectomy were performed shortly thereafter, and the teeth began to appear slowly after the age of 15 months. By the age of two years the child had started to walk and talk, but had not learned any habits of personal cleanliness.

Present History.—The little boy appeared perfectly well when put to bed on November 25, 1928. During the night he was restless, did not sleep, and vomited once. At eight in the morning he 'went into convulsions,' 'was stiff all over and blue in the face,' then relaxed and sank into continuing unconsciousness. He was admitted to hospital a few hours later.

State on Admission.—He was at once seen to be in a state of deep coma; no reflexes could be elicited, and breathing was irregular. The large size of the head was apparent; it was suggestive of hydrocephalus. The optic discs were clear. There were no signs of rickets.

Death followed two hours after admission.

Autopsy.—The head was abnormally large, the face appearing rather tiny in proportion. The fontanelles were closed.

Measurements.—Circumference of head: 55 cm. (normal, 47).

Nasion toinion: 35 cm.

Ear (meatus) to ear over vertex: 35 cm.

Length of child: 80 cm. (normal, 82).

Heart: normal, no congenital anomaly.

Lungs: some terminal congestion only.

Abdomen: normal viscera.

Thymus: well developed, but not unusually so for age.

Skull: the bones were rather thin.

Brain : on removal of the calvaria the cranial cavity was seen to be completely filled by the brain, which was therefore impressively large. The membranes were normal, but little or no fluid was noticed in the subarachnoid spaces ; the brain was distinctly ' dry.' It weighed complete, without the dura, 1,644 g.

To the naked eye the convolutions were full, plump, and rounded. On section of the hemispheres, instead of hydrocephalus (which had been confidently surmised by the resident medical officer), the ventricles were seen to be quite small and remarkably dry ; the ependymal lining was everywhere dull, instead of glistening.*

Among the clinical features of this case that deserve note are the large size of the head, remarked soon after birth, and the fact that death followed an unexpected series of convulsions. These facts, naturally enough, led to the diagnosis of internal hydrocephalus, which was, however, completely belied by post-mortem examination, when cerebral fluid was seen to be meagre in amount and both ventricular and subarachnoid systems very dry.

In all these respects the case offers close resemblances to that recorded by Haberland²⁸—so much so as to warrant the inference that they both represent a special and peculiar type. His case, as already said, was that of a male child of two ; the parents, in this instance, were alcoholic, and one of the other six siblings was a high-grade imbecile (age 11 years). The child's head was noticed even at birth to be large, and its size disproportionately increased thereafter right up to the time of death. Just as in my own case, the child suddenly developed a series of epileptic convulsions, passed into coma, and died a few hours thereafter. The circumference of the head was 55 cm. (normal, 47), and it was considered hydrocephalic ; the length of the body was 78 cm. (normal, 82). On opening of the skull and examination of the brain, the latter was seen to be symmetrically and harmoniously enlarged, and very little fluid was found anywhere, while the ventricles were of normal dimensions. It weighed 1,712 g.

Case II.—William D., age three-and-a-half years.

Family History.—This showed nothing of note. Both parents and grandparents were apparently healthy and normal. The patient was the first of two children—the other was normal in all respects. Both father and mother were 23 when the child was born.

Previous History.—His birth was a face presentation, and there was some degree of asphyxia neonatorum. He had always been backward, and noticed to have a large head. Continually crying, he was slow even in sitting up, had to be fed, did not learn to indicate his bodily needs, and was still unable to articulate when two years old.

Present History.—Because of this obvious retardation and helplessness he was admitted to hospital at the age of two years and ten months.

On Admission.—The child could not stand or walk, was ' wet and dirty,' unusually helpless for his age, and unable to speak. Examination did not disclose any trouble in heart, lungs, or other viscera. His weight was 2 st. 1 lb. The tonsils were large

* I owe these notes to the kindness of Dr. S. Berman, then one of the medical officers of Fulham Hospital.

and fleshy. Examination of the nervous system was apparently negative. The most prominent feature of the case was the large size of the head, which was thought to be hydrocephalic (fig. 3). No fits had occurred at any time, nor were any observed in hospital. On admission the anterior fontanelle was not entirely closed, but this development took place during his stay there. No improvement was noted in his condition except that he was just beginning to try to walk when death followed an infection.

Autopsy.—No disease was found in any of the organs of chest and abdomen.

FIG. 3.—Large head (not typically hydrocephalic) and (adenoidal) facies of W.D. (Case II).

The head measured 51.2 cm. in circumference (normal 47 cm.). When the calvaria was removed the brain was seen to fill the whole of the cranial cavity, its surface being covered with large, plump convolutions (fig. 4). Without the dura, it weighed 1,502 g. (normal 1080 g.)*

Unfortunately, in regard to my own Case I, I neither saw the patient during life nor was present at the autopsy. The brain was not kept

* I owe this case to the kindness of Dr. Brown, then one of the medical officers of the Fountain Hospital, Tooting.

intact, and I was only able to secure some pieces for microscopical investigation.

PATHOLOGY OF PERSONAL CASE I

The full and 'packed' appearance of the cerebral gyri was very noticeable. Both grey and white matter preserved normal proportions; the depth of the cortex, on the whole, tended to exceed slightly that of the normal two-year-old brain. The corpus callosum seemed to be of appropriate dimensions for the

FIG. 4.—Right hemisphere of Case II., showing large, crowded convolutions.

size of the brain—in a word, there was a harmonious general overdevelopment of brain structure without any manifest disproportion among its constituent parts (fig. 5).

Microscopically, however, definite pathological change became apparent. Nissl preparations showed that the cytoplasm of the ganglion-cells of the cortex was more or less uniformly stained throughout; despite repeated technical efforts, it would not differentiate properly so as to disclose the presence of Nissl substance. Instead, it was coloured more or less homogeneously, with occasionally some slight signs of granulation towards the periphery (fig. 6). The outline of the cell-bodies, sometimes rather rounded, more generally maintained its angular or polygonal contour; but many specimens of pyramidal cells in the third and fifth layers were flattened and

'drawn-out,' and stained deeply without a trace of differentiation (fig. 7). Not only were cellular shape and cytoplasm thus altered on a widespread scale, but the nuclei also. In place of their usual more or less circular form nearly all in the pyramidal layers were oval or elongated, sometimes almost triangular, in the same axis as the drawn-out cytoplasm, and refused to

FIG. 5.—Case I. Vertical transverse section of hemisphere, showing proportions of grey and white matter.

differentiate—in other words, no nuclear structural details could be discovered (fig. 8). Most of them stained very deeply.

The Bielschowsky method, moreover, disclosed a fair number of rather freakish forms among the large pyramidal cells and Betz-cells, with irregular vacuolation in their cytoplasm and in some specimens along cell-processes, while neurofibrillar network seemed very incomplete (figs. 9 and 10). This technique, further, accentuated the peculiar elongated character of a great number of cells in the third and fifth layers (fig. 11).

Histologically the variety of cellular change resembles the 'chronic cell degeneration' of Nissl yet is certainly not identical with it, especially as

FIG. 6.—A Betz-cell from the motor cortex of Case I., showing its peculiar staining reactions.

FIG. 7.—Large pyramidal cells from the cortex (Case I.), with elongated nuclei.

regards the nucleus. To this point attention is again directed below. No cells of a hypertrophic or 'giant' character were seen anywhere.

Their total numbers, however, were somewhat reduced in a given section, but no considerable departure from normal orientation and architectonic arrangement was found.

The white matter did not appear abnormal; interfascicular oligoden-

FIG. 8.—Large pyramidal cell (Case I.), with undifferentiated cytoplasm and darkly staining elongated nucleus.

FIG. 9.

FIG. 10.

FIGS. 9 AND 10.—Vacuolated cortical ganglion-cells (Case I.), stained by Bielschowsky's method.

droglia seemed in all respects as usual. There was no change in protoplasmic glia or microglia in the cortex, unless for doubtful quantitative increase in the latter; at all events no conspicuous areas of gliosis were to be found, although occasional microglial elements were noticed in the immediate vicinity of some

nerve-cells. The blood-vessels of both grey and white matter exhibited normal appearances, and there was no sign of perivascular reaction.

In summary, therefore, the outstanding pathological features of the case were constituted by a well-proportioned and harmonious growth of nerve-cells and fibres, without gliosis or other interstitial reaction, but with a peculiar, generalized dysplasia of the ganglion-cells of the different cortical layers, notably the third and fifth; this consisted in a flattening or lateral shrinkage

FIG. 11.—Long drawn-out cells of the third cortical layer (Case I.), Bielschowsky's method.

and elongation of the cytoplasm of many, its homogeneous coloration and the absence of Nissl granules, and also in a similar oval lengthening of the nucleus, which itself stained very deeply and failed to disclose normal nuclear structure. Here, then, we seem to be dealing with pure megalencephaly in the sense of increase of total quantity of neural substance, made up of increase in individual elements, grossly out of proportion to the age of the infant, but coupled with evident anomalies of individual cell-constitution.

COMPARISON WITH OTHER CASES

Paucity of material for purposes of comparison makes it somewhat difficult to reach any firm conclusions. (1) In the case described by Peter,²⁷ that of a youth of 22, classed by him as megalencephaly, the brain weighed 1,470 g. This is doubtless above the average, and since the patient was a congenital idiot the weight becomes more striking. But the chief feature of

the brain was the *dysharmonic* development of its constituent parts; the cerebellum (as mentioned above) was much too heavy in proportion to the rest, while the corpus callosum was remarkably small. Thus the case does not by any means correspond to that here described. From the standpoint of histopathology, however, Peter's case showed cortical cell-changes not unlike those of my own case, viz. deeply staining cytoplasm with no differentiation, and long-drawn-out cell-processes (often manifesting a corkscrew-like appearance, it is true, which was not noticed in the latter). Further, Peter considered that some of the cell-layers were very poor in quantity of cells (especially strata IV, V, and VI). So far as I have noticed he makes no allusion to the condition of the cell-nuclei. (2) Fletcher's¹ case of megalencephaly (age 10, brain weight 2,065 g.) was distinguished by uniform increase in bulk of the brain, but its principal histological feature was the large amount of neuroglia in both grey and white matter, whereas the nerve-cells of the cortex are stated to have shown no marked alteration in either size or number and to have been otherwise normal. The case, presumably, belongs to a class in which interstitial hyperplasia accounts for the augmented bulk more than any other factor. (3) Similar comment is pertinent to that recorded by Schmincke²⁰; his patient was an epileptic dement (age 35, brain weight 2,155 g.), in whose brain was found pronounced hyperplasia of the protoplasmic glia round vessels and in the neighbourhood of nerve-cells, with fatty changes in both vessel-walls and glia-cells. Some distortion of orientation was observed in cortical nerve-cells, notably the pyramidal cells of the third layer. (4) Volland's,²² too, that of a feeble-minded epileptic (age 22, brain weight 1,874 g.) belongs to the interstitial hyperplasia variety, although he considered that in respect of both size and numbers the layer of large pyramidal cells was overdeveloped. (5) As for de Lange's²⁹ (age seven months, brain weight 1,750 g.), the architectonics of the cortex were everywhere normal except for a few heterotopias, the Betz-cells were rather plumper than usual, with fewer dendrites, and glia was undisturbed. She does not appear to make any allusion to either Nissl substance or nuclei. (6) Though Haberland's²⁸ case (age two years, brain weight 1,712 g.) is, as already stated, close to my own in a number of ways, there are regrettably no histopathological details in his record. (7) Another example of megalencephalic idiocy is that of Peter and Schlüter³⁰ (age three-and-a-half, brain weight, 1,770 g.). In this case a pronounced degree of dysharmony existed in the brain, its white matter throughout being extremely reduced, whereas cellular architectonics were preserved.

It is evident, then, from this brief résumé of even such cases of megalencephaly as were accompanied by mental abnormality, no constant pathological finding can be discovered. We are possibly justified in distinguishing an interstitial from a parenchymatous variety, yet this deduction may not be altogether warranted when additional material comes to be surveyed minutely. For the present, it must suffice to confirm the occurrence of a type of megal-

encephaly, associated clinically with retarded development and epilepsy, in which there is little if any glial proliferation, but characterized by a general, widespread, defect of the larger cortical cells (mainly those of the third and fifth layers); their numbers in any given section are not greatly diminished, but they have undergone some change, the details of which have been narrated and which is disclosed by resort to the usual histological techniques.

ÆTIOLOGY AND PATHOGENESIS

Discussion becomes speculative when questions of ætiology and pathogenesis are approached, but it may none the less prove suggestive.

As a preliminary, certain data in connexion with the factors of somatic and visceral growth deserve scrutiny. In his introduction to Atkinson's³¹ recent monograph on acromegaly Sir Arthur Keith seeks to distinguish two separate growth mechanisms in the animal body; first, the processes which turn the baby's body into that of an adult, and which, increased or diminished, are responsible for the appearance of gigantism or dwarfism; and, second, what he terms 'the mechanism of functional hypertrophism'—growth responses mediated, in his opinion, by the pituitary. As hypertrophy of the blacksmith's biceps is due to exercise, so, in acromegaly, is there, in his view, an exaggeration of structure precisely in those tissues and parts which respond to increased exercise of the whole body—the hands, feet, muscular attachments, jaws, muscles of mastication, etc. Ingenious as the latter supposition is, it cannot explain all the facts of acromegaly. In that condition numerous tissues not obviously related to muscular exercise—skin, viscera, hair, scalp, skull, ears, mucous membranes, etc.—often share in the hyperplasia. The interest of acromegaly for our present purpose lies in quite another direction. What of hypertrophy of the *brain*? Atkinson has analysed 265 post-mortem examinations in cases of the disease, and states that in eight only was the brain found to be enlarged, i.e. in 3 per cent.—a trivial proportion. Besides, on studying the data more closely, we find he includes Rolleston's case, in which the brain weighed 1,389 g.—a figure that does not put it into the category of brain hypertrophy, while another (Israel's), also included, was clinically doubtful. These exclusions reduce the percentage to 2.2. As for the others, the brain weighed 1,870 in Holsti's case, 1,800 g. in that of Fritsche and Klebs; it was affirmed to be 'large' or 'enlarged' (weights seemingly not given) in those of Bailey, Brooks, Klebs, and Lubarsch. In the absence of figures the degree of 'largeness' observed by more than one of these writers cannot be estimated. At all events only one conclusion is permissible, viz. that overgrowth of the brain is not among the consequences of acromegalic pituitarism—the brain is perhaps the sole organ in the whole body not subject to the hypertrophying influence of disordered *pituitary* function. Splanchnomegaly, for example, is common in the disease, but certainly not 'encephalomegaly.' This conclusion seems to me deeply significant, and will be referred to again immediately.

Even from the point of view of megalencephaly as here understood, the heavy-weight brains in the acromegalic cases of Holsti and of Fritsche and Klebs do not lend any assistance, for in neither case was there any impairment of cerebral function ; they belong therefore to the 'normal' group of brains above the mean in weight. Since a considerable number of such cases have been reported without the slightest sign of dyspituitarism, it is proper to infer that there is no connexion between the two.

As for other glands of the endocrine system, little need be said. It is true that the rare condition of anencephaly has been attended in not a few instances by lesions of the *suprarenals*, principally in the form of aplasia. This can hardly be considered the cause of anencephaly ; it is, rather, the sequel to failure of cerebral development, which ipso facto dispenses with any call on the glands for lecithin production, as required for nascent nervous tissue. Were the adrenals responsible for megalencephaly, or integrally associated with it, they should accordingly be the seat of *increased* function and hyperplasia ; hence such findings as those reported by Anton ²¹ in a case of what he terms 'true hypertrophy of the brain,' viz. cystic degeneration, lend no support to the hypothesis. Besides, in numerous examples of the condition the glands have been normal. The *thyroid* cannot be blamed, for any lesions it has shown have been inconstant and trivial. In regard to the *thymus*, there is perhaps a little more to be said, though its mere persistence can scarcely be considered pathological, still less pathogenic. Thus a large thymus was seen by Virchow ³² in the case of a child of three whose brain weighed 1,911 g. ; also by von Hanseemann ³³ (epileptic, age 16, brain weight 1,860 g.), by Fritsche and Klebs ³⁴ in their acromegalic case (brain functions normal, weight 1,800 g.), and by one or two more. In my own case it was well developed, but not beyond normal limits for a child of two. On the other hand, among a series of 27 suicide cases collected by Bartel, ³⁵ many of which showed a status lymphaticus in greater or less degree, were four specimens of brain hypertrophy out of 13 brains weighed, the weights ranging from 1,500 to 1,650 g. In one, however, the thymus had disappeared, while in another the 'lymphatic system was weakly developed.' Such observations do not favour the contention of a causal relationship between the cerebral and the physical condition as strongly as the author appears to assume. Again, a series of 34 (suicides and others) cases of brain hypertrophy have been published by Miloslavich, ³⁶ mostly accompanied by a status thymolymphaticus. Among the 34 were such brain weights as 1,720, 1,740, and 1,880 g., all from suicides with status lymphaticus, but no details as to the cause of death are provided, nor any record of the histological features of the brains. From his material Miloslavich has drawn up the following averages :—

	Average Brain Weight.
Suicides with status lymphaticus . . .	1,521·5 g.
Suicides without status lymphaticus . . .	1,338·0 g.

These figures doubtless seem impressive, but other facts of observation should not be overlooked. In numerous cases of status lymphaticus, as indeed both these authors illustrate, the brain is not heavier than the normal for age and sex ; further, more heavy brains (over 1,800 g.) have been recorded without that lymphatic affection than with it. Miloslavich's tables do not inform us whether any terminal œdema, congestion or swelling due to the manner of suicide may have added to the weight of any of the brains examined. The thymus hyperplasia of some cases of myasthenia is unattended by cerebral hyperplasia. Finally, in respect of the *pineal*, although so-called macrogenitosomia præcox occasionally accompanies tumours of that gland the bigness of body is not associated with bigness of brain.

Our conclusion, supported as it is by that of de Lange, Fritze, Schmincke and others who have discussed the subject, must be that as yet no convincing evidence of pathogenic links between megalencephaly and affections of any of the ductless glands has been advanced.

Allusion was made above to the apparent fact that in cachectic diseases the brain wastes very much less than any other organ, while, as we have just seen, it does not hypertrophy when other viscera overgrow at the bidding of acromegalic dyspituitarism. Further, the megalencephalic is not macrosomatic. For that matter, neither is the micrencephalic of necessity the owner of a small body. Nothing is more striking in anencephaly than the well-developed trunk, limbs, face, and musculature generally of the brainless infant. In some way or other, the brain is almost entirely independent of hormonal influences derived from endocrine glands, and this is perhaps the more peculiar seeing that the hypophysis is intimately connected, anatomically and physiologically, with the diencephalon.

We are thus faced with two questions : (1) why and how is the brain not submitted to the hypertrophying action of pathological growth hormones in dyspituitarism ? and (2) how does a growth hormone act locally in megalencephaly ? One question may be in reality the counterpart of the other ; but answers are exceedingly difficult even to foreshadow.

The clinician occasionally meets with instances of local hypertrophy, i.e. of partial macrosomia, e.g. the cheiromegaly or megalodactyly of some cases of syringomyelia. He also sometimes sees examples of hemihypertrophy where the whole of one side of the body is involved, or of macromely, one limb only being concerned, or of overgrowth confined to one side of the face. For long I have pondered over the idea that there might be some kind of localization in the pituitary, or rather that anatomical relationships between the gland and the diencephalon might have topographical significance, one set controlling growth on one side of the body. The pituitary is a median organ, whereas its diencephalic connexions are probably bilateral. I rather think now that the idea is misconceived, in the sense that the facts of observation can be looked at in another way. For instance, in cases of infantile cerebral hemiplegia the affected side of the body is frequently smaller than the other.

As we know, further, this poor development of the hemiplegic side is often attended by relative reduction in bulk of the opposite cerebral hemisphere. Thus it would appear that somatic growth is in some way associated with integrity of the neural systems supplying the part or parts concerned. Many times the idea has recurred to my mind : what would be the state of affairs if acromegaly were to develop in a patient who in childhood had suffered from either poliomyelitis or cerebral hemiplegia ? Unfortunately, so far as is known to me, no case of the kind is on record. None the less, clinical observations justify the hypothesis that both humoral and neural factors have to be considered when an explanation of local hypertrophies (or hypotrophies, for that matter) is sought. The somatic growth hormone, doubtless of pituitary origin, is conveyed by the bloodstream, we must suppose, and presumably therefore is a diffusely acting substance, but its functions are conditioned by local neural processes. Without some such view as this it appears difficult to understand why infantile hemiplegic limbs fail to grow (generally the arm more than the leg), or why one side only of the body should persistently over-grow ; and still more difficult to see how hypertrophy may be restricted to face or fingers. If we exclude the action of growth hormones of glandular derivation, on the assumption that the small hand of infantile cerebral hemiplegia is the sequel to failure of trophic neural influence only, we are then confronted with the question of what neural trophicity is, and what its mechanism.

NEUROHUMORAL ACTIVITY

In my opinion some light is thrown on these vexed problems by the work of Prof. G. H. Parker³⁷ of Harvard, whose recent little book on *Humoral Agents in Nervous Activity* is well worth attention by the neurologist, although it deals principally with comparative physiology. Commencing with study of the movement of chromatophores in the skin of various members of the animal series, Prof. Parker shows that their colour control, as it may be termed, is under the influence of both neural and humoral mechanisms ; sometimes the optic apparatus responds to external stimuli and in its turn excites secretory action on the part of a hormone-producing organ, which via the blood-stream affects the chromatophores ; sometimes the latter can be shown to be immediately responsive to injected humoral substances (pituin, adrenalin, and the like). This leads to the hypothesis that so-called nerve-control of chromatophores may in reality be due to hormones secreted by nerve-terminals themselves, close to the colour-cells. In other words, the two types of control can be unified by a theory asserting that both occur in every instance.

Perhaps the idea that nervous tissue should be endowed with secretory function will seem a rather startling novelty, yet it is neither very new nor by any means purely guesswork. The medulla of the suprarenals consists of modified sympathetic ganglion-cells, and adrenalin is their secretion product.

Pituitrin, also, comes from a well-defined nervous organ. Other hormonal substances, as Parker shows, appear to come from the terminals of sympathetic nerve-fibres. He then widens his field, adducing evidence in favour of the view that all innervated muscle, smooth or striate, may in activity produce substances having humoral function, as determined by such test organs as the heart, stomach, and other viscera, the salivary glands, etc. Of still greater interest for our subject is the contention that sensory cells in the periphery, e.g. taste-buds, are kept in condition by hormonal substances secreted by the terminals of sensory fibres round them, that this is the clue to trophicity and that both normal nerve impulses and trophic impulses pass over the same route but are mutually independent. Obviously, as regards the receptor system, the former pass from periphery to centre, the latter in the opposite direction. Finally, the same worker applies the neuro-humoral hypothesis to the effector or adjustor system, claiming that the nerve impulse passes from the sensory to the motor side, or from one motor neurone to another, by means of local hormonal action. He thus explains the phenomenon of polarization of the synapse. In Gerard's³⁸ words, 'it is conceivable that the end of the axon acts as a miniature gland and, when stimulated, produces some chemical which is able to excite an adjacent or neighbouring dendrite.' A surmise of the kind, in respect of conductivity, had previously been put on record by Sherrington himself. Parker does not specifically refer to trophic influence as regards the effector system, but in its case, by analogy, the presumption is that both neural and trophic influences pass in the same direction. As the clinician knows, under certain circumstances lesions of the upper motor neurone are followed by trophic muscular change in the periphery. Parker, moreover, has been able to collect evidence, which need not now be summarized, showing that the secretory side of the synapse is structurally different from the receptive side.

It may seem a far cry from such a theory of neurohumoral activity, based on many facts of experimental comparative pathology, to the problems with which we are here concerned. Yet the observations adduced by Parker and others clearly suggest that the nervous system has its own set of hormone-producing mechanisms and that trophicity is integrally bound up therewith. Despite manifold lacunæ, the theory can be utilized, in my opinion, as a kind of working hypothesis. If the brain contains within itself the apparatus whereby its own trophic growth is regulated, may we not conceive of the brain itself as a gland, its own gland? By whatever route discussion proceeds we are always brought back to the same impasse, viz. that the brain is unaffected by the growth or trophic hormones of dyspituitarism notwithstanding their otherwise more or less universal action, that it does not share much, if at all, in general cachexia, and that it sometimes exhibits harmonious hypertrophy strictly confined to itself. The line of approach here sketched seems capable of opening up pathogenic possibilities scarcely comprehensible otherwise.

No doubt some will consider it desirable, or imperative, to distinguish

between trophicity and growth. That the trophic condition of neuronc units should be maintained by secretory substances from axon terminals may appear a feasible conception, but it may be argued that this will not account for congenital or antenatal hyperplasia of neural elements amounting in bulk to increase of total quantity, or hypertrophy. It does not appear to me that the objection is as well-founded as might seem to be the case. For the problem of overgrowth is surely the problem of trophic influences; in any part of the body, and any tissue, the two cannot be separated—witness the hyperplasia of keloid scars, nævoids, etc., while other examples readily suggest themselves. Indeed, the problem of benign or malignant hyperplasias is virtually identical. The extraordinary propensity of the nervous system to tumour overgrowths of such frequency and variety, unequalled by any other somatic tissues, may be in some way related to the conception under consideration, viz. that of a neural hormonal system. At all events, it would appear fundamentally unsatisfying to assign megalencephaly to an 'error of development' without seeking at the same time to discover how the stimulus to overgrowth may act and what mechanism it may utilize. If hormones are secreted by brain tissues, independent of somatic hormones, regulated by some mechanism of its own, we can at least imagine that such a glandular system might be disturbed in its activities and affect the neuraxis only, by way of hyper- or hypotrophy respectively. We can also imagine that it might remain unaffected by circulating pituitary or other glandular hormones which lead to tissue overgrowth almost everywhere else. Can there be an ultimate biological reason for this protection? The cerebrum is enclosed in a non-distensible bony box; has it to be safeguarded from too much increase in size? There is room for other organs of the body to overgrow in acromegaly, and they do.

Little has been said of micrencephaly hitherto, since it lies outside the immediate subject of this discussion. But we may naturally ask whether the hypoplasia of micrencephaly is capable of being understood better by reference to a postulated neural hormonal system. Recent work by Murphy and Goldstein³⁹ has shown that in a series of 75 children whose mothers were subjected to irradiation with X-rays during the foetal existence of the former about one-fourth were micrencephalic, and the suggestion was made that this irradiation arrested development along the polar axis, affecting particularly the growing brain. The facts are curious, though apparently well authenticated. Since, presumably, irradiation in these cases has not been specially directed to the foetal head, it becomes necessary to imagine that this external agency has acted specifically on the brain, for limbs and bones do not remain of necessity small, as has already been stated. That is to say, such a pathogenic theory raises difficulties as much as it may conceivably solve others. Nor must we overlook the fact that some micrencephalics are more or less normal mentally; four cases of the kind have been collected by Hechst,⁴⁰ and a personal one added. Inaba's⁴¹ was that of a woman of 26 with a brain

weight of only 851 g. ; he found, however, that in Economo's cortical area II, where normally a given measured 'unit' contains about 115 cells, his patient's brain had 352 cells, and in area III 362 instead of the normal 119. Thus reduction in space was compensated for by the presence of three times as many cells. Other investigators, however, have not discovered similar crowding of cells in their cases of 'normophrenic' micrencephaly. Be this as it may, if the condition is to be regarded as an arrest of development involving principally or solely the growing brain, it can be compared to any somatic hypoplasia such as is known to be associated with underfunction of somatic glands ; but the point is, that this underfunction does not cause it. Hence we are again virtually compelled to assume that an independent growth system is concerned in micrencephaly, and there is no insurmountable difficulty in imagining it to be a neural harmonic one.

THE NATURE OF MEGALENCEPHALY

Following the line of thought here set down in a very tentative way, we might consider megalencephaly a total as opposed to a partial or local hyperplasia of brain substance—in other words, a 'tumour.' This indeed was done by Virchow⁴² many years ago, when he proposed that general brain hypertrophy might be termed a 'cephaloma'—not a 'tumour of the brain,' but, as it were, 'the whole brain a tumour'—and sought to distinguish between a physiological and a pathological 'cephaloma.' As was insisted on at the outset, physiological increase of brain bulk ought on theoretical grounds to be accompanied by increase of mental power and should not come within the range of the term 'megalencephaly' as here defined. We have seen, however, that big and heavy brains may not have the quality distinguishing their owners from the average man ; and also that, on the contrary, they may be associated with mental or nervous abnormality. The last group, for which I reserve the word, presents, as histopathological examinations show, a variety of structural anomalies. Thus it is not, perhaps, unwarranted to apply Virchow's expression, 'cephaloma,' to them, though it does not perhaps greatly appeal. But what seems certain is, that the cerebral hypertrophy is combined with dystrophy, in the sense that cytological defect accompanies the overgrowth. The latter, therefore, is doubly abnormal—there is too much of it, and its constituent elements have departed from normal standards. To determine the nature of this last-mentioned change—in my own case, at least—is far from easy. It does not correspond strictly to the 'chronic cell degeneration' of Nissl, nor, for that matter, is there histological evidence of toxic-infective or toxidegenerative processes. To denominate it an 'abiotrophy' does not help in any way. It can hardly signify mere immaturity, to be gradually overcome, for in various cases of megalencephaly the subjects of the condition have remained at a low intellectual level throughout their lives. At present, indeed, the interpretation of the histopathological

findings is obscure, and further examination of material must be undertaken ere any more definite pronouncement can be made.

Other features of interest—in particular, the association of a big, dry brain with epileptic fits—must also be left over for another occasion.

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