ARHINENCEPHALY

BY

R. M. STEWART

(RECEIVED 27TH APRIL, 1939)

No human brain has yet been described in which all the structures which are believed to be subservient to the sense of smell have been absent, and consequently the designation " arhinencephaly " is misleading in that it suggests complete absence of a functional unit. In the majority of recorded cases the maldevelopment present has been either a partial or a complete absence of the olfactory bulbs and parts of the hippocampal formation with its association and commissural systems.

In this limited sense the term " arhinencephaly " may perhaps be sanctioned on the grounds that it affords a concise and convenient title for a condition which otherwise would be difficult to define within the compass of a few words.

Report of case

H.E.B., a male idiot aged 17 years, was admitted to Leavesden Hospital on 10th August, 1926. Height : 49 in., Weight : 4 st. 7 lb. He was completely helpless, dirty in habits, unable to speak, feed himself, or to walk without assistance. He sucked his fingers and salivated constantly. A right internal strabismus was present. Physically he was in poor condition, with cyanosed hands and feet. Major epileptic fits occurred about once a month. In May 1929 he developed physical signs of pulmonary tuberculosis. A month later a swelling appeared over the left parietal eminence ; on 8th November 1 ounce of thick pus was evacuated from it. A diagnosis of Pott's puffy tumour was made. Death from hæmoptysis occurred on 14th November.

Post Mortem.—An autopsy was held 19 hours after death. The body was that of an emaciated young adult male of small stature. Both lower limbs showed contractures at the knee-joints. A pear-shaped parietal tumour firmly attached to the scalp was found to contain semi-solid caseous material. At its base a circular area of caries of the parietal bone was present with slight downward projection of the inner table, to which the thickened dura mater was firmly adherent. Scrapings from the carious area revealed large numbers of tubercle bacilli.

The pia mater was diffusely thickened, but showed no adhesions or evidence of inflammation at the base. Both lungs were in a state of extensive tuberculous consolidation with cavity formation. The liver was the seat of amyloid degeneration. The other organs showed no changes of importance.

Description of brain

Macroscopic Examination.—The brain is exceptionally large and heavy, its weight, including pia-arachnoid, being 1,506 gm. Right cerebral hemisphere,

645 gm. ; left cerebral hemisphere, 649.5 gm. Cerebellum and brain stem, 211.5 gm. The convolutions are large, of simple pattern, and fairly symmetrical. On the right hemisphere the pre- and post-central gyri pursue a normal course ; on the left side their conformation is most irregular.

All the cranial nerves, with the exception of the olfactory, are unusually well developed ; the fossa interpeduncularis is very deep, the orbital surfaces

Fig. 1.—Base of brain, showing complete absence of olfactory bulbs and tracts. Note the presence on the orbital surfaces of the frontal lobes of short irregular sulci ; there are no true gyri recti.

of the frontal lobes are large, and there is complete absence of the bulbus and tractus olfactorius on both sides (Fig. 1). The sulci present on this surface are short and irregular in form ; on the right side a sulcus runs forwards and outwards for about 2 cm. and terminates by dividing into two short and obliquely placed branches : on the left side a shorter sulcus ends by dividing into two small branches more transversely placed than on the opposite side. It is doubtful whether the short and broad gyri bounded by these sulci can be

looked on as gyri recti. There is no olfactory trigone, no area parolfactoria, no anterior perforated substance, and no diagonal band of Broca.

On the mesial surface of each hemisphere the most striking feature is the diminutive size of the divided corpus callosum, which has a length of only 6 cm. (Fig. 2). Although underdeveloped as a whole, it is particularly its posterior half which is thin and attenuated, the splenium being no thicker than the middle third of the body; ending immediately above the pineal body, it completely fails to cover the pulvinar; the latter forms a conspicuous prominence on the mesial aspect of the hemisphere. The smallness of the corpus callosum gives the impression of an unusual expanse of parietal and occipital cortex behind it. On this aspect the gyrus cinguli is seen as a well-developed

Fig. 2.—Mesial aspect of cerebral hemisphere. The corpus callosum is rudimentary and the absence of the splenium leaves the pulvinar, pul., exposed; on the infero-mesial aspect a well-developed hippocampal gyrus, h., and uncus, u., are conspicuous. Other structures depicted are the gyrus subcallosus, g.s., the anterior pillar of the fornix, f., the anterior commissure, a., the corpus mammillare, c.m.

convolution, but unusually free from secondary sulci. The gyrus hippocampi is likewise conspicuous and possesses a well-marked uncus, bent sharply in the usual manner. There is, however, no band of Giacomini and the gyrus intralimbicus, gyrus semilunaris, and gyrus ambiens cannot be defined.

The fimbria, the body of the fornix, its anterior pillars, and the septum pellucidum are readily recognized, and are of normal appearance. The gyrus dentatus is likewise present, but it conveys the impression of underdevelopment, being decidedly less prominent than in the normal brain. Other areas connected with the olfactory system which cannot be identified are the gyrus fasciolaris and the gyri Andreae Retzii. While the massa intermedia is of normal dimensions, the anterior commissure is perhaps thinner than normal, though

in a vertical coronal section through the hemispheres in this plane there is no difficulty in following its temporal fibres as they pass outwards horizontally beneath the lenticular nucleus. In the same coronal section it is possible to identify the nucleus amygdalæ.

Careful scrutiny of the dorsal surface of the corpus callosum fails to reveal any evidence of the indusium griseum and striæ medullares longitudinales.

Other tracts forming part of the olfactory projection system which can be recognized are the tænia thalami and the tænia semicircularis, the latter accompanied by the striate vein.

TABLE SHOWING THE DEFECTS PRESENT IN THE RHINENCEPHALON.

Olfactory bulbs	Absent.	Gyrus ambiens	Not identified.
Olfactory tracts	Absent.	Gyrus dentatus	Reduced in size.
Olfactory trigone	Absent.	Band of Giacomini	Absent.
Area parolfactoria	Absent.	Gyrus supracallosus	Attenuated.
Anterior perforated substance	Absent.	Gyrus fasciolaris	Absent.
Gyrus subcallosus	Normal.	*Gyri Andreae Retzii	Absent.
Diagonal band of Broca	Absent.	Fimbria	Normal.
Gyrus cinguli	Normal.	Body of fornix	Normal.
Isthmus hippocampi	Normal.	Anterior pillars of fornix	Normal.
Gyrus hippocampi	Normal.	Septum pellucidum	Normal.
Gyrus uncinatus	Normal.	Anterior commissure :	
Gyrus intralimbicus	Not identified.	1. Olfactory fibres	? Absent.
Gyrus semilunaris	Not identified.	2. Temporal fibres	Normal.

Microscopic Examination.—An examination of Nissl preparations made from the superior frontal gyrus, the pre- and post-central gyri shows changes which are characteristic of profound idiocy. Many of the pyramidal nerve cells show poorly developed cell bodies with irregular alignment and an actual numerical deficiency, especially in layers 3 and 4. Various stages of chronic chromatolysis can be found. The cortical vessels show no change, but there is a considerable degree of marginal gliosis.

Corpus callosum : coronal sections of the body of the corpus callosum stained by the method of Loyez show a thin stratum of fibres running in a longitudinal direction immediately above the dense layer of transverse commissural fibres. This stratum, though not uniform in thickness, shows no aggregation into strands. In other words, the medial and lateral longitudinal striæ are represented only by a thin layer of fibres. Normally, the nervi Lancisii are accompanied by small oval ganglion cells which constitute the induseum griseum, but none of these can be found.

Frontal section through the area dentata and gyrus hippocampus immediately caudad to the uncus (Fig. 3). The Hippocampal gyrus. Its cortex is well developed both in the subiculum and præsubiculum : its thickness, 2·3 mm., is within the limits of the normal and its peculiar cellular lamination is well defined. Thus from without inwards, it is possible to recognize : (1) a broad plexiform layer ; (2) nests or islets of large and small stellate cells constituting the so-called glomeruli ; (3) a thick layer of regular and slender

* Frequently absent in normal brains.

pyramidal cells ; (4) a thin compact layer of densely arranged large pyramidal cells ; (5) a broad layer of spindle-shaped cells. The tangential fibres in the plexiform layer of the subiculum and præsubiculum stain uniformly with myelin sheath stains and are not noticeably fewer than normal.

Fig. 3.—Microphotograph of the hippocampal gyrus, h.g., and the dentate gyrus (fascia dentata) f.d. Both areas show a normal cellular lamination, but there is a general reduction in the size of the dentate gyrus. p. : pyramidal cells of fascia dentata. g. : stratum granulosum. a. : alveus. Cresyl violet stain : X7.

Fascia Dentata : even without comparison with the normal control it is obvious that the dentate gyrus is considerably reduced in volume, and this reduction affects all its strata except perhaps the layer of granular cells (stratum granulosum) in which the normal arrangement of densely packed small cells appears to be preserved (Fig. 4). Encircled by the stratum granulosum, the medium sized pyramids, distributed in the normal irregular radiating manner, show no numerical deficiency, though owing to the small volume of the entire fascia dentata their total number must be much less than in the normal brain. The layer of large pyramidal cells lying internal to the medullary centre of the hippocampal gyrus is, however, markedly narrowed, though no cell gaps can be seen ; the stratum radiatum formed by their processes is poorly defined. The third and fourth layers, stratum granulosum and stratum lacunosum respectively, are likewise difficult to distinguish. The superficial layers of

nerve fibres are slightly thinner than normal. The nerve fibres which constitute the alveus stain rather poorly by Loyez' method and appear finer in comparison with those in normal sections.

Fig. 4.—Outline drawings of unstained blocks of the hippocampal and dentate gyri : (a) from normal control : (b) from arhinencephalic brain. The dentate gyrus is considerably better, developed in the control block (a). h.g. : hippocampal gyrus. f.d. : dentate gyrus. $\times 2\frac{1}{2}$.

There is no noticeable change in the fimbria.

Glia : There is no evidence of fibrillary gliosis in either the hippocampal convolutions or the fascia dentata.

Discussion

Following Schwalbe and Josephy (1913), arhinencephalic brains may conveniently be divided into two groups :

1. Cyclopic brains, complete or partial, in which an arrest of growth has taken place at the cephalic end of the embryonic plate, with fusion of the olfactory bulbs and optic vesicles.
2. Brains characterized by absence of the olfactory bulbs and tracts without gross malformation of the cerebral hemispheres.

Cyclopia : Kunderat (1882) has dealt exhaustively with this type in his monograph "Arhinencephaly," and subsequent contributions have been made by Schwalbe and Josephy, Ranke (1913), Klopstick (1921), Van Duyse (1921), Rothschild (1924, 1927), Gamper (1926), Politzer (1930), and Henze (1934).

The salient features of the cyclopic brain include incomplete division of the end brain, hydrocephalus, defects of the eyes and optic tracts, and absence of the olfactory tracts.

Closely related to the typical cyclopic brains are those in which, although there is no fused or median eye, the end brain remains incompletely divided. To this category belong the arhinencephalic brains described by Goldstein and Riese (1925), Kummer (1923), de Jong (1927) and Kuhlenback and Globus (1936).

Absence of the olfactory bulbs and tracts without gross malformation of the cerebral hemispheres : arhinencephalic brains of this type are unquestionably rarer than those in the former group, and probably not more than fifteen examples have been placed on record. Many of the accounts are fragmentary and in only a few have adequate histological investigations been carried out. The latter are referred to below.

In most of the lower vertebrates smell is the dominant sense, and in consequence the entire cerebral hemisphere is concerned with the perception of smell ; in other words, in macrosmatic vertebrates the hemisphere is primarily an olfactory receptive nucleus. On the other hand, in the most highly organized types of brain—those of man and the other primates—to whom the sense of smell is relatively unimportant, the portion of the brain believed to be concerned with olfaction is relegated to a comparatively small area. None the less, even in the human brain the rhinencephalon is by no means inconspicuous. The limbic lobe which constitutes the central or cortical part of the rhinencephalon occupies an area of considerable extent on the mesial aspect and from the point of view of size the hippocampal gyrus—one of its constituent parts—is quite as impressive as, say, the motor cortex in the neopallium. But whether in man olfactory impressions are the only ones to be discharged into the whole limbic lobe is very debatable. Indeed, taste and smell are so closely interrelated in the processes of nutrition that it may well be that research will one day show that this part of the rhinencephalon is concerned just as much with gustatory as with olfactory reactions. A survey of the anatomical findings in the literature devoted to arhinencephaly indicates that they afford little uniformity on which to base a confident pronouncement on the cortical representation of smell. It is perhaps hardly necessary to state that conclusions drawn from naked-eye inspection of the brain unsupported by histological study at the most possess a limited value ; unfortunately the majority of the recorded cases of arhinencephaly fall into this category. Prominent among the notable exceptions is the remarkable case described by de Jong (1927), in which although no trace of the olfactory bulbs and tracts could be found, not only were the cornu ammonis and fascia dentata present but on histological investigation these areas were found to be actually better developed than in a normal brain of the same post-natal age.

On the other hand, a definite reduction in the size of the cornu ammonis has been reported on more than one occasion. In the brain described by Tanaka (1920) there was evidence of sclerosis in the cornu ammonis, accompanied by atrophy of the hippocampal gyrus on both sides. Tanaka's patient was, however, an epileptic and since sclerosis in this territory is not infrequently determined by the functional disturbance of the circulation which accompanies convulsions, it is quite possible that the changes in his case were related, not to a primary arrest of development of the olfactory bulbs, but to the long-standing epilepsy.

In the first of Uyematsu's (1921) two cases of unilateral absence of the olfactory bulb some degree of sclerosis of the homolateral cornu ammonis was also present, the corresponding convolution on the other side being normal.

But in this case, too, there was a history of convulsions ; and as in cases of even long-standing epilepsy sclerosis of Ammon's horn may remain strictly unilateral, it cannot be claimed with any degree of certainty that absence of the olfactory bulb conditioned the sclerosis. As in Tanaka's case, this may have been epileptic in origin.

In his second case there was also a history of seizures. Histological examination revealed slight degeneration of the cornu ammonis, equal in intensity on the two sides. The author concludes that greater importance is to be attached in both cases to the more advanced regressive changes in the pyriform lobe, which he regards as an end result of the loss of the peripheral olfactory apparatus.

In the brain of the epileptic idiot reported in this communication there was also a slight reduction in the size of the cornu ammonis on both sides, but without any evidence of neuroglial sclerosis, the changes being, in fact, entirely quantitative ; consequently they may legitimately be held to be related to the absence of the olfactory bulbs and tracts.

An extremely interesting feature in this case was the persistence of a number of foramina in the cribriform plate of the ethmoid notwithstanding complete absence of the olfactory bulbs. Such a finding, which was also present in the cases described by C. Bernard (1856), Duval (1884), and Mirsalis (1929), clearly indicates that at one stage of development olfactory nerves must have been present. Their development in the sixth week of foetal life precedes the formation of the cerebral meninges and cribriform plates (Keith, 1933), and consequently the foramina may owe their formation to the penetration of nerve fibres. From embryological studies it is apparent that the development of this part of the brain is peculiar in that the olfactory sense epithelium and olfactory nerves develop separately from the central part of the rhinencephalon.

In the development of the forebrain Ariens Kappers (1929) attributes a preponderant role to the paired olfactory placodes. When the placodes fail to exert that influence arhinencephaly is established and pairing of the cerebral vesicles does not take place. As proof of this, he cites the experiments of Burr (1924) on amphibia. On transplantation of one olfactory placode to another part of the head he was able to observe the hemispherical wall growing out to the transplanted placode. But as Kuhlenbeck and Globus (1936) point out, though Kapper's theory affords an explanation for the lack of development of the olfactory bulbs and tracts, it does not afford a satisfactory explanation of why arhinencephaly should sometimes be associated with normally developed hemispheres and sometimes with a highly defective end brain.

From an analysis of the observations cited in this paper, it is clear that complete absence of the olfactory bulbs and tracts, which must of necessity deprive the pallial rhinencephalon of olfactory impulses, in no way excludes the possibility of normal development of certain of its complex divisions. Thus, among the possibilities, are : (a) no naked eye abnormality, as in Issajew's (1932) case ; (b) an actual overdevelopment of cortical olfactory areas, such as de Jong has described ; (c) degenerative changes in the hippocampal

convolution, with or without sclerosis of the cornu ammonis, as in the reports by Tanaka and Uyematsu ; (d) changes almost entirely confined to the dentate gyrus, as in the cases described by Oldberg (1934) and the writer.

Such findings permit the conclusion, previously arrived at by Ranke (1913) and quoted by Kuhlenbeck and Globus, that in arhinencephaly cortical differentiation is to a high degree independent of the differentiation of corresponding peripheral centres. With this consideration in mind, it follows that our knowledge of the functional significance of the rhinencephalon is not likely to be advanced by the study of developmental defects in the human brain. On the other hand, if it be permissible to accept the homologies of comparative neurology, considerable importance must be attached to defects in the fascia dentata, for in anosmatic animals, such as the dolphin, this structure is the only central part of the rhinencephalon which is wholly wanting (Hill, 1893). But, as Herrick (1933) remarks, even in those animals in which the rhinencephalon is highly developed, olfactory sensation is never an efficient localizing sense. Odours may be discriminated, but they cannot be accurately localized without the use of other senses, and accordingly none of the olfactory areas can be said to be truly olfactory centres in a sense comparable to centres for vision or hearing ; their function is associative rather than initiative or interpretative. If this be true of macrosomatic mammals it must obviously apply with even greater force to man, who is emancipated from the dominating influence of olfactory impressions.

Summary

The brain of an epileptic idiot is described in which there was complete absence of the olfactory bulbs and tracts. No abnormality could be found in the hippocampal convolutions but on both sides the fascia dentata was considerably reduced in size. Histological examination confirmed these observations.

REFERENCES

- Burr, H. S. (1924). *J. comp. Neurol.*, **37**, 455.
 de Jong (1927). *Z. ges. Neurol. Psychiat.*, **108**, 734.
 Duval, M. (1884). *Bull. Soc. Anthropol., Paris*, **7**, 829.
 Gamper, E. (1926). *Z. ges. Neurol. Psychiat.*, **28**, 969.
 Goldstein, K., and Riese, W. (1925). *J. Psychol. Neurol.*, **32**, 291.
 Henze, K. (1934). *Beitr. prakt. theoret. Hals-, Nasen-, Ohrenh.*, **31**, 241.
 Herrick, C. J. (1933). *Proc. nat. Acad. Sci. Wash.*, **19**, 7.
 Hill, A. (1893). *Philos. Trans.*, **184**, 389.
 Issajew, P. O. (1932). *Anat. Anz.*, **74**, 398.
 Kappers, C. U. A. (1929). *Evolution of the Nervous System in Invertebrates, Vertebrates and Man*.
 Keith, Arthur (1933). *Human Embryology and Morphology*, 5th Ed., p. 183.
 Klopstock, A. (1921). *Mschr. Geburtsch. Gynäk.*, **56**, 59.
 Kuhlenbeck, H. and Globus, J. H. (1936). *Arch. Neurol. Psychiat., Chicago*, **36**, 58.
 Kummer, A. (1923). *Inaug. Dissert., Amsterdam*.
 Kundrat, H. (1882). *Wien med. Bl.*, **51**, 1395.

- Mirsalis, T. (1929). *Anat. Anz.*, **67**, 353.
Oldberg, S. (1934). *Upsala Läkareför Förh.*, **39**, 395.
Poltzer, G. (1930). *Z. ges. Anat.*, **93**, 188.
Ranke, O. (1913). *Neurol. Zbl.*, **32**, 880.
Rothschild, P. (1930). *Beitr. path. Anat.*, **73**, 65.
Schwalbe, E. and Josephy, H. (1913). In Schwalbe, *Morphologie der Missbildungen des Menschen und der Tiere*, part 3, sec. 2.
Tanaka, F. (1920). *Arch. Neurol. Psychiat., Chicago*, **4**, 151.
Uyematsu, S. (1921). *Ibid.*, **6**, 146.
Van Duyse, G. M. (1921). *Bull Acad. Méd. Belg.*, **5**, 497.