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THE THIRTY-FOURTH MAUDSLEY LECTURE: EMERGENT PATTERNS OF THE PATHOLOGY OF MENTAL DISEASE*

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I SHOULD like to express my deep gratitude to you, Mr. President, to the immediate Past President, Dr. L. C. Cook and to the Association for the great honour that has been bestowed upon me by your invitation to deliver a lecture in this august series. It is a custom that the lecturer should pay homage to Henry Maudsley to whose memory these lectures are dedicated: may I reserve my homage until we come to the active part Maudsley played in the course of events with which this lecture will be concerned.

For some time past I have been interested in the historical aspects of neuropathology, and I have chosen the subject for this lecture, because I thought that —at a time of breath-taking developments in all the sciences—a brief pause and a retrospective glance at the past may well help to resolve some of our present perplexities. Needless to say, what competence I have is in the somatic aspects of pathology, and it is with these, and especially cerebral pathology, that I shall mainly deal.

I propose to go back no further than the re-awakening of the scientific spirit during the Renaissance. What Antiquity† had to say of cerebral function was swept aside by the pneuma theory, the essence of which was that the substance of the brain is a mere capsule for the ventricles in which the incorporeal "animal spirits" reside. This concept has been wrongly attributed to Galen; according to Walter Pagel (1958) it had its origin in Christian-Patristic doctrines of the 4th century A.D. It suited scholastic thought well and was only demolished in 1543 by Vesalius in his *De Fabrica*. Vesalius found water in the ventricles and thus became the discoverer of the cerebrospinal

* Delivered (in slightly abbreviated form) before the Royal Medico-Psychological Association on 12 November, 1959.

† The ancient concepts of the brain and its relation to the mind have been recently described by Woollam (1958).

fluid. He transferred the activity of the animal spirits to the brain itself, although he did not publish detailed views on their function in the brain substance (Foster, 1901; Singer, 1952).

Figure 1 gives a typical illustration of the "pneuma" concept: fantasy and imagination are located in the anterior ventricles; they form the "sensorium commune", a term introduced by Aristotle to designate a central place of activity of the soul upon which all senses converge and from which perception, movement and the higher mental faculties radiate. Intelligence resides in the middle, and memory in the posterior ventricles. The vermis (i.e. the choroid plexus), operating between anterior and middle chambers, was thought, by alternate contraction and relaxation, to control the activities of the spirits in the different chambers. Much of this crude concept was due to ratiocination or, as Vesalius put it, "figments of men who had never studied the handiwork of God".* The localization of the "sensorium commune" may have been suggested by the strikingly preponderant growth of the frontal region in the human skull and brain. It is of interest that in our time Freeman and Watts (1942, 1950) have once again associated the frontal lobes with imagination and fantasy.

Descartes (1662), a hundred years after Vesalius, is the next important figure, although he was a philosopher and not a practising natural scientist. Hence all his assumptions were deductive, and, as Walter Riese (1958) has pointed out, the "modern reader must begin by renouncing his observational knowledge". As is well known, Descartes regarded the animal body as a machine to which in man alone was a rational immortal soul added, which took up residence in the pineal gland, chosen for its central position at the entrance of the ventricles and because it was only loosely attached to the rest of the brain. This gland and the ventricles were the reservoirs of the (now corporeal) animal spirits which are compared to air or a subtle fluid. In Descartes' system, the brain itself had but a shadowy existence, serving only as the centre for the hollow nerve tubes which connected with the periphery and opened into the ventricles through theoretically assumed orifices.

With Thomas Willis, and the publication of *Cerebri Anatome* in 1664 and *De Anima Brutorum* in 1672, we enter an entirely new epoch. This is not to deny that he was a child of his time who still largely adhered to the teaching of Hippocrates and his four humours. This admixed with fashionable iatrochemical terms (which, incidentally, he introduced into this country) makes curious reading, particularly in the chapters dealing with materia medica and with mania, melancholia and stupidity, where he describes the degeneration of the animal spirits by adjectives such as burning, obscure, thick, dark, dry and watery, acetous, corrosive, and sulphureous like the Stygian waters. Likewise he adopted the crude mechanical terms of iatrophysics; for example, when speaking of the invisible flame of the blood, and the explosion of animal spirits, of the inner chamber of the soul as fitted with dioptric mirrors, of the corpora striata as an objective glass and of the corpus callosum as a whitened wall.

He also adopted Galen's animal spirits, but, for him, as for Descartes, they had become corporeal: Willis describes them as "subtile bodies", as the "beaming forth of divers rays of light" and makes them "inspire and fill full the medullary trunks . . . like the chest of a musical organ which receives the wind to be blown into all the pipes". No doubt, again iatrophysics; but one gains the impression that, had he known of electricity, he would have

* Quotation from Foster (1901).

accepted the electric current as fulfilling the functions of the animal spirits.

Like Descartes to whom he more than once pays ardent tribute, he distinguishes an immortal rational soul, created by God only for man, from the corporeal (animal) soul, but both have their close association with different parts of the brain. Only emotions are excluded: with Aristotle and some of Willis's more recent predecessors he still attributed these to the heart.*

With all this we are less concerned than with Willis's discoveries and views on the anatomy and function of the brain, and here again our concern is less with the arterial circle to which Willis's name has been attached† or with his description of the cranial nerves than with cerebral anatomy‡ in its relation to mental and other important function.

Table I summarizes Willis's main observations and views relevant to our

TABLE I

Thomas Willis (1664)

"Animal spirits" secreted from the blood in cerebral and cerebellar cortex.

Caudate nucleus (first described by him) the seat of "sensus communis" and responsible for voluntary movement and perception.

Imagination in *corpus callosum.*

Memory in *cerebral cortex*, in which the "animal spirits" rest after activity.

Animal instinct in *middle of brain.*

Involuntary action in *cerebellum.*

theme. We note that the animal spirits are secreted from the blood within the cerebral and cerebellar cortex which are also their resting places. The process of creation is conceived of as a chemical one, not unlike that of alcohol fermentation, a view which Willis shared with Sylvius (1679), also like himself a leading iatrochemist.

Imagination is considered to be a function of the corpus callosum (and cerebral white matter) while the cerebral cortex, as resting place, is related to memory (and hence intelligence).

The corpus striatum, or as he calls it the "streaked or chamfered bodies", is concerned with sensory perception and motion; it is also his "sensorium commune". The striate body, which he first described, was for him the foremost end of the medulla. "These bodies placed between the brain . . . and its appendix . . . receive(s) the strokes of all sensible things" and are the origin also of "the first instincts of spontaneous local motions". This sounds like an anticipation of reflex activity and has been interpreted as such by Foster (1901) and Sherrington (1946). From the striatum the animal spirits or (as we would call

* Vinchon and Vié (1928) take this as meaning the autonomic system, controlled by the cerebellum which innervates heart and other viscera. If this should, in fact, have been Willis's meaning, it would be an almost visionary anticipation of the modern view of the physiology of emotion and emotional expression.

† Grünthal (1957), as others before him, has pointed out that the accessory nerve was described 100 years before Willis by Eustachio (but the illustrations were published only in 1714 by Lancisi); and that the arterial circle was anticipated 6 years before *Cerebri Anatome* by Wepfer (1658) who is best known for his post-mortem findings in patients dying from apoplexy.

‡ Foster is inclined to ascribe the important discoveries published in *Cerebri Anatome* to Willis's collaborator Richard Lower, basing this opinion on the published report of Willis's contemporary Anthony Wood (1817). Wood's opinion seems to have been biased, however. Willis paid, in the preface of *Cerebri Anatome*, a very generous tribute to Lower, and their relations seem to have been harmonious to the end (Symonds, 1955).

them now) the motor impulses, travel down to the medulla and the spinal cord from where they are carried by the nerves to the periphery.

Only *spontaneous* motor activity is associated with the striatum, involuntary motor action is allocated to the cerebellum, a distinction which, as Neuburger (1897) has pointed out, has ever since remained fundamental. Willis chose the cerebellum because he (wrongly) believed that it gave origin to the vagal and sympathetic nerves, because of its unvarying structure in all animal and human brains (in contrast to the cerebral cortex) and lastly, because he observed that in animal experiments as well as in human post-mortems lesions in posterior regions of the brain were almost invariably fatal, with disturbance of heart action and respiration. The cerebellum, as control centre of visceral activity, was later replaced by the medulla, following the experimental and pathological observations of Pourfour du Petit (1710), Lorry (1760) and Morgagni (1761). It was Legallois (1812) who finally established the existence of medullary centres as regulators of cardiac and respiratory function. Notions of cerebellar function differed widely until Flourens (1824) finally recognized it as a centre for the co-ordination of movements.

Willis's modern critics (for example, Foster (1901), Zilboorg (1941) and Mettler (1947) never tire of emphasizing the role of speculation in all these assumptions. Speculation certainly played a part; some of it was inspired, for example the localizing of animal instinct in the middle of the brain (i.e. not far from the midbrain and diencephalic centres which we today continue to relate to the mechanisms of instinctual drives). However, one cannot ignore the considerable, although primitive, observational basis for many of his hypotheses. Those that led him to the cerebellar autonomic theory have already been mentioned. In his chapter on Palsy he described a post-mortem in which the anterior cavity of the brain was filled with blood, which pressed upon one of the "streaked Bodies", thus causing motor disturbances, upon the corpus callosum with the consequence of "Hebetude and Stupefaction" and upon the optic thalamus, causing loss of eyesight. In chronic paralysis he found the striatum discoloured "like filth and dirt" and their striae obliterated.

The importance of the cerebral cortex for memory (and hence intelligence) he deduced from his comparative observations that its "folds and rollings about are far more and greater in man than in any other living creature, to wit, for the various and manifold actings of the Superior Faculties . . . Those gyrations or turnings about in four-footed beasts are fewer . . . In the lesser four-footed beasts, also in fowls and fishes, the superficies of the brain being plain and even, wants all cranelings and turnings about". Nevertheless the cerebral cortex is subordinated to the corpus callosum and cerebral white matter, for he had observed that "the Animals which excel in Memory, Imagination and Appetite . . . are furnished with a more ample Marrow". In lower animals the "cortex of the brain (may be) greater, but the medullary part very small". Comparative observation also compelled him to discount the importance of the pineal gland for the higher mental activities.

In his classification of nervous and mental disease, Willis followed the tradition of his times: chapter headings such as Mania, Melancholia, Stupidity, Palsy, Convulsions, Incubus, Hysteria, etc., are found also in the writings of Felix Plater (1602–3) who is regarded as the father of classification of mental disease, and of Montalto (1614), Sennert (1629–52) and others. Willis, however, added the first description of myasthenia gravis and, more important to our present inquiry, the first hint of dementia paralytica. In an often quoted paragraph he described cases "visited with dullness of mind and forgetfulness

and then with stupidity and foolishness, they would afterwards fall into paralysis . . . either general paralysis or hemiplegia or certain partial weakness of the limbs would ensue". Stupidity, which obviously comprehended both oligophrenia and dementia, was caused either by anatomical lesions of the cerebral white matter or by disintegration of the animal spirits. In this distinction, one may perhaps see a very early anticipation of the division between organic and functional psychoses as well as the difference between Willis's functional pathological standpoint and the "solidism" of the later morbid anatomists.

Epileptic convulsions he considered to be explosions of the animal spirits in the region of the corpus striatum, a notion which mutatis mutandis we meet again 200 years later in Hughlings Jackson's theory of explosive discharge of nerve cells. Hysteria and Incubus were partially assigned to the cerebellum with its control over involuntary action.

Some of Willis's basic concepts left a lasting impression: with his demarcation between voluntary and involuntary movement and their separate control centres in the brain, he has become one of the earliest architects of the autonomic system as we know it today (Neuburger, 1897; Dow, 1940). His association of control of voluntary motion with the corpus striatum was maintained—with one possible exception—until the time of Hughlings Jackson (who, in his earlier writings still accepted it) and the experimental discovery of the motor cortex by Fritsch and Hitzig (1870). It was accepted by Theophile Bonet (1679, 1700) in his book on morbid anatomy fittingly called *Sepulchretum*. In the preface to this book Willis heads the list of those to whom Bonet makes acknowledgments. Morgagni, writing 80 years later (1761), frequently refers to Willis's writings and to the *Sepulchretum*; he too accepts Willis's striatal thesis with slight modifications.* So did Caldani, in 1786, on the strength of experimental investigations. In Carpenter's 1853 edition of the *Principles of Physiology* (lately much quoted by Walshe (1957, 1958)), the striate body still controls backward movement, while the cerebellum is responsible for forward motion. Even after the discovery of Fritsch and Hitzig and their confirmation by Ferrier (1874), Meynert (1884) adhered to a subcortical highest motor centre, since he maintained the cortex was concerned only with psychic function. The exception which I mentioned concerns the work of the French surgeons and experimentalists of the 18th century who, as we shall presently see, despite their still primitive techniques, almost anticipated by 150 years the discovery of the motor cortex by Fritsch and Hitzig.

And, thirdly, Thomas Willis was among the very first to introduce the *cerebral cortex* as a substrate of important psychical function. It is strange how slowly the configuration and the functional significance of the cerebral cortex was grasped (Neuburger, 1897; Grünthal, 1957), although its intricate pattern must be almost self-evident on opening the skull. Leonardo da Vinci, a most acute observer of anatomical detail, left the convolutions a blank (Fig. 2), whereas he paid careful attention to making casts of the ventricles. Vesalius re-affirmed Erasistratus' almost 2,000 years older description of the cortical pattern as resembling coils of small intestine or cloud formation (Fig. 3), and this impression is gathered even more from some of the drawings (Fig. 4) in Descartes' *De Homine* (1662). In contrast, in *Cerebri Anatome* (Fig. 5) the drawings of the base of the brain are distinctly more realistic. They were executed by Christopher Wren, but the example of Leonardo da Vinci shows

* Morgagni also mentioned hardness of the cerebral white matter and abnormalities of the pineal gland as the chief causes of insanity.

that this advance cannot be exclusively attributed to the qualities of the artist. No further progress was made until Soemmerring (1778), a contemporary of Kant in Königsberg, Rolando (1809) and Gall and Spurzheim (1810) produced descriptions and drawings which approximate to modern macroscopic impressions of the convolutional pattern (Fig. 6). Later they were brought to even greater perfection by Leuret and Gratiolet (1839–1857) and by Retzius (1896).* Increasing awareness of the functional importance of the cerebral cortex went together with improved anatomical accuracy. Gall and Spurzheim made it the seat of a plurality of mental faculties with differential localization: their teaching of Phrenology has fallen into disrepute, but not their association of speech with the frontal lobe. This—indirectly—influenced Broca (1861) and, thus Gall becomes the true initiator of cortical localization (Neuburger, 1897; Grünthal and Strauss, 1949; Jefferson, 1953; Ackerknecht, 1958).

None of the immediate successors of Willis revealed his breadth of vision, particularly in respect of cortical function. Table II shows that there were even

TABLE II

"*Sensorium Commune*"

Dura mater: Pacchioni (1701) and Baglivi (1704). Rejected by Schlichting (1750) and Lorry (1760).

Cerebro-spinal Fluid: Soemmerring (1796).

Corpus callosum or cerebral white matter: Vieussens (1684); Boerhaave (1708); Lancisi (1739); La Peyronie (1741); Hartley (1749); Albrecht von Haller (1757–66); Burdach (1819–26).

Basal ganglia: Corpus striatum (Willis, 1664). Thalamus and "sensory ganglia", "automatic apparatus" (Carpenter, 1853).

Medulla: Andrew Harper (1789); Chiarugi (1793); Rolando (1809); Thomas Laycock (1860) and others.

near-relapses into scholastic views. With Pacchioni (1701) and Baglivi (1704) originated the hypothesis that the dura mater was the most important part of the body, the motor of the movement seen in the exposed brain. It held sway until the role of respiration in this apparent movement was demonstrated (Schlichting, 1750; Lorry, 1760). Soemmerring (1796) designated the cerebrospinal fluid as the "organ of the soul". The discrepancy between Soemmerring, the careful neuro-anatomist, and the writer of the "organ of the soul" is explained by the current belief at that time that the cerebral cortex was compounded of glands, a belief which goes back to Malpighi (1669), the discoverer of capillaries and an early, no less successful, pioneer microscopist of the nervous system.

Among the many who attached significance to the cerebral white matter we notice (in Table II) Boerhaave (1708) and La Peyronie (1741) one of the French surgeons for whom the corpus callosum was "le siège de l'âme". Albrecht von Haller (1757–1766) also found the cerebral cortex (and its membranes) unresponsive and, therefore, functionally unimportant. Responses to irritation were only obtained by thrusting a needle deep into the white matter. In general, however, he was against any appreciable focal localization in the brain, and many of Willis's (and others') earlier achievements were lost through his and his disciples' negative attitude.

* For further detail and illustrations *vide* Grünthal (1957).

The "sensorum commune" of Carpenter (1853) was located in what he called the "automatic apparatus" which he based on the thalamus and "sensory ganglia" such as the olfactory bulbs, corpora quadrigemina, auditory and gustatory ganglia in the medulla. The cerebral cortex, however, provided "unconscious cerebration". Consciousness and memory were functions of the automatic apparatus.

Some writers even went back to the medulla as the "common sensory". Among these, as late as 1860, Thomas Laycock regarded cerebral and cerebellar hemispheres merely as extensive peripheries; and even Rolando (1809) maintained his medullary sensorium commune despite his experimental discovery of the deleterious effect of destruction of the cerebral hemispheres upon higher mental function. Perhaps the most drastic supporter of the medulla was Andrew Harper (1789), who persisted on how effectually the sensorium commune or "prime movement is secured by the cortical and cineritious part of the brain" almost disparagingly dismissing the "intermediate meanders, circumvolutions and reticulations which constitute the glandular part".* Harper was one of the writers of treatises on psychiatry which were characteristic of the 18th century, particularly its second half, and which included in this country the monographs published by Battie (1758), Perfect (1787), Cullen (1781), John Brown (1780), Crichton (1798) and Cox (1806). Although most of these writers maintained—in varying degree—that mental disturbances are largely caused by lesions or disturbances of the brain and its membranes, they added few observational data. Often the pathology was confined to enumeration of "causes" such as bony abnormalities, insolation, inflammation and—above all—congestion of meningeal and cerebral blood vessels which was widely held to be an important pathogenic factor in insanity. A vascular factor was suggested by enlargement and ossification of cerebral arteries (clearly alluding to arteriosclerosis) which had already been mentioned, among others, by Willis, and was also stressed by Harper, Crichton and Andrew Marshal (1815).

No systematic investigations of the pathology of insanity appeared much before the end of the 18th and the beginning of the 19th century: then came contributions by Greding (1781, 1790), a German psychiatrist, whose work was translated by Crichton in abbreviated form; Haslam (1798); Crowther (1811), and Andrew Marshal (1815). Although the detail of their macroscopic pathological observations is now only of historical interest,† it

* That Harper did not deny the existence of a pathology of these "glandular parts" becomes clear from the following passage: "From all these discussions, it appears to me, at least, abundantly evident that no general, partial, particular affection, praeternatural appearance or morbid change, cognizable to the senses, within the brain, nor any stimulant, irritative or debilitating cause in the circulatory system, can possibly be capable of inducing or predisposing to insanity . . . it has been closely demonstrated that Insanity is a disease of the mind independent of any corporal exciting cause" and he concludes (p. 29) ". . . the proximate cause and specific existence of Insanity to be a positive, immediate discord, in the intrinsic motions and operations of the mental faculty . . . its exact seat to be the prime movement".

† Greding reported macroscopic findings in 216 cases of insanity, including mania, melancholia, idiocy and epilepsy. He paid attention to size and thickness of skull, to venous sinuses, meninges, ventricles, cerebral cortex and white matter, cerebellum, pituitary, pineal gland, etc. The one or other abnormality was present in every case, but the only consistent change appears to have been a tendency to softness in the cerebrum, and to hardness in the pituitary. The findings in the visceral organs were not significant. Few insane people died suddenly or in convulsions, and there was no close relation between insanity and gout, rheumatism or other painful disorder.

Somewhat similar post-mortem investigations (though on smaller material) were reported by Haslam and by Marshal, the latter attributing the pathological changes in the nervous system to alterations of blood supply. Crowther's opinion on the causal significance of the post-mortem findings is, on the whole, critical; his argument is somewhat reminiscent of that of Harper.

is important to record that these investigators (with the exception of Crowther) were convinced that insanity was always associated with anatomical changes in the brain. The strongest expression of this belief has been given by Haslam who asserted "that madness has always been connected with disease of the brain and its membranes", and is revealed post-mortem in every case of an unselected variety of mental patients, and without exception. It is also interesting to note that—with Greding, Haslam and Marshal—somatic pathology had become morbid anatomy. This was in keeping with the transition from humoral pathology to "solidism" which took place during the closing period of the 18th century, mainly as a consequence of Morgagni's assault upon humoral pathology.

Haslam* is credited with the first clinical description of dementia paralytica —his case 15. However, from the point of view of pathology, this case differed from the others only in greater quantity of cerebrospinal fluid. While, in the words of Tuke (1882) Haslam "may seem to have stumbled upon G.P.I.", it is the great merit of Bayle (1826) and Calmeil (1826), both disciples of Esquirol, that they laid the basis for dementia paralytica as a clinico-pathological entity. That their results were obtained without the aid of the microscope underlines the magnitude of their achievement. Ackerknecht (1959) rightly points out that about a third of the inmates of a mental hospital suffered from the disease at that time. If other syphilitic conditions, encephalitis, senile and arteriosclerotic psychoses and oligophrenias are added, this figure may easily have reached or even surpassed 50 per cent. The temptation to look for similar changes in the remaining cases must have been great, the more so as the range of the normal at that time was ill-defined.

The dogma of invariable anatomical changes in the brains of the insane took a firmer and more enduring hold in Germany than in other countries. This was due partly to the influence of their own "somaticist" school, but also to the influence of British and French organic trends. The sudden rise of neuro-histology in the 1830s must have acted as a considerable stimulus: within a few years major discoveries were made by Ehrenberg (1836), who was the first to demonstrate a nerve cell under the microscope; Purkinje, Valentin, Schleiden, Schwann, Robert Remak, von Köllicker and others (Fig. 7). Upon this basis Rudolf Virchow was soon to build his *Cellularpathologie* (1858), and although he was not much concerned with the psychiatric aspects, he acted as a powerful support for others, of whom the most important were Griesinger, Schroeder van der Kolk and Meynert. Of these, Schroeder van der Kolk, of Utrecht (1863, publishing in German), was perhaps the most dogmatic. He never failed to discover pathological changes in cases of mental disease: in the frontal cortex, when intellectual deterioration had been present; and in the upper and hind lobes in melancholic patients.

Griesinger (1845, 1861, 1867) repeatedly re-affirmed that for him the true answer to the problem of insanity would be given by cerebral and, in particular, cortical morbid anatomy. He admits, however, that a classification of mental diseases according to their nature—that is, according to the anatomical changes of the brain—was at that time not possible. Dividing the psychoses into two large groups: one of emotions and emotional states, the other of false modes of thought and will, he continues: "pathological anatomy shows, even at present,

* Haslam made other contributions to psychiatry of which Leigh (1955) has given a sympathetic account. This author also mentions that Pinel, customarily "somewhat sarcastic in his references to England . . . clearly has a considerable respect for Haslam".

that in the first group, or in the initial stages of insanity, it is rare to find important organic alterations . . . whilst in the second group . . . very often exist palpable organic alterations . . . particularly atrophy of the brain, more or less extensive, with oedema of the membranes and chronic hydrocephalus. Here, also is to be found the basis of a true diagnosis, that is anatomical diagnosis (1867, p. 207).

Theodor Meynert (1867, 1884, 1890) showed an even greater anatomical bias. He was so convinced that cerebral anatomy would solve the problem of mental disease that he objected even to the use of the term "psychiatry" (Zilboorg), which for him was synonymous with cerebral anatomy. In his general scheme of the brain, he considers that all afferent sensory fibres terminate in basal or subcortical centres which are also the starting point of descending motor tracts. For example, the fibres of the optic tract, he thought, ended in the grey matter of the superior corpora quadrigemina. The cerebral cortex is a completely independent "organ"; it is in connection with the subcortical motor and sensory centres, but all impulses that reach it have lost their material "sensual" character and have become "images"; their intricate association through the arcuate fibres builds up consciousness and the ego. Civilized behaviour develops through the effect of inhibitory cortical impulses upon the lower subcortical centres. The surface position of the cerebral cortex favours its wide encompassing (umgreifende) function. The cortex, though concerned exclusively with psychic phenomena, is not uniform in structure. It is rather a complex of "organs", and certain structural differences, e.g. the hippocampus and the medial occipital cortex (the large nerve cells there bear the name of Meynert) suggest also differences of function. Although the discoveries of Hitzig and Fritsch, Jackson, Ferrier and others were known to Meynert, they did not impinge upon his view of the exclusive psychic function of the cerebral cortex: only psychomotor phenomena, "psychical" deafness and "psychical" blindness could be of cortical origin. Such was Meynert's authority that Hitzig (1900) in his Jacksonian lecture in London seems to have accepted the "psychomotor" nature of the cortical motor phenomena which he together with Fritsch had charted.

According to Meynert cerebral function and, in particular, the complex processes of cortical association are accompanied by hyperaemia. Normally the extent of this "Funktionshyperaemie" is limited, since the brain and its cortical surface are enclosed within a rigid bony capsule and generalized hyperaemia would therefore inevitably result in oedema and swelling of the brain and, thus, produce abnormal mental and neurological phenomena. The opposite, lack of nutrition, would also result in mental and/or bodily disease and, if lasting, would give rise to anatomical damage in the brain.

On the basis of this general concept of brain function, Meynert attempts a classification of mental disease. Mania and melancholia are diseases due to cortical irritation. All hallucinations are due to abnormal subcortical function. Hypochondria, hysteria, neurasthenia and epilepsy (apart from the localized cortical Jacksonian type) are subcortical or bulbar phenomena. Epileptic seizures are conceived of as being caused by vasomotor constriction of arteries at the base of the brain and this concept is extended to the transient hysterical paralyses and sensory disturbances which—interestingly—are attributed to spasm of the thin-walled and recurrent anterior choroidal artery. Paranoia he thought was caused by an irreversible anatomical lesion, possibly manifesting itself as general atrophy of the brain.

The views of Griesinger and Meynert, as well as of Maudsley and other "system builders", have been criticized by Zilboorg for their materialist tendencies. Aubrey Lewis (1951) has already corrected this statement as erroneous, in so far as Maudsley was concerned. Neither Griesinger nor Meynert were materialists, though naturally they expressed their views in the language of associational psychology which was the widely accepted contemporary theory. Both repeatedly and emphatically stressed that the relationship between mind and matter remained mysterious. Both more or less adhered to the philosophies of Herbart, Fechner and Lotze, whom they frequently quote. These were predominantly idealistic, following in the wake of the great German idealist systems of the first half of the nineteenth century. If such superficial analogies are of any avail, one may compare Meynert's concept of brain function, in its aesthetic simplicity with that of Plato, as outlined in *Timeo* (Magoun, 1958). In Plato's view the divine part of the soul was localized in the spherical marrow of the cranial cavity which resembled in shape the Earth and the Universe, while the mortal portions inhabited the vertebral canal and spinal cord, just as Meynert's hemispherical cortex, which was responsible for all higher mental function, "encompassed" the subcortical regions which were concerned with lower and peripheral function.

Meynert's teaching inspired, among others, Flechsig, Wernicke, Forel and Freud (the neurologist), and through Wernicke and his school it has maintained some of its momentum into the present time. On the other hand, the reaction against the almost exclusively anatomical bias underlying the "systems" of Griesinger, Meynert and others was also considerable. Maudsley (1867), for instance, politely but definitely rejected Schroeder van der Kolk's claim that morbid anatomical changes may be detected at the autopsy of all cases of mental disease. To him "it is beyond doubt that important molecular or chemical changes may take place in those inner recesses to which we have not yet gained access". He also draws attention to the researches of Du Bois Reymond and others who "have shown that there are currents of electricity engendered in nerve". Ferrier's (1878) indictment that "morbid anatomy (is) far from being co-extensive with pathology" and that "deep mental abnormalities leave no trace discoverable by dissection and even the most advanced investigation" is equally incisive. In Germany, the reaction also gathered momentum. Oscar Vogt (Lewey, 1953) relates how on a visit to Kraepelin in 1894 he found him full of doubt about the value of anatomical research in mental disease (a judgment which he modified ten years later, impressed by the work of Nissl and Brodmann). The term "brain mythology" came to be used increasingly against, in particular, Meynert's trends of thought. Interestingly the phrase had been coined by Nissl (Bumke, 1925) who, in turn, was soon to embark together with Alzheimer and with collaborators from many lands upon the pathological anatomy of the psychoses.

In retrospect, it is now clear that their principal achievement in the field of psychiatry was the histopathology of the dementias: diffuse or widely disseminated degeneration, followed by disappearance of the neurones in the cerebral cortex and white matter invariably resulted in intellectual deterioration, or in early life, arrest of intellectual development; no matter whether the nature of the brain process was inflammatory, vascular, anoxic or due to malformation, trauma, nutritional deficiency, abiotrophy or senility. In the early days the list also included dementia praecox, but although powerful claims are still presented in our days, they have not been generally accepted. Today th

most comprehensive investigations have been conducted by the Vogt's (1952) and their disciples. The histological cell changes which they report in many cortical and subcortical areas of schizophrenic patients are not, however, specific and it is not easy to differentiate them from the normal range. It is the conviction of many workers including myself (1952) that more sensitive methods will be required to determine their significance.

Notwithstanding this limitation the achievement of morbid anatomy in the field of the dementias was formidable: it remains one of the solid pillars upon which psychiatric diagnosis and teaching rests. I cannot agree with Ackerknecht (1958) that "histology has not yielded any final answers or practical results for psychiatry and, in this, has been largely unimportant and even worthless" (although he acknowledges the "scientific" value of the work). This sweeping statement in an otherwise so objective historical treatise, hardly does justice to the many practising psychiatrists, from the times of Greding, Haslam, Esquirol, Meynert, Hitzig, Flechsig, von Gudden, Nissl, Alzheimer to Adolf Meyer, who carried out work in neuro-anatomy and neuropathology in order to unravel some of the secrets of mental disease. The psychiatrist is too often inclined to disown such achievements and to credit them to neurology or to any other branch of medicine. In fact, as this review shows, neuropathological investigations were initiated, and—to a large extent—developed in psychiatric institutions. Behind this attitude hides a curious "purist" assumption that problems of the mind require special methods for their solution, something akin to the approach which we have already encountered in Harper's argument. One wonders what will happen to the schizophrenias and the other functional psychoses: will they also be disowned by the psychiatrist once biochemistry or any other science has provided what is likely to be—at least partially—a physical substrate?

The search for a somatic basis for the functional psychoses has been a central task of pathology in the recent past. Since intellectual deterioration is not a primary sign of these psychoses, which display their abnormalities rather in the emotional sphere of the personality, attention has understandably tended to shift from the cortex to subcortical regions. This shift of interest was precipitated by the exciting new knowledge of extrapyramidal syndromes in the first two decades of this century, and by the dramatic natural experiment of lethargic encephalitis, with its symptoms of hypersomnia, loss of initiative, psychopathy-like behaviour, and of hallucinatory and compulsive phenomena in the course of oculogyric crises, which were all encountered as sequelae of circumscribed lesions of the grey matter surrounding the third ventricle and aqueduct. The area which has been submitted to the most intense scrutiny by pathologists as well as by experimental physiologists and biochemists, roughly comprehends the hypothalamus, closely linked through the pituitary gland to the endocrine system, the thalamus and thalamo-frontal radiation, the prefrontal region and the so-called rhinencephalon. Time prevents me from adequately describing the successive stages of this research, nor is such a description necessary, since the work is still fresh in our minds. I should, however, like to say a few words about the frontal lobe.

Since the crow-bar case described by Harlow in 1848, and subsequent descriptions by Ferrier (1878), Welt (1887) and many others, it has been known that bilateral lesions of the prefrontal region may cause changes in the personality and, in particular, in the affective sphere. A considerable landmark in the evolution of the frontal lobe syndrome were the careful experimental

investigations which Bianchi (1920) carried out from about 1895 onwards. In a polemic which has become famous, Bianchi defended the function of the prefrontal lobes as seat of intellectual and emotional synthesis against Emil Flechsig's (1896) thesis, that the parieto-temporo-occipital association zone is the most important region for human mental activity. As it turned out, both were right: Flechsig, in stressing the importance of this zone for the symbolic tools of intelligence: language, praxis, gnosis, and memory, while the frontal region is increasingly recognized as being concerned with the consciousness of the self (Freeman and Watts) and ego function. In the chart which was the outcome of Karl Kleist's (1934, 1937) clinico-anatomical experiences of head injuries in the first world war, the personal ego is associated with the orbital region, while the corporeal (visceral) ego is brought into connection with the cingular region. Although one cannot accept Kleist's pin point localization of mental faculties, this conception of the association of frontal and cingular regions with ego function was, in the words of Freeman and Watts, an act of "penetrating insight" which profoundly affected all subsequent discussion.

With the advent of prefrontal leucotomy and of selective blind, open or stereotaxic interventions, and with the subsequent introduction of temporal lobectomy in cases of temporal lobe epilepsy, the frontal (and temporal) lobes have become of practical concern in psychiatry. I will not here consider the therapeutic value of these surgical interventions. Indications for frontal lobe surgery have in the recent past become much more restricted, and, in many conditions, its place has been taken by chemotherapy, which may eventually supersede it. The impact which neurosurgery has made in mental disease is deeper than the therapeutic issue alone: the neurosurgeon, during the therapeutic intervention, acts almost as a neurophysiologist, making important observations which often amount to a physiological experiment. Jefferson (in his Stephen Paget lecture (1955)), has dwelt on the ethics of man as an experimental animal, pointing out that in certain investigations man is the most suitable, and whenever higher nervous and mental activities are involved the only animal from which experimental observations of a basic physiological nature may be obtained. He urged that this fact imposes a special responsibility on the neurosurgeon and his collaborators. Animal experimentation does not, however, diminish in importance. It usually precedes the "experimental" procedures in the human brain and always supplements them. Jacobsen's (1935) frontal lobectomies in chimpanzees probably hastened the introduction of prefrontal leucotomy by Moniz (1936); but without the maturation of modern neurosurgical techniques, this type of brain experimentation would not have been possible.

The present situation has much which recalls the brain surgery of France in the 18th century. At that time burr holes were made in cases of contrecoup and this intervention became fashionable and was applied to a great variety of conditions. Eventually the fashion petered out, but it left its important landmarks: not only was La Peyronie (1741) able to study the significance of lesions in the white cerebral matter for mental function, but, more important still, Pourfour du Petit (1710) established the relationship of the pyramidal tract to motor function, described its crossing and, tentatively at least, associated *incomplete* paralysis of the extremities with malfunction of the opposite parietal cortex. He and his followers were early pioneers of the motor cortex (Neuburger), although they did not grasp the full significance of their findings,

and continued to implicate the striatum as the principal control centre of movement.

The neurosurgeon of today has at his disposal techniques which are infinitely superior, and he is also powerfully aided by the electrophysiologist who, in turn, is able to supply him with methods of electrical stimulation and action potential recording which in accuracy attain almost to microscopic levels; he is aided also clinically by a far more advanced neurology, psychiatry and psychology. It is, perhaps, too early yet to assess the permanent gains in knowledge we may have reached from the present neurosurgical era, but it is permissible to say that it has led to a far clearer understanding both of frontal lobe function in its relation to the sphere of the ego, and of temporal lobe function, with its role, in Penfield's (1958) view, in recall and interpretation of past experience. Thalamus and hypothalamus with their adjacent regions are being explored by direct stereotaxic interventions in animals and in man, and the recent operations for extrapyramidal disease are adding other centres to this list: hypophysectomy, now often practised in cases of carcinoma, is providing opportunities for studying anew the complex cerebro-hypophyseal connections, in man, and the sites and pathways of hormonal secretion. The carrying-out of temporal lobectomy in cases of temporal lobe epilepsy has provided interesting new information on the centres in the infero-medial temporal region—Ammon's Horn, uncus and amygdaloid complex, and their manifold connections.

The functional concept of the "visceral brain" or "limbic lobe" is perhaps one of the most interesting crystallizations of this new experimental approach. It has been slowly emerging during the last three decades, beginning with Cannon's (1915) and Bard's (1928) experimental investigations and with Kleist's experiences in head injuries. It acquired its basic form, when Papez (1937) presented his "proposed mechanism of emotion and emotional expression" linking mammillary body, anterior thalamic nuclei and the cingular region with the hippocampus. Maclean (1949) added posterior orbital cortex, temporal pole, insula, amygdala and other areas between frontal and temporal cortex. Much of the evidence concerning "visceral" activities remains controversial and it seems that speculation has outstripped the available facts. The same may be said about "the ascending reticular formation", another interesting crystallization of recent experimental work and observations in man. Its location in brain stem, hypo- and subthalamus, intralaminary and reticular thalamic nuclei is—so far—only approximate, and despite recent anatomical studies (Olszewski, 1954; Nauta *et al.*, 1954, 1958; Papez, 1956; Brodal, 1957), the anatomical pathways are not yet fully elucidated. It seems to the present writer that much that previously had been conceived of as hypothalamic activation of the cerebral cortex (and which was based upon solid experimental and clinico-pathological experience) has been somewhat summarily incorporated into this new "formation" which is probably composed of several relatively independent relay-systems. Of these the pontine and midbrain relay may be identical with the ascending pathways linking the medullary centres with the hypothalamus, from which in turn, fibres connect with the thalamus.

It is important that this large hypothetical element in these useful concepts is well understood. Perhaps they have become too much like household words, ready on occasion to be introduced like the "deus ex machina" of the ancient theatre. We no longer think now in terms of the "sensorium commune", and the phrase "brain mythology" refers, as we have seen, to a specific period of

the closing 19th century. We have yet to learn that no generation is quite immune to the dangers of either.

The *biochemist* is the latest arrival in the field of the pathology of mental diseases. Although since the days of iatrochemistry chemists have concerned themselves with the phenomena of mental abnormality,* it was not until our own time that the biochemist—with infinitely matured techniques and knowledge, has undertaken in earnest to grapple with the problems of psychiatry and neurology. Fabing (1958) has tabulated important avenues of biochemical research which are at present in progress, and Gould (1959) has supplemented these with a review on research into the field of hormones and nutritional deficiency. The very diversity of the approaches indicates that this whole province is in an experimental stage. The neurohormones and their derivatives, among them serotonin and adrenochrome, have been foremost in the limelight, because of their pharmacological resemblance with or antagonism to mescal and lysergic acid. Theories have been propounded—though at the moment not yet verified—as to their possible pathogenic role in schizophrenia and kindred psychoses.

I do not believe that this promising biochemical outlook will replace the older morphologically orientated approaches. Biochemists (Waelsch, 1957), have recently become very much aware of the complexity of the brain, and of the possibility of a focal disturbance underlying psychotic manifestations. Gjessing (1938) always postulated that an abnormality in or near the hypothalamus may be at the root of nitrogen retention in periodic catatonia. Feldberg and Sherwood (1955) in their intraventricular experiments with neurohormones, and other substances, were also led to believe that the main action was on the grey matter surrounding the 3rd ventricle and aqueduct. This tallies with the well-known occurrence of manic syndromes and stupor after hypothalamic lesions in man. Although these organic syndromes may not be fully comparable with corresponding states in the functional psychoses, they clearly represent interesting pointers to the site of abnormal function.†

It is also noteworthy that the quantity of neurohormones (sympathin, serotonin, substance P) is greatest in the diencephalon and the tectal areas of the midbrain (M. Vogt, 1954; Amin *et al.*, 1954); and Holzbauer and Vogt (1956) have in addition reported reduced values of sympathin after injection of reserpine.

All this points to the possibility of a localized pathology for some of the psychoses, and, hence, the anatomical histological approach is likely to retain an important place. Histology itself, however, is at present under the tremendous impact of recent advances in biochemistry and biophysics, and its future contributions are likely to be made not so much by its traditional methods as by new histochemical, microchemical and ultramicroscopic techniques.

Envoy

This brings me to the end of our journey. It is clearly not possible to give a summary, as the whole of this lecture is a summary report on developments

* For developments during the 19th century McIlwain (1958) should be consulted.

† Mayer-Gross (1959) has discussed the possibility that the frequent synaesthetic phenomena in the so-called model psychoses may depend on abnormalities in the reticular formation. Another interesting aspect of the problem has been raised by Baldwin *et al.* (1959) who have shown that the response of chimpanzees to lysergic acid is abolished by previous (bilateral) ablation of the lateral temporal convolutions (but not by that of the prefrontal cortex). Their results not only underline the importance of the temporal cortex to perceptual representation, but also point to a focal pathology of the manifestations caused by "hallucinogenic" drugs.

over a vast period of time. I am painfully conscious of its many omissions and other shortcomings, some of which were dictated by the time limit of the lecture. Much sustained effort will be required before a history of neuropathology in relation to mental disease can be written. Furthermore, for the sake of clarity, I have had to concentrate upon a main theme; other important ramifications (and names) have had to be suppressed.

Although among the builders of neuropathology we find distinguished workers of many lands, it may have come as a surprise to some who are cognizant only of the later stages, to realize how considerable the British share has been. We have the authority of J. B. Friedreich, one of the German somaticists of the early 19th century, that the organic point of view had been learned from the English. We have met Haslam and Andrew Marshal who were among the earliest to carry out systematic pathological examinations of the brains of mental patients. They generalized their findings too much, which was excusable at the time, and they identified pathology with morbid anatomy —a mistake of even greater consequence, as we have seen. Among the earlier critics of this "solidism" are Maudsley and Ferrier. I entirely agree with Aubrey Lewis' relevant passages in his enlightened portrait of Maudsley, in the Maudsley Lecture of 1950. Maudsley's criticism has an almost modern ring; the shift of emphasis in present-day psychiatry towards genetic, biochemical and neuro-physiological research would have caused him no surprise: what greater homage could be paid to the man whose name is remembered in this series of lectures! Sir Aubrey compared Maudsley with Kraepelin—and this is correct as far as their position in clinical psychiatry in their respective countries is concerned. Chronologically Meynert would have been a closer comparison: both men published major and characteristic treatises in the same year, 1867. What a difference between the sober realism of Maudsley and the lofty, but quickly-dating hypotheses of Meynert! Maudsley, of course, was not an anatomist, nor was he practising any other ancillary science, while Meynert has a considerable number of anatomical discoveries to his credit, and he must be regarded as the founder of cytoarchitectonics, which had its remarkable achievements but, in its excesses, has not quite shed its romantic origin.

At the beginning of the modern era we met the towering figure of Thomas Willis. In this country his fame rests more on the arterial circle which bears his name and the description of cranial nerves and of myasthenia gravis, than on his basic contributions to the understanding of cerebral function. Only in recent years has he been rightly acclaimed as the father of comparative neurology (Dow, 1940), and of the autonomic nervous system (Sheehan, 1936). It was in the main left to Frenchmen to emphasize his important place in the development of neuropsychiatry: to Calmeil (1845), himself a pioneer in the field, who considered that what Thomas Willis had to say amounted almost to a complete treatise on cerebral pathology; to Soury (1899), who praised Willis's wide perspectives, his truly ingenious penetration of the phenomena of life and his depth and sweep of language recalling that of Shakespeare; and lastly to Vinchon and Vié (1928) who hailed him as a "maître de neuropsychiatrie". Modern opinion has been somewhat biased by Foster, who over-emphasized what was time-bound in Willis and probably unduly (Symonds) minimized Willis's anatomical merits in favour of his associate Richard Lower. Zilboorg also made severe strictures on the work of Willis, who (he said) laid "the foundation of a psychiatry without psychology which . . . while rendering inestimable service to neuro-anatomy, neurophysiology, and neuropathology

almost totally discarded the study of the very psychological phenomena which these men seem to have set out to study". Zilboorg was anxious to trace a line of development from Weyer, Stahl, Pinel, to the modern psychopathology of Freud, in which naturally Willis would not have a place. But surely, both the organic and psychological approaches are indispensable for the understanding of mental disease and should be pursued side by side.

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