Papers and Originals

Experiment and Neurological Surgery*

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At the end of Stephen Paget's biography of Victor Horsley is a list of his published writings; they number 130 and cover a period of 35 years, from 1880, when Horsley was 23, until 1915, the year preceding his death. Two-thirds are concerned with the nervous system, and 18 report the results of experiments devised to elucidate brain function. This work, much of it shared with Beevor, Schäfer, Semon, Loewenthal, and Clarke, was for the most part concentrated on the cerebral control of movement. That this aspect of brain function should have attracted him was perhaps inevitable. Among his teachers at University College were Burdon-Sanderson and Schäfer; by the time he was appointed to the staff of the National Hospital he had visited Continental centres, and Charcot gave him a testimonial (Hurwitz, 1962). The observations by Fritsch and Hitzig and by Ferrier, that contralateral limb movements could be evoked by electrical stimulation of certain areas of the cerebral cortex, were published within the 10 years previous to his appointment as house-surgeon. In this same 10 years appeared the description by Betz of the giant pyramidal cells which he found in the electrically excitable part of the cortex of the dog's brain, Bartholow had stimulated the cortex of man, and Hughlings Jackson had written a series of papers on epilepsy. Thus, to a dynamic and highly intelligent young doctor with an insatiable appetite for knowledge, investigation of the central nervous system must have been intensely attractive. His anatomical and physiological observations on the brain were continued in spite of an increasingly busy life as a surgeon; his researches on the cerebellum with Clarke did not appear until 1908, and on the pituitary gland in 1911, when he was aged 54. Notwithstanding his absorption in this field he devoted time to other matters of surgical interest, notably bacteriology and diseases of the thyroid gland, and in later years to sociological problems.

Experiments on Cortical Stimulation

Horsley's earlier work (1884-91) was concerned with the detailed mapping of the movements elicited by electrical stimulation of the cortex of the monkey and the orang-utan. Particular movements could be obtained from more than one area but most strongly from one particular point; movements of the digits and in particular hallux and pollex were represented over a much wider field than movements of the more proximal joints of the limbs, expressing the need in normal activity for richness of variety of movement of the extremity of the limb, whereas the proximal part of the limb employs a more stereotyped activity. Another notable finding for modern theories was that a turning movement of the head and eyes could be obtained from a wide area of cortex. After these experiments on cortical stimulation Horsley similarly explored

the internal capsule in detail, proving that fibres responding to stimulation by limb movements occupied its middle portion, and it is interesting to compare this with the map of motor and sensory responses to stimulation of the human capsule carried out during stereotaxic operations (Bertrand *et al.*, 1965). In logical sequence the pattern of these experiments was continued, identifying the pathways through the crus cerebri, and detecting the electrical changes in the spinal cord which followed stimulation of the excitable cortex.

Observations were continued but in much greater detail and refinement by Sherrington and his co-workers over the next 20 years, culminating in the paper with Leyton "On the motor area of the cerebral cortex" published in 1917. It was now possible to demonstrate a great advance in knowledge of the results of stimulation carried out on 28 anthropoid apes. In no experiment was a muscular response obtained from the cortex posterior to the central sulcus; there was no precise correspondence between the movement elicited and the anatomical location of the stimulus even when both hemispheres of the same animal were compared, though there was a similarity in the general patterns obtained. The important principle of functional instability of cortical motor points was established: that "the responses of a cortical point may be easily and greatly modified by precurrent, especially closely precurrent, stimulation either of itself or of neighbouring, especially closely adjacent, cortical points."

Three phenomena were described—the facilitation, the reversal, and the deviation of responses. Facilitation affects the delimitation of the anterior border of the motor strip. If a series of points are stimulated in succession from behind forwards, the anterior limit of the field is found to lie further anterior than if determined by stimulating a series of points from before backwards—a matter of practical concern to the surgeon. Sherrington pointed out that certain simple compound movements, usually of total flexion and of total extension of a limb, can be seen in the spinal and in the decerebrate animal. The motor cortex synthesizes small localized movements, breaks up the compound movements available from lower levels, and weaves them into various combinations. Functional instability—facilitation, reversal, and deviation—is all that the inadequate electrical stimulus can reveal of the mechanism for the multitudinous combination of delicate and precise movements for the execution of which the precentral gyrus is essential.

Stimulation of Human Cortex

Stimulation of the human cortex was first performed in 1874 by Bartholomew (Walker, 1957). The practical experience gained during animal experiments was soon applied by Horsley to patients; in 1884 he stimulated the surface of an occipital encephalocele to determine whether it contained brain, and thereafter he made use of cortical stimulation in order to

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identify the precentral gyrus and to explore the excitability of other areas (Horsley, 1909). Other surgeons followed suit, but the most extensive experience and scientific accounts of the results were those of Foerster and of Penfield. Both took the opportunities presented by operations, mostly carried out under local anaesthesia, to stimulate that area of cortex which happened to be exposed. Their observations confirmed those made on laboratory animals, and greatly extended them. Until that time motor responses to electrical stimulation of cortex posterior to the central fissure had been obtained only in lower animals and with a strong stimulus (Horsley, 1909). Cushing in 1909 obtained no response from the postcentral gyrus in two patients, but made the comment that a glioma of the precentral gyrus may cause no sensory loss while one of the postcentral gyrus caused hemiparesis, though post-mortem examination revealed no degeneration in the medullary pyramid. The paresis which occurs with strictly postcentral lesions is now well recognized and is evidence of the functional necessity of the postcentral gyrus for skilled volitional activity.

Foerster published accounts of his observations in 1936, and his diagram "The outcome of electrical explorations of almost 300 human brains exposed by operation" shows that motor responses were obtained from as far forward as the middle of the superior frontal convolution, from the postcentral gyrus, the superior parietal lobe behind this and neighbouring occipital lobe, and the posterior part of the superior temporal gyrus, in addition to the classically accepted precentral gyrus. He stated that the precentral gyrus was characterized by a low threshold of excitability, and by the highly differentiated discrete simple movements which could be evoked. The movements evoked from the postcentral gyrus required a stronger stimulus than those from the precentral gyrus, but in other respects they were similar; if the precentral gyrus was excised they were no longer obtained and an increase in the stimulus strength gave rise only to mass movements.

Movements derived from other areas of the brain, the extrapyramidal areas, required a stronger stimulus, the latent interval was longer, and the movements were compound, involving the whole of the opposite half of the body: head and eyes turned away from the side stimulated, the arm abducted and flexed, and the leg flexed: less commonly the movement was of extension. Foerster called these movements "synergic" and the areas of cortex whence they were evoked "extrapyramidal," a term which requires clarification. It is unfortunate and apt to lead to confusion that the word "pyramid" has two quite separate connotations in the brain. It is used to identify certain cells of the cortex found in the region of the central sulcus, the largest of which were described by Betz; "pyramid" is also the name of a structure in the medulla oblongata. "Extrapyramidal" relates to the medullary pyramid and describes those motor pathways to the spinal cord which do not traverse the medullary pyramid.

Motor and Sensory Responses Evoked by Stimulation

In 1950 Penfield gave a detailed account of his many years of experience. The complex psychical disturbances evoked by stimulation were related to epileptic disorders of the area of brain examined; to that extent they may be "peculiar" to the individual, and I do not propose to comment on them, except to emphasize that such carefully recorded observations provide a corpus of great value to workers in this field. They are comparable to the classical accounts of tumour behaviour and of operations which Cushing left for our education; such reference sources cannot be too detailed. The observations which Penfield made on the precentral and postcentral gyri are of historical importance. Analyses of the sensory responses revealed that 75% were from postcentral cortex and 25% from precentral; the majority were from points close to the central fissure, rarely more than 1 cm. from it. Excision of a piece

of the postcentral gyrus did not abolish sensory responses from the adjacent precentral gyrus if these had been present before the resection: no clinically demonstrable sensory defect could be detected as a result of ablation of precentral gyrus, though sensations had been evoked from it. Bilateral and ipsilateral sensory responses were rarely experienced and then virtually exclusively referred to the face. Analysis of the motor responses showed that 80% were from precentral cortex and 20% from postcentral; those derived from the postcentral gyrus were not abolished by resecting the adjacent precentral gyrus, differing from Foerster's experience perhaps by reason of the parameters of stimulation. Bilateral and ipsilateral responses were almost entirely restricted to the muscles of the face, jaw, and tongue. Ipsilateral responses have been reported by Bates (1953) in patients with infantile hemiplegia subjected to hemispherectomy; stimulation of the medial surface of the sound hemisphere caused complex movements of the ipsilateral—that is, the hemiplegic limbs—as well as of the contralateral limbs; in a considerable proportion of the points stimulated movement began on the ipsilateral side. Instability of cortical response, the principle enunciated by Sherrington, has received ample confirmation from the experiments of Liddell and Phillips (1951), in which variation in the frequency of the stimulating current markedly altered the pattern of the muscular responses. The lowest thresholds were for movements of the digits of the upper limb, of the lower limb, and of the tongue or the angle of the mouth. These are the parts in which Jacksonian epilepsy is most frequently initiated. Phillips (1966) has reviewed the diverse effects produced by varying the parameters of stimulation, a matter of considerable concern to neurosurgeons.

In view of the fluidity of response of the precentral gyrus to electrical stimulation it is important to know whether in a particular individual the basic pattern, under comparable operational conditions, remains constant. Bates (1954) had the opportunity to test the repeatability of responses in three patients in whom a second craniotomy proved necessary several months after the first; the topography of the excitable points of the precentral gyrus and the pattern of responses were similar on the two occasions.

Experiments of Denny-Brown

Ipsilateral and bilateral responses and the synergic movements derived from the extrapyramidal areas are of great significance. They have received particular attention from Denny-Brown and his colleagues. The following example chosen from his many experiments (Denny-Brown, 1966, pp. 120, 121) illustrates the facilitation by one stimulus of a concurrent stimulus applied at a different point, in this case on the opposite hemisphere. A point of threshold excitability was found in the *left* precentral region (of a macaque monkey), at which stimulation evoked flexion of the hip and internal rotation of the ankle on the right side. When a second, concurrent, stimulus was applied to the homologous area of the *right* frontal cortex the movement in the right limb was sustained when the stimulus applied to the left cortex was discontinued; the movement of the right limb could be evoked by stimulation of the right cortex alone, for several repetitions; thereafter the responses died out. A strong stimulus applied to the right cortex, after facilitation from the left, evoked epileptic discharge comprising clonic movements of the right limbs with turning of the head to the right. It is a well-known clinical experience that the lateralizing features of an epileptic seizure are not always reliable for determining on which side of the brain the causative lesion is situated. This series of experiments provides insight into the possible explanation.

Synergic movements can be obtained in the limbs of both sides by stimulation of frontal cortex, after resection of the posterior portion of the precentral cortex; as the ablation becomes more generous in an anterior direction, synergic

responses cease (Denny-Brown, 1966, pp. 133, 134). In other experiments it was shown that section of the pyramid in the medulla does not abolish the synergic responses (Denny-Brown, 1966, pp. 151–158) and that generous resection of area four was much more disabling, by virtue of loss of extrapyramidal area, than pyramid section in which extrapyramidal pathways are retained.

Denny-Brown concludes that recovery of movement in the limbs opposite to pyramid section is dependent on retention of function in extrapyramidal cortex, both ipsilateral and contralateral. These experiments have practical application for neurosurgeons; in the importance of conserving cortex and in the understanding of recovery from hemiplegia, which varies according to the anatomical level of the lesion in addition to its superficial extent. Often in glioma surgery the circumstances are such that the potential for future recovery of function has to be sacrificed to the exigencies of pathological changes. But this is often not so in the surgery of epilepsy and in the removal of meningiomas and other essentially benign lesions. Sacrifice of the posterior part of the frontal lobe, adjacent to the precentral cortex, should not be heedless; preservation of cortex giving origin to extrapyramidal motor pathways may be of great value in providing a moderately useful limb instead of an encumbrance. And, as Denny-Brown has emphasized, the survival of even a small group of giant Betz cells can potentiate a remarkable degree of recovery of skilled movement.

Rigidity of Limbs

Only a few other aspects of the work of Denny-Brown can be touched on, but the following has a link with Horsley. In 1889 he described a case of thrombosis of the superior longitudinal (sagittal) sinus secondary to suppuration in the face and scalp. The interest for Horsley lay in the pattern of fits from which the patient suffered in the terminal stages; they were of the adverse type, with movements similar to the synergies which we have been considering. Horsley predicted where the lesions might be situated on the frontal cortex, and post-mortem examination showed him to be correct. There were haemorrhagic effusions in the posterior third of the middle frontal convolution on one side and further forward and nearer the midline on the other. They were secondary to thrombosis of the cortical veins draining these areas, associated with thrombosis of the longitudinal sinus. No details are available of the neurological status of the patient. When primary thrombosis of the superior longitudinal sinus is widespread, and if it blocks or spreads into the cortical veins, hemiparesis and quadriplegia develop. The onset of the weakness of the limbs is more commonly arm before leg; tone may be normal, but is rarely markedly increased. Holmes and Sargent (1915), in their classical paper on injuries to the vertex of the head sustained in the early battles of the 1914–18 war, described a neurological state in which the legs were more paralysed than the arms, and in severe cases there was intense rigidity of the limbs. This hypertonus developed immediately, at the time of wounding, and was remarked on by those soldiers who did not lose consciousness when wounded. The distribution of the paralysis and rigidity, leg greater than arm, was ascribed to venous congestion and occlusion as a result of damage to the sinus, affecting veins draining the leg area more than those draining the arm area, because alternative venous pathways were more likely to lessen congestion of the latter, the inferior part of the cortex. But, as mentioned above, this does not conform to the pattern usually seen in primary sinus thrombosis. Holmes and Sargent's illustration of a specimen of such an injury reveals extensive bruising of neighbouring areas of frontal and parietal cortex; tangential injuries to the skull are now recognized as causing widespread superficial cortical damage. The immediate paralysis which follows ablation of motor cortex,

either in the experimental animal or in the human, is characterized by initial flaccidity; spasticity develops in man only after many days or several weeks. Denny-Brown resected large portions of cortex on both sides to include the extrapyramidal areas but preserving the precentral gyrus. This gave rise immediately to a rigidity of all limbs; when the animal was suspended in the air the upper limbs were flexed and the lower extended. The fixed attitude was called dystonia, and it was much more pronounced after bilateral than after unilateral ablation. In one experiment the precentral cortex necrosed; this added spasticity to the rigidity of the extrapyramidal lesion, producing spastic dystonia (Denny-Brown, 1966, p. 173). These are the experimental counterparts of the clinical condition constituting the "longitudinal sinus syndrome" of Holmes and Sargent, which is explicable on the basis of bilateral frontoparietal decortication from contusion, rather than venous congestion or infarction, though this may well aggravate the lesion. It is noteworthy that Holmes and Sargent recognized the unusual quality of the rigidity, that it had not the clasp-knife character of spasticity.

Cerebral Control of Movement

In the Eighth Sherrington Lectures Denny-Brown (1966) reviews the experiments which he has been carrying out for many years on the cerebral control of movement. They carry the Sherrington methods of investigation to higher levels in an anatomical and physiological sense and at the same time develop the theme of integration. After ablations of cortex and of deep areas, involving neurosurgical skill and nursing of a very high order, the animals have been observed by a clinical neurologist, alive to the significance of posture, tone, reflex, and behaviour. These experiments and his conclusions should be studied by all neurosurgeons; from his observations on the results of carefully designed experiments we shall be able the better to perceive abnormal movements and postures as understandable physiological reactions at a lower level, to predict more accurately the degree of recovery of function, and to direct rehabilitation more intelligently. Denny-Brown points out that in man, and more regularly in monkeys, certain primitive movements or automatisms are released by cortical lesions.

The grasp reflex, and a more intense variety of similar phenomenon, the instinctive grasp reaction, both evoked by contact with the skin, are released by frontal lobe lesions; an opposite reaction, the avoiding reaction, by parietal lobe lesions. The frontal extrapyramidal areas are concerned with crude movements of avoidance, the parietal with those of exploration or projection. These and other instinctive reactions or reflexes are normally kept in equilibrium by the balanced integrative action of cortex and subcortical centres. "The small eversions, abductions, rotations that enable precise palpation and exploration or withdrawal depend on the integrity of the pre- and postcentral gyrus." (Denny-Brown, 1966, p. 206). The tightly knit functions of the precentral and postcentral gyri were part of Horsley's (1909) views, for he could not conceive of a movement occurring without an afferent stimulus, and this was elaborated 40 years later by Walshe (1947), who stated that "a sensory afflux is a condition of willed movement." Recent work reviewed by Phillips (1966) on recordings from microelectrodes in the precentral cortex is illuminating. Motor neurones are excited or inhibited by a variety of stimuli applied to the contralateral limbs, including pressure, movement of hairs and of joints, and electrical stimulation of toe-pads. Observation of the effects of lesions in the basal ganglia leads Denny-Brown to state that "the pyramidal system is useless to the organism without the extrapyramidal system. There is no foundation for the concept of two independent types of movement, voluntary and automatic. The contribution of the rolandic and pyramidal system to movement provides a more delicate type of projected stereotactic exploratory

reaction for which the extrapyramidal reactions are a necessary substrate" (Denny-Brown, 1962, p. 130).

Failure of Postural Fixation

Martin (1967) has demonstrated very beautifully that quite simple experiments may clarify the disturbances seen in certain neurological disorders. His studies were particularly directed to the disturbances of posture, of equilibrium, and of movement consequent on disease of the basal ganglia. Failure of postural fixation may be seen in some cases of Parkinsonism as a gradual drooping forwards of the head, though a willed effort will set it erect for a short time, or an involuntary spasm may hyperextend the neck. This was seen to a greater degree in some patients when on hands and knees in the "all-fours" position; the experimental counterpart occurs in the monkey with bilateral destruction of the pallidum. Disturbance of gait is a common symptom in these patients. Normally the centre of gravity moves from side to side and forwards and backwards during locomotion, organized and balanced by appropriate and highly integrated muscular activity. "Placing" the centre of gravity in an inappropriate position relative to the base may render walking impossible, or cause the patients to lose balance; holding a weight in front of the body may adjust the position of the centre of gravity so that the difficulty is overcome. If the side-to-side movement is lacking, progress is difficult, but can be overcome if an assistant provides the rocking motion. Failure to recover when the seated body is suddenly tilted to one side is demonstrable in patients who may otherwise be physically active and have relatively little rigidity.

Cinematograph examination of patients with hemiballismus showed that the involuntary movements took the pattern of typical but excessive reactions to tilting. Similar slow-motion analysis of cinematograph films of epileptic seizures (other than typical Jacksonian) might prove a rewarding piece of research in the better understanding of their origin. The movements and postures seen in some attacks are very reminiscent of the descriptions of the effects of stimulating extrapyramidal areas of cortex; for instance, those of Bates (1953). Many of the movements of restless patients in the advanced stages of brain compression have an "involuntary" quality different from the restlessness of confusion due to a depressed level of consciousness. They might be seen to be similar to the rotatory tremors and the hemiballismus which may result from experimental mid-brain lesions (Denny-Brown, 1962).

Apparatus and Techniques

Closely linked with Horsley's research on cerebral localization was his interest in epilepsy; it provided a vindication in man of hypotheses derived from experiment, and its surgical relief an example of applied physiology. His first operation at the National Hospital after his appointment to the staff was on a patient with epilepsy, on 25 May 1886. The evolution of apparatus capable of amplifying and recording the minute changes of electrical potentials which occur on the surface and within the brain which has resulted in the development of electroencephalography would have intrigued him, and the ability to record electrical disturbances from within the brain results largely from his research into the functions of the cerebellum.

As is well known, Horsley required a technique which would enable him to make small discrete lesions in the cerebellar nuclei while inflicting only minimal damage to superficial structures. These requirements were met by the apparatus designed by Clarke, and which now carries their name. Introduced in 1908 (Horsley and Clarke, 1908) it remained for 40 years an instrument used exclusively in animal surgery. Spiegel *et al.* (1947) described an apparatus, suitable for attaching to the human

head, which they had used for making lesions in the dorso-medial nucleus of the thalamus as an alternative to leucotomy. Various instruments have since been designed and various radiological techniques devised in order to simplify and to improve the accuracy of the placement of the electrode or leucotome with which the lesion is made. I do not propose to discuss these but to draw attention to one small field, the use of stereotaxic methods in the study of epilepsy. These provide a means of sampling and of comparing electrical abnormalities within the substance of the brain on the two sides.

New Methods of Investigation

Horsley was studying anatomy and physiology at University College when the electrical activity of the brain was discovered, by Caton in this country in 1875 and independently by Danilevsky in Russia and by Beck in Poland shortly afterwards. These observations may be regarded as the beginning of electroencephalography (Brazier, 1960). Progress was slow, awaiting improvements in detection, amplification, and recording, until 1901, when Kaufman (aged only 24) in St. Petersburg began studying the electrical manifestations of induced epilepsy. In 1914 Cybulski presented to the Polish Academy of Sciences a paper on this topic illustrated by records, and Hans Berger is said to have begun in 1902 to verify Caton's original observations, though he published nothing until 1929 (Walker, 1957). Thereafter the clinical possibilities of this new method of investigation rapidly became apparent, and in 1935 Gibbs, Davis, and Lennox described the 3 per second spike-and-wave abnormality which distinguishes petit mal.

The next step was the application of the recording electrodes to the surface of the human brain exposed at craniotomy, and priority for this should be awarded to Foerster and Altenburger (1935). Adrian and Matthews visited the London Hospital in 1934 and carried out the procedure during an operation by Cairns for a parietal glioma (Adrian and Matthews, 1934). Electroencephalography is now a routine technique during operations for the relief of epilepsy. The need to detect the electrical events occurring in the depths of the brain, their time relationships to those occurring in the cortex, and their pathways of spread has led to the insertion of fine electrodes into various basal nuclei masses; stereotaxis provides the means of aiming at a particular point and achieving contact with a high degree of accuracy. Walter and Dovey (1946) demonstrated the changes occurring in the E.E.G. recorded from an electrode inserted manually into a glioma. In 1944 Bickford and Cairns left a multistrand electrode within the track of an intracerebral battle injury for several days and obtained good recordings (Woltman, 1953). In the definitive study of a patient with epilepsy leashes of fine wire are placed in selected areas through small holes in the skull and left in situ for several weeks, without ill effect. Repeated examinations can be made to verify the persistence of abnormality and the chances of obtaining information during a spontaneous seizure are much improved; a seizure record provides an opportunity for determining electrically its site of origin, which may be of great value in deciding treatment.

Spread of Epileptic Discharge

In some patients with focal epilepsy a localized E.E.G. abnormality may be detected in the scalp record on one side only or there may be a similar "mirror" focus in the homologous area on the other side. Repeated records may show that the focus on one side can be considered the leading or major one, or that each is independent of the other. In some instances the mirror focus appears as part of a spread of the E.E.G. abnormality, which becomes generalized as the focal fit terminates in a convulsion. Is this due to spread through the

cortex, or by the implication of more central mechanisms? There is evidence that a mirror focus is due to transmission of impulses across the corpus callosum; the development of mirror foci opposite an epileptogenic lesion created in the brains of cats and rabbits can be prevented by division of the corpus callosum (Morrell, 1960). But generalization of the discharge probably depends on spread to basal nuclei and perhaps to the reticular formation. With the aid of multiple electrodes Walker and his co-workers have demonstrated the march of events in experimental epilepsy: to the contralateral homologous cortex and to the ipsilateral putamen most frequently, and to the prefrontal cortex, thalamus, pallidum, and cerebellum. He considers that generalization of a seizure depends on the involvement of a critical mass of discharging tissue (Walker, 1961).

At the London Hospital we started using implanted electrodes in the study of selected cases of epilepsy in 1952. These have comprised thin plastic plates carrying electrodes, inserted through burr-holes, so as to lie on the cortex in the subdural space; and lashes of fine insulated wires of decreasing lengths, bared at the tips so as to form a sequence of contacts in line. They have been inserted into the frontal lobes so as to sample orbital and medial cortex, and into the amygdalum and the hippocampus on each side (Fischer-Williams and Cooper, 1963). In some cases it has been possible to determine on which side a bilateral temporal abnormality is dominant and thus to decide on the correct side for a lobectomy. In others the method has revealed the multiplicity of independent areas of abnormality, and thus avoided a useless operation. As other observers have noted, not only do the cortical plates show abnormality not visible in scalp records because the voltage is about four times greater, but discharges may be detected by the deep contacts which do not show in the record from the cortex. Jasper (1964) states that, in his experience, discharge from the amygdalum or hippocampus does not result in automatism with amnesia unless there is also involvement of the cortex of both temporal lobes.

Cerebral Circulation

Finally, I would like to draw attention to another field of experimental work in which future applications are likely to be of great practical value—namely, the cerebral circulation. Horsley showed an interest in this, for in 1889 with Spencer he published a paper concerning the effects of compression of the common carotid artery. His aim was to demonstrate a method of controlling haemorrhage from the middle cerebral artery of a monkey; he recorded the pallor of the cerebral cortex when the common carotid blood flow was obstructed, an operation now employed in the treatment of certain intracranial aneurysms. He also observed that electrical excitability ceased immediately. In the famous experiments on the effects of raised intracranial pressure carried out in the laboratory of Kronecker in Berne in 1900 Cushing (1908) devised inspection windows in the skull in order to observe the behaviour of the cortical vessels.

Florey (1925) observed that in asphyxia the cerebral veins and capillaries dilated, and demonstrated changes in the calibre of larger arteries (though not of veins) as a result of a mechanical or an electrical stimulus. Pushing or rubbing an artery, even only one side of it, provoked localized narrowing which might last 10 minutes. Reactions of this kind, usually spoken of as spasm, are now a popular field for research in view of the part which they may play in damaging the brain by ischaemia when an intracranial aneurysm ruptures. Florey observed that occasionally the segment of the artery stimulated might dilate instead of narrowing, but this phenomenon has not been observed by recent workers, or has been ignored. Abnormalities of the cerebral circulation may develop in, and remain localized to, circumscribed areas of the brain. Penfield made a preliminary report in 1933 on the cessation of arterial

pulsation, the cortical anaemia, and the hyperaemia which may accompany an epileptic fit—observations made during craniotomy. The phenomena were considered in greater detail in a later article (Penfield, 1937). Focal increase in blood flow has been shown to accompany the increase in activity of a particular part of the brain in the animal (Schmidt and Hendrix, 1937) and in man (Walter and Crow, 1964).

Measurement of Cerebral Blood Flow

The study of cerebral blood flow has been hampered by the lack of methods for its direct quantitative measurement which were applicable to man. Until 20 years ago the only method of demonstrating changes in flow was by a thermocouple applied to or introduced into the brain (Gibbs, 1933), an increase in the amount of blood passing through the adjacent area being recorded by a rise of temperature. Though such systems were sensitive, they only recorded relative degrees of change.

A precise and simple method of quantitative measurement that could be used repeatedly in a human subject without harm was devised by Kety and Schmidt (1948) shortly after the end of the war. "It consists in applying . . . the Fick Principle, which in its simplest form states that the quantity of a given substance taken up by an organ in a given time from the arterial blood equals the amount of the substance carried to the organ by the arterial blood minus the amount removed by the venous blood during the same time" (Schmidt, 1950). The substance must be inert and must rapidly diffuse through the blood-brain barrier; Kety used nitrous oxide gas. The gas is inhaled in an appropriate concentration and samples of blood for the analysis of gas content are collected simultaneously from an artery and from the superior jugular bulb at the end of the first, the third, the fifth, and the tenth minutes of inhalation, by which time the concentration of venous blood has practically attained that in the arterial. The concentration of gas in the brain is then in virtual equilibrium with that in the arterial blood. The blood flow can be calculated by an appropriate formula, in which the only unknown factor is the weight of the brain. For a normal man a standard weight of 1,400 g. is assumed. The accuracy of this technique was tested against direct measurements of cerebral blood flow in monkeys (Kety and Schmidt, 1948) and was found satisfactory, and the method has now become a criterion for other techniques.

Another method, introduced at about the same time, depends on the degree to which a given quantity of dye injected into an internal carotid artery is diluted in its passage through the brain, as estimated from samples of internal jugular blood. The advantages and disadvantages have been discussed by Schmidt (1950), who gives a list of the values of the cerebral blood flow at rest and in various abnormal situations and in patients with a variety of diseases. The average in normal controls was 54 ml./100 g./min.; the highest (164 ml.) was found in patients with a cerebral hemangioma and the lowest (25 ml.) in polycythaemia. One of the earliest applications of the new technique was to compare the effect on the cerebral blood flow of reducing raised intracranial pressure by two different methods; by tapping the lateral ventricle in one group of patients, and by the intravenous administration of a hypertonic solution of glucose in another group. In both groups the blood flow was increased, but the hypertonic glucose solution was followed by an appreciably greater increase (Shenkin *et al.*, 1948).

The local changes which occur in the circulation within a small volume of brain tissue have been studied by simultaneous records of changes in temperature (by implanted micro-thermistor) and in the free or "available" oxygen (polarography). For the latter, an insulated electrode with bared tip is placed on or in the brain, and a constant small electric potential applied (about 0.6 V.). Oxygen in the vicinity of the electrode is electrolysed and the current which flows is

proportional to the concentration of oxygen in solution (Davies and Brink, 1942). These methods have been used to study the collateral circulation in cerebral arterial occlusion (Meyer *et al.*, 1954) and the changes which may accompany head injury (Meyer and Denny-Brown, 1955). The implantation of multiple electrodes into the brain for the purpose of inducing temporary or permanent lesions in the treatment of certain mental disorders has provided the opportunity for making similar studies of the white and grey matter in patients under diverse circumstances (Walter and Crow, 1964).

Electromagnetic Method

In 1938 Katz and Kolin devised an electromagnetic method of demonstrating variations in the velocity of flow through an artery. This depends on the observation that blood moving through a magnetic field at right angles to its lines of force induces an E.M.F. perpendicular to the line of force at right angles to the direction of the flow, a phenomenon due to the electrolytes acting as electroconductors. Appropriate apparatus has been constructed for studying fluctuations in the flow of blood through the carotid arteries of the neck, and Hardesty *et al.* (1961) have made important and practical contributions to our knowledge of the effects of occlusion of the common carotid artery. They found that in approximately half the patients studied blood flow to the head continued in the internal carotid artery at a low level; in the other patients a reverse flow, from the head, at a low level was demonstrated. This work confirms the findings previously made by angiography (R. Johnson, personal communication, 1968) that blood may flow from the internal carotid to the external carotid, through the bifurcation above a ligated common carotid artery. Hemiplegia may complicate ligation of the common carotid (as it may ligation of the internal carotid) and in these cases may be an example of the so-called "steal" phenomenon.

Mention was made earlier of the pioneer observations by Florey on the changes in calibre of cerebral arteries as a result of mechanical and electrical stimuli. The phenomenon has been regarded as spasm of the muscular coat of the artery, and Byrom (1954, 1968) has made a special study of cerebral arterial spasm in experimental hypertension. Narrowing of the major cerebral arteries and their branches has long been recognized as a feature to be seen in the angiograms of patients who have recently sustained a rupture of a cerebral aneurysm. By some the narrowing is considered to represent spasm, while others consider that the vessels are compressed and stretched by the swelling of the surrounding brain. Whatever the precise cause, the effect is a local interference with blood flow, a matter of importance in its relation to ischaemic brain damage, to its treatment, and to the timing of operation on the aneurysm. If the condition is spasm an understanding of its cause might lead to its prevention or its treatment. Echlin (1965) has made observations confirming those of Florey, and in addition found that contraction of arteries occurred in the segments bathed in fresh blood. Serotonin and blood serum had less effect. On the other hand, Symon (1967) was unable to confirm this reactivity of the cerebral vessels to blood.

Recent Methods

The most recent methods of measuring blood flow, developed over the past five years or so, are similar in principle to the nitrous oxide method, but are of much wider application. Nitrous oxide is replaced by a rapidly diffusible inert radioactive isotope: krypton-85 and xenon-133 are at present used; they are gases which are so quickly eliminated by the lungs that recirculation of isotope is negligible in quantity. The technique was devised by Lassen and Ingvar (1961) and has been widely exploited, with various modifications. A solution of the isotope in saline is rapidly injected into the internal carotid artery and the radioactivity of the brain is estimated and recorded over a

10-minute period by an external collimator and detector. A clearance curve is obtained which is determined by the dose of isotope, its relative solubility in the brain, and the blood flow. From the curve the mean blood flow can be calculated. The rate at which a substance is washed out of the brain will be related to the various tissue compartments of the brain; for example, the rates for grey and white matter will differ owing to variations in the richness of their capillary beds. The volume percentage of the capillaries per unit of human brain tissue varies from 0.3% in the white matter of the fornix to 3.3% in some areas of the cerebellar cortex (Lierse and Horstmann, 1965). It has been shown that the mean clearance curve is compounded largely of two curves, one for the grey matter and one for the white (Kety, 1965). The former has a half-time of about 0.6 minute and the latter of about 4.5 minutes. The applications of this technique are likely to prove very wide. It has been used to determine the flow separately in grey and white matter in the human brain during operations by injecting minute amounts and using small detecting instruments (Espagno and Lazorthes, 1965; Nilsson, 1965), to identify the extent of the effect on an angiomatous malformation of clipping feeding arteries (Feindel *et al.*, 1965), and to demonstrate impaired flow due to an expanding lesion (Ekberg *et al.*, 1965). Parallel with the results of using an electromagnetic flowmeter on the carotid artery in the neck, it has been shown by the isotope clearance technique that where the blood flow fell less than 25% after clamping the internal carotid artery no hemiplegic complications occurred; whereas in each patient in whom the reduction in flow was more than 25% such complication occurred immediately or later (Jennett *et al.*, 1966). Other fields in which determination of cerebral blood flow will prove valuable are anaesthesia, respiratory complications, acute and chronic head injury, the correlation with arterial P_{CO_2} and P_{O_2} , with states of low blood pressure whether induced therapeutically or spontaneous, and in the use of hyperbaric oxygen.

Conclusion

I have endeavoured in this lecture to emphasize the importance that Horsley placed on experiment, and to trace the development of a few of his interests. Such developments do not have parallel margins; they steadily diverge, opening up fresh fields for inquiry and providing unexpected applications to man. As I said in the introduction, the nervous system must have offered obvious attractions to Horsley, and those attractions, now more widely spread, still present themselves to the young man on the look-out for an absorbing career. I see two problems which confront him, and which at any rate in medicine seem peculiar to the present time. One is the difficulty of engaging in research during the early years of life when the mind is most productive of original ideas, a theme developed by the late Lord Brain (1959) in his Schorstein lecture "The Neurological Tradition at The London Hospital," whose alternative title was "The Importance of being Thirty." The other is the difficulty of finding the time for such work when later the young surgeon becomes more immersed in clinical responsibility.

The title of this lecture was purposely worded *Experiment and Neurological Surgery*, as distinct from *Experiment in Neurological Surgery*. For those who have the aptitude and the desire, it should be possible to achieve a combination of both interests, not necessarily to an equal degree, but to an extent which provides satisfaction to an inquiring mind. For this to be practicable a more generous quota of hospital staff establishment is necessary, as has been emphasized by the Royal Commission in connexion with teaching requirements. Expansion of establishment depends on finance, but for this purpose the sum required is not great compared with other items of the National Health Service budget. The granting of it requires perception of the need.

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Prevention of Rhesus Immunization. A Controlled Clinical Trial with a Comparatively Low Dose of Anti-D Immunoglobulin

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Summary: A controlled clinical trial was carried out to test the effectiveness of a comparatively low dose of anti-D immunoglobulin (250 µg) in preventing rhesus immunization.

In the control group 17 out of 329 women (5%) formed rhesus antibodies, whereas in the treated group only 3 out of 333 women (0.9%) showed active immunization, all three of whom had an exceptionally large transplacental bleeding.

Introduction

Clinical trials carried out in Great Britain and in the United States have convincingly shown that rhesus immunization can in nearly all cases be prevented by the administration of anti-D immunoglobulin shortly after delivery of a rhesus-positive infant (Combined Study, 1966; Freda *et al.*, 1967).

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Progress is also being made in other countries to introduce this kind of prophylaxis. At present, however, the widespread application is severely limited by the supply of anti-D plasma from which the immunoglobulin is prepared. For this reason it is important to determine the minimum effective dose for the prevention of rhesus immunization.

In the New York and Liverpool trials doses of approximately 5,000 and 1,000 µg. of anti-D immunoglobulin respectively were used (Clarke, 1967), with practically 100% therapeutic effectiveness. Recently Ascari *et al.* (1968) published the results of a trial in which a dose of 300 µg. had been used, with similar success.

The present study records the effect of a 250 µg. dose.

Material and Methods

Patient Selection.—Ten obstetrical clinics participated in the trial over a period of 12 months. The patients comprised all non-immunized rhesus-negative women who were delivered of a rhesus-positive child, irrespective of parity or ABO compatibility. Women were randomized by treating those with odd-numbered birthdays. The immunoglobulin was administered by intramuscular injection within 24 hours after delivery.