Monitoring the Brain

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The function of the brain is at the center of the anesthesiologist’s professional life, yet it is remarkable how little attention has been given to it in anesthetic research until recently. The main reason has not been lack of interest, but the scarcity and complexity of methods for monitoring cerebral function. The methodology is now much better understood and consequently more straightforward, as I hope this paper will demonstrate.

Level of Responsiveness

By far the most valuable monitor of cerebral function is the assessment of responsiveness, in which term is included not only level of consciousness but also neurolologic status. At the highest level the clinician assesses responsiveness to ideas and concepts, capacity for memory, mental arithmetic, etc., and at the lowest, reflex response to pain. Despite all the advances in methodology, the assessment of responsiveness by the skilled observer remains the most discriminative method of testing cerebral function. For example, assessment by intelligent close relatives of a patient’s intellectual ability after head injury provides a most sensitive test.

The problem with such measurements is their lack of objectivity and quantification. In the management of acute head injury, nurses are encouraged to write a succinct but detailed account of their observations, but this depends on a largely subjective interpretation of the responses elicited and results in inconsistencies, as was demonstrated when a group of observers were asked to assess the same patient.1 To deal with the problem of recording patient responsiveness reliably and reproducibly, Teasdale and Jennett2 produced a simple scoring system in which responsiveness is assessed as three types of behavior: motor responsiveness, verbal performance, and eye-opening. Each of these main types of behavior is subdivided into different levels of response. The observations made are plotted on a chart (see fig. 1), of which the vertical axis consists of the data observed while the horizontal axis carries a suitable time scale. Plotting the observed responses on this chart results in three lines (one for each type of behavior), which move upward with clinical improvement and downward with deterioration. Of course, the use of this, or a similar schema, in no way detracts from the importance of the regular full neurologic assessment. For details of the assessment methods applicable to intensive care situations, the reader is referred to reviews by Plum and Posner3 and by Shapira.4

The scale devised by Teasdale and Jennett2 can be incorporated in a clinical chart, which also allows the recording of pulse rate, blood pressure, temperature, respiratory rate, and pupil size. The latter “vegetative” measurements are particularly important when it is suspected that intracranial compression or shift of the brain may occur. With intracranial compression, the heart rate slows progressively and sinus arrhythmia becomes marked, the blood pressure rises slightly, and respiration slows and becomes irregular. At a late stage in the development of compression marked hypertension appears, at first with further slowing of the heart rate, but later with tachycardia. By the time extreme hypertension and tachycardia coexist, final circulatory collapse is near. However, this sequence in the development of circulatory and respiratory signs with compression of the brain is often disturbed and obscured in individual patients by the many complicating factors that may interact, e.g., hypothermia and blood loss from associated chest and visceral injuries.

Unilateral pupillary dilatation due to tentorial compression appears before marked hypertension occurs, but it also is a relatively late sign. In studies in dogs, Fitch and McDowall5 found that space-occupying lesions had reached 80 per cent of the volume that produced severe hypertension and circulatory


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failure before unilateral pupillary dilatation occurred.

In agreement with the above-mentioned experimental findings, Truwitt has reported that circulatory signs appear so late in the development of intracranial compression that these signs occurred in advance of changes in level of responsiveness in only one of 40 patients. In view of this, Teasdale has expressed the opinion that the regular nursing observations of pulse, blood pressure and respiratory rate are more often helpful in the detection and assessment of associated extracranial injuries than for the diagnosis of developing intracranial compression.

At the extreme lower end of the cerebral function scale is the problem of diagnosing brain death i.e., severe structural brain damage, which is irrecoverable and so severe as to prevent survival without artificial ventilation of the lungs. It has long been held that a cardinal feature of brain death is the absence of electrical activity of the brain when the full EEG is recorded on no fewer than two occasions separated by a specified time interval (the duration of the interval has varied from one authority to another). The importance of the EEG in making the diagnosis has been questioned recently, and medical opinion is moving towards denoting the role of the EEG in this context. One consideration in using the EEG for diagnosing brain death is that a very few individuals normally have a flat EEG, when relaxed with the eyes closed. (In such individuals, however, cerebral electrical activity is readily demonstrated when a small dose of thiopental or diazepam is injected intravenously.) The following clinical signs have therefore been deemed sufficient evidence in themselves. All the signs must be present, and there must be no possibility of drug-induced depression or hypothermia:

1) No spontaneous respiratory activity over a three-minute period when the patient is disconnected from the ventilator on two occasions, at least 12 hours apart. In carrying out this test, hypoxia is avoided by ventilating the patient with 100 per cent oxygen prior to disconnection from the ventilator and by attaching the tracheal airway to a reservoir of oxygen during disconnection. In order that the respiratory center be stimulated, the test must start from normocapnia, which should be confirmed by blood-gas analysis. When muscle relaxants have been administered, adequate neuromuscular transmission should be confirmed with a peripheral nerve stimulator. This test would not, of course, be appropriate in the very rare instance of a patient with a severe head injury who also had absence of respiratory responsiveness to CO₂ as a result of chronic obstructive pulmonary disease.

2) Absence of brain-stem reflexes: a) pupils fixed in the absence of damage to the second or third nerve; b) corneal reflex absent; c) no oculovestibular reflex; d) no motor response above the foramen magnum. Note, however, that brain death may exist in the presence of spinal reflexes, e.g., limb withdrawal in response to pain.
The Electroencephalogram (EEG)

The EEG is commonly used as a monitor of cerebral function. Since the electrical activity of the brain is recorded at the skin surface, each electrode is averaging the electrical activity of many millions of neurons (about two million neurons are contained in each square centimeter of human cortical surface). The electrical activity responsible for the EEG is that which arises from excitatory and inhibitory postsynaptic potentials in the larger dendrites of the neurons of the cortex. Deeper structures play no part in the development of the EEG, other than through the alterations they may produce in the postsynaptic potentials of the cortical neurons. During states of alertness, mental activity, orientation or emotion, the EEG shows a "desynchronized" pattern with no obvious underlying frequency of the combined activities of all the many neurons influencing each electrode. During rest, sedation, mental inactivity and anesthesia, the EEG becomes "synchronized," that is, the electrical activities of the neurons are coordinated in time to produce waves of varying frequency and amplitude. Within the broad classification of the synchronized EEG there are several subdivisions, based on frequency of synchronized electrical waveforms, i.e., alpha = 8–13 Hz; beta > 13 Hz; theta = 4–7 Hz; delta = <4 Hz.

The patterns associated with anesthesia have been described many times. During the lightest levels of nitrous oxide anesthesia the EEG is synchronized, but at a fast frequency that may be indistinguishable from that of a conscious subject relaxed with the eyes closed. Induction of anesthesia with a sleep dose of barbiturate often leads to an increase in the frequency of activity, so that it comes to lie in the beta range. With potent anesthetic agents, as anesthetic depth increases the basic frequency slows, usually with a progressive increase in amplitude of the waves. At very deep levels, isoelectric or silent periods appear, separated by bursts of electrical activity, so-called "burst suppression" (see fig. 2). Finally, all electric activity disappears and the record becomes isoelectric.

Studies of the action potentials (spike potentials) of individual neurons (which are not directly related to the wave patterns seen on the surface EEG) show that, at the lightest levels of anesthesia, there is no decrease in the rate of neuronal firing, but that the discharges become grouped together in runs of two or more. One of the characteristic changes in cortical neuronal activity induced by anesthesia is therefore an alteration in the temporal pattern, but not necessarily in the total of neuronal activity. At deeper levels of anesthesia there is also a decrease in the summed total activity.

Anesthesia also alters the balance of electrical activity between excitatory and inhibitory circuits acting upon the cortical neurons. With certain drugs like ketamine the new balance is in favor of increased excitation, yet the drug produces anesthesia, which emphasizes the point that changes in the spatial (excitatory-inhibitory) pattern of electrical activity together with changes in the temporal (grouped-single spike discharges) pattern are as characteristic of electrical activity of the brain during anesthesia as are changes in total firing rate.

In patients in coma, similar changes in frequency and amplitude of the EEG are seen, and can be used as estimates of depth of coma. After head injury, areas of excitatory activity or frank seizure discharge are commonly also seen, this usually being ascribed to damage to inhibitory circuits, allowing escape of certain groups of neurons from the normal balance of inhibitory-excitatory influences. In acute anoxia the amplitude of all EEG frequencies at first increases and later decreases as the hypoxia becomes more severe. The predominant rhythm shifts to slower frequencies and eventually the record becomes isoelectric. Changes also occur with deviations from normal P\text{CO}₂; extreme hypocapnia produces slow, high-amplitude waves, while hypercapnia produces "arousal" and depressant effects at various P\text{CO}₂ levels.

Despite all the information contained in the EEG, anesthesiologists have made little use of the technique in monitoring cerebral function in the operating room, with the possible exception of monitoring during open-heart surgery. One reason is that the equipment is
Fig. 2. EEG changes with alphadione (Althesin). The top line is the EEG obtained from a baboon lightly anesthetized with nitrous oxide–oxygen–0.7 per cent halothane. At the arrow, alphadione, 50 μg/kg, was injected into a central vein and resulted, in a few seconds, in an almost isoelectric EEG. The third line shows the EEG 1 min, 30 sec after injection of alphadione, at which time there was a pattern of burst suppression. The fifth line is the EEG 4 min after alphadione administration, at which time it was returning towards the initial pattern, but still contained more slow high-voltage activity than before the injection. The other records are of the EEG.

expensive and was, until relatively recently, cumbersome. Moreover, the recording is very susceptible to electrical interference, leading to numerous artefacts. Anesthesiologists have been deterred from using simplified two-electrode systems, which is unfortunate since considerable information about general changes, like anesthetically-induced CNS depression, can be gained from such simplified EEG recordings. Another reason for the failure to use the EEG is the difficulty in interpreting the records, though I believe this has been exaggerated since the generalized changes with which anesthesiologists are concerned are not difficult to recognize.

In order to help the non-expert EEG interpreter, Bickford and colleagues have described a computerized display of EEG activity in which the basic EEG is analyzed by computer into its various frequency wave bands and the electrical power in each wave band accumulated over a certain period (4 sec). This information is displayed on an X-Y plotter with frequency on the X axis and power on the Y axis. Further plots are made for subsequent time intervals, one above the other, with the result that the observer can see readily any tendency towards a shift in the predominant frequency of the EEG.

Another attempt to simplify the interpretation of the EEG in the clinical situation is the "integrated EEG" described by Maynard, Prior and Scott. In this system, cerebral electrical activity is sensed by two electrodes placed one on each side over the parietal regions. The signal is passed througha
wide-band frequency filter that filters out frequencies below 2 Hz and those above 15 Hz, thus minimizing artefacts and electrical interference. The signal is amplified, rectified, integrated, logarithmically compressed, and displayed on a slow-running chart recorder as a line, the height of which above the baseline indicates total power and the undulations of which indicate fluctuations in power from one moment to another. Upward movement of the line indicates a more "active" EEG and downward movement the converse (fig. 3). The system therefore is basically a two-electrode EEG with the frequency-amplitude information simplified to a single line, the deflection of which relates to the total power of the electrical activity. A second channel provides a continuous monitor of the electrode impedance between the two electrodes, thus allowing artefacts such as diathermy to be distinguished.

Investigators at the London Hospital have described their experience of the clinical employment of this system, "the cerebral function monitor" (available commercially), in a number of acute situations, including resuscitation after cardiac arrest, open-heart surgery, management of various forms of brain damage, treatment of drug overdosage, treatment of status epilepticus, and postoperative care. In their experience the system can be used for long periods in clini-

Fig. 3. Examples of cerebral function monitor tracings: a, decline in cerebral activity and, finally, death following cardiac arrest; b, gradual increase in cerebral activity, as may be seen in the patient recovering from a barbiturate overdose; c, persistently near-zero-level tracing in a patient whose conventional EEG is isoelectric; d, a series of stereotyped "sharp waves" associated with clinical seizures. (Reproduced from Scott D: Understanding EEG, London, Duckworth, 1976, by permission of the author and publisher.)
cal situations without skilled technical assistance. Clinicians apparently readily learn to interpret the information displayed and find it useful in clinical management. The continuous display of electrode impedance is a major factor in allowing the system to be used for long periods without failure to detect serious electrode faults. It is, of course, necessary to bear in mind that the record displayed can never contain more information than the EEG from one pair of electrodes and so can deal with generalized changes in brain function only. For this reason, Prior *et al.* recommend that the continuous surveillance provided by the cerebral function meter be supplemented at regular intervals by a full EEG recording.

One theoretical objection to the system is that the record obtained is neither a record of electrical frequency nor one of amplitude, but a composite of the two expressed as a single quantity. Furthermore, the record gives no separate information about frequency, which has in the past been a major discriminant in EEG analysis. In this context it is important to remember, when looking at a record obtained from the cerebral function meter, that the undulations of the line do not represent EEG frequency, although superficially they look similar, due to the slow chart speed used. It must be the case that the expert neurophysiologist would gain more from studying the original electrical record, even from only two electrodes, but this is probably not true for the occasional EEG reader, which category would include almost all anesthesiologists.

Certainly, conventional EEG recording has never been widely accepted as a continuous monitor during surgery or intensive care, and a simplified approach such as this is necessary, so that the information available from recording brain electrical activity is not lost to the clinician when dealing with acutely-ill patients. It has also been found useful in supporting a diagnosis of brain "death," since it allows the electrical activity of the brain to be assessed over long periods.

In experimental, and in a few clinical, situations, e.g., during stereotaxic surgery, it is possible to record the electrical activity from groups of neurons deep within the brain, in contradistinction to the electrical activity of the cortical surface neurons, which is all that is reflected by the conventional EEG. Such recordings show unexpected changes in electrical activity in response to certain drugs, e.g., alphadione (Althesin), which produces marked electrical depression of the surface EEG and also causes increases in frequency in the hippocampal EEG of the cat. Such studies provide further evidence for the statement made above, that the action of anesthetic drugs is not simply one of depression of the brain but includes changes in the spatial pattern of electrical activity.

Other studies of neuronal electrical activity involve recording the electrical activity produced in response to repeated specific stimulation, visual, tactile, painful, or other. The electrical responses to such stimuli, "evoked potentials," are very sensitive to depressant drugs.

In order to "see" evoked potentials among all the other electrical activity recorded from an area of brain, it is necessary to repeat the specific stimulus many times. The electrical recordings are then superimposed, usually within a computer's memory, so that the "random" background activity is cancelled out while the electrical response to the stimulus is continually overwritten and reinforced. Such measurements tell much about the actions of drugs on neuronal circuits but, at least at present, play no part in clinical monitoring in the operating room or intensive care unit.

**Cerebral Blood Flow**

Many techniques for measuring cerebral blood flow (CBF) in man and in animals have yielded valuable information about normal physiology, about drug effects, and about pathologic changes in cerebrovascular control, but none has gained wide acceptance for clinical monitoring. The reasons for this are based on the one hand on the limited

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1 This section is, in part, an updated extension of an earlier review (McDowall, 1969). In the present paper fundamental principles have been dealt with only briefly in order to allow a fuller discussion of recent developments, especially those holding clinical promise. The reader interested in fundamental and theoretical details of CBF measurement techniques may wish to refer to the earlier review also.
value of measuring mean overall cerebral perfusion, and on the other, on the invasive nature of those methods that would provide valuable information about regional blood flow.

**INERT GAS-CLEARANCE TECHNIQUE BASED ON ARTERIOVENOUS SAMPLING**

This technique, introduced by Kety and Schmidt, yields values for mean cerebral blood flow for the area of brain that drains into the vein from which the venous blood samples are obtained. Since this is usually the jugular bulb, the flow result is a mean for virtually the whole of one hemisphere. This mean value conceals enormous differences among flows in different areas of brain (see fig. 4). During consciousness there are differences in flow among different areas of cortex that depend on the pattern of afferent input at the time of measurement. Deep grey matter nuclei have flow values that, in many cases, are considerably higher than cortical flow. Most important of all is the fact that most pathologic conditions produce regional alterations in cerebral perfusion pattern, and these differences are obscured in the mean value given by the Kety–Schmidt method.

The method does give information, however, about generalized changes in flow. For example, many of the important contributions on anesthetic drug effects from Philadelphia have been obtained with this method in slightly modified form. Generalized flow depression occurs in barbiturate overdosage and in coma following head injury, and the reduction in CBF correlates well with the depth of coma. These are but two of innumerable examples of the contributions of the Kety–Schmidt method to the understanding of CBF control in man that could be given but, even so, the information is not of immediate monitoring value.

The trauma to the patient in using the Kety–Schmidt method consists of cannulation of one artery (any artery) and one internal jugular vein. Since many patients in intensive care situations have arterial lines in situ, and since internal jugular vein catheterization by the retrograde route is simple and safe, the invasiveness of the technique is moderate and acceptable in many acute clinical situations.

**RADIOACTIVE INERT GAS-CLEARANCE TECHNIQUE WITH TISSUE RADIOISOTOPE COUNTING**

This method, introduced by Lassen and Ingvar, involves measurement of the rate of
clearance of a radioactive inert diffusible gas from brain tissue, after its injection as a bolus into the internal carotid artery. The gas used is commonly xenon-133, since it is an inert and diffusible gas that, as a gamma-emitting isotope, can be detected through the closed skull. It has another important characteristic, low blood solubility, so that 80 per cent is excreted during one passage through the lungs. This greatly limits recirculation of the isotope in the arterial blood, which would otherwise contaminate the brain clearance curves and result in falsely low values for CBF. The advantage of this method is that flow can be measured regionally within the brain by suitable positioning and focussing of the radioisotope detectors (fig. 5). Some centers employ as many as 32 detectors, and others use the gamma camera in order to visualize the regional pattern of CBF (rCBF). Most clinically apparent pathologic conditions are regional and produce regional, often in addition to generalized, changes in cerebral perfusion. For example, a patient who has recently sustained a head injury may have areas of high perfusion induced by local tissue acidosis in areas of contusion, while the surrounding brain may have depressed perfusion resulting from the generalized depression of cerebral function. Of course, merely knowing that an individual patient who has a head injury has areas of high and low CBF does not necessarily contribute to his clinical management (though the information may have prognostic implications), but this regional CBF method can be used to determine whether, in an individual patient, particular therapeutic measures produce improved perfusion in low-blood-flow areas or not. Such information could be of great value.
in the clinical management of many patients, since studies to date show that the effects of various therapeutic techniques vary in an unpredictable way from patient to patient, e.g., the occurrence of inverse "steal" with hyperventilation.\(^{37}\)

There is one serious technical problem with the application of this technique to areas of disease, since the solubility of xenon-133 in diseased brain tissue is not known. For this reason some investigators quote their results in abnormal areas of brain as "rates of xenon clearance" and do not attempt to make calculations of blood flow values. Another technical difficulty that arises is in lesions of very low vascularity is that the absence of radioactivity in a brain area may allow the detector to "see through" to underlying white and deep grey matter. It is very easy for the clearance from such a detector to be misinterpreted unless one knows from angiography that this possibility exists.

The radioactive inert gas-clearance technique has been extensively used for diagnostic and investigative work, often in association with cerebral angiography, but it cannot be regarded as a routine monitoring technique because of the need for internal carotid injection of the isotope. Repeated puncture of the carotid artery is not desirable, and indwelling catheters carry the risk of embolus formation. Since it is clear, however, that the ability to measure rCBF repeatedly would be of considerable clinical value, much interest centers around the inhalational modification of the radioactive inert gas-clearance technique.

**Inhalational Modification of the Radioactive Inert Gas Clearance Technique**

Soon after the introduction of the radioactive inert gas-clearance technique, several groups began work on the problems of an "atraumatic" inhalational technique to avoid the necessity of intracarotid injection.\(^{28,29}\) The problems with the inhalational method of administration include: 1) the radioactive gas is distributed to all tissues of the body so that, at the end of the period of inhalation, significant amounts of radioactivity return in the venous blood to the lungs and, in the case of xenon, 20 per cent of this recirculates in the arterial blood to "contaminate" the brain clearance curves; 2) at the end of inert gas inhalation, alveolar gas contains a large amount of radioactive xenon, which washes out in the usual exponential fashion so that there is not the square-wave end in the brain input of radioactivity that is achieved by arterial bolus injection; 3) at the end of inert gas inhalation there is considerable radioactivity in the upper airway, and this radioactivity may interfere with radiosotope clearance measurements from some of the frontally-placed counters; 4) among the tissues that receive radioactive gas during inhalation are the skin and muscle of the scalp, which lie between the detectors and the brain; 5) the radioactive count rates are lower over the brain with inhalational, compared with arterial, input of the tracer, so that the counting fields must be wider, with consequent loss of regional discrimination.

In order to reduce these problems, Obst and colleagues\(^{30}\) have studied over a number of years different durations of inhalation of the radioactive gas and different periods of counting after the end of inhalation of the gas. On the basis of this experience, they recommended a short period of inhalation (1 min) to reduce the radioactivity distributed to relatively slowly-perfused tissues. This is followed by a 10-minute recording of clearance which is analyzed as a two-compartment clearance. Although the second compartment is in fact a mixture of several rates of clearance, including those of white matter of brain and muscle of scalp, this method gives values for the first, or fast, component that agree well with those obtained by the arterial-injection method.\(^{31}\) Before this curve analysis can be done, however, it is necessary to apply a correction for arterial recirculation of the isotope, which is obtained from a counter in the expired-air line that monitors end-tidal xenon activity. As a result of progress in dealing with these technical problems, the inhalational method is being used increasingly for repeated measurements of CBF in acute situations.\(^{41,42}\)

An alternative atraumatic method involves intravenous injection of the radioactive gas.\(^{8,31}\) This method has problems virtually identical to those of the inhalational method,
since a large amount of radioactive gas enters the alveolar gas and the remainder is distributed widely throughout the body.

**Carotid Artery Measurements**

When all the problems of the inhalational xenon-clearance method are solved, the clinician will have an atrumatic method for making repeated measurements of CBF, but it will never provide a continuous monitor of CBF: for that we have to turn to carotid-artery measurements. Flow in the internal carotid artery can be continuously measured with a flow probe placed around the artery, using either the electromagnetic or the ultrasonic principle. This requirement for probe placement obviously seriously limits the applicability of the technique, so attempts have been made to measure carotid-artery flow with an ultrasonic detector placed on the skin surface overlying the artery, but quantification of such records is difficult, though progress has been made.

Methods of carotid flow measurement have an additional major limitation: they measure flow in the monitored artery only. Of course, in normal man most of this flow is destined for cerebral perfusion, but it may not be so in pathologic situations such as carotice cavernous fistula. Furthermore, even in normal man, the proportion of cerebral perfusion supplied by one carotid artery may vary because of the efficient collateral circulation in the circle of Willis. In any event, no information about regional perfusion in the brain is obtained from carotid-artery measurements. Such measurements are useful during carotid-artery surgery.

During such operations as carotid thrombendarterectomy and carotid ligation, the adequacy of cerebral perfusion is sometimes assessed not from direct flow measurement, but by measurement of the blood pressure in the internal carotid artery above a temporary occluding ligature. This pressure, distal to an occlusion, is the "carotid stump pressure." Stump pressures close to systemic arterial pressure correlate with satisfactory cerebral perfusion, while low stump pressures tend to be associated with poor perfusion. For example, Trojaborg and Boysen found that a stump pressure of less than 50 mm Hg was accompanied by EEG slowing and low cerebral blood flow. This relationship between stump pressure and flow is not very precise, however, since stump pressure depends on carotid vascular resistance as well as on flow, and furthermore, a satisfactory stump pressure may indicate adequate mean flow in the area of distribution of one carotid artery, but it may not reveal focal areas of low flow.

**Other Flow Measurement Techniques**

Most other techniques are limited in their application to animal experiments but, under special circumstances, some may be applicable to man. For example, local CBF measurement by heat clearance, which requires the placement of probes on or in the brain, has been used in patients. The number of instances when such methods can be used is too limited to warrant a full description here.

**Cerebral Metabolism**

When CBF is known, cerebral metabolism can be calculated as the product of CBF and arteriovenous difference for any metabolite, provided the venous concentration of that metabolite is in equilibrium with brain tissue. For the brain, the venous blood sample is usually obtained from the jugular bulb. For such a calculation to be valid, the CBF value and the metabolite concentrations in the venous blood must refer to the same territory of brain, and this condition is rigidly fulfilled only when CBF is measured by the Kety–Schmidt technique. However, many results have been obtained using radioactive gas-clearance flow values, and this is acceptable provided the following conditions are fulfilled: 1) perfusion over the cortical grey matter is fairly uniform, e.g., during halothane anesthesia; or 2) radioactive gas clearance is measured by a widely-collimated detector that "sees" virtually the entire hemisphere ipsilateral to the sampled jugular vein; or 3) regional flow values are available for many areas, covering among them the entire hemisphere. The difficulty in using radioactive gas-clearance flows for metabolic calculations is greatest when tCBF varies widely among regions, as it often does in diseased brain. In such circumstances, the contribu-
tions of different regions to the venous blood sample are unknown.

Values obtained from calculations based on the product of CBF and AV metabolite difference are, in fact, measurements of brain uptake or output of the metabolite in question. Uptake can be considered equal to consumption, or output equal to production, only when there is rapid equilibration between brain and blood concentrations and when brain stores of the metabolite do not change during the period of measurement. These criteria are most fully met when measuring oxygen uptake, for oxygen diffuses rapidly and brain storage is negligible. Measurements of CO₂ output and glucose uptake are usually accepted, but lactate and pyruvate measurements are more questionable, since there is a considerable delay in the transmission of these substances across the blood-brain barrier and brain stores can fluctuate widely in short periods.

An additional difficulty in measuring metabolic modalities in this manner is the large number of measurement errors that are multiplied together in these calculations. In this context it is pertinent to point out that duplicate measurements of CBF under steady-state conditions in the same subject can differ by 20 per cent. There are also, of course, analytical errors in the measurement of blood metabolite concentrations, and these are compounded by the subtraction of venous from arterial values. The consequence of all this is that, in any individual patient, sequential measurements of metabolic activity must show large changes before the differences can be accepted as real. The problem is reduced when dealing with pooled data, but that is not the situation in clinical monitoring.

Despite these limitations, it has been stated: "As clinical experience with measurements of regional cerebral blood flow (rCBF) and cerebral metabolism continues to accumulate, it is ever more apparent that there is poor correlation between CBF and neurological status, and between CBF and survival. In contrast, there is a much better correlation of neurological status and prognosis with cerebral metabolic rate for oxygen (CMRO₂)."

Jugular venous blood samples have been used without CBF measurement for monitoring brain function. In particular, jugular venous blood oxygen tension or saturation has been measured to detect cerebral hypoxia during such situations as carotid clamping and deliberately-induced hypotension. The normal value is 40 mm Hg at 17-19 mm Hg produced by systemic hypoxia, unconsciousness supervenes. However, jugular venous blood P_O₂ appears to be an unsatisfactory measure of the adequacy of brain oxygenation in ischemic situations, in that venous blood P_O₂ is often well-maintained although ischemia is present. The mean jugular venous blood P_O₂ is an average of P_O₂ values in many brain areas. Poorly-perfused areas will contribute little blood to the venous sample, and so will be underestimated in the mean jugular venous blood P_O₂.

Arteriovenous differences, in the absence of flow measurement, have been used as "indices" of perfusion or metabolism. Such indices have to be treated with great caution, since, as the concentration of any metabolite in venous blood depends on both flow and metabolism, it is an independent measure of neither. This condemnation is too sweeping, however, in that arteriovenous oxygen differences can be used as measures of CBF in circumstances of unchanged cerebral function over short periods, and very wide AV differences for O₂, CO₂ or glucose provide reasonable evidence that CBF is depressed.

The adequacy of oxygenation and perfusion of the brain has also been assessed from measurements of P_O₂ and acid-base status of cerebrospinal fluid. CSF can be obtained from one lateral ventricle, particularly when a ventricular catheter is in position for ICP measurements, from the cisterna magna rarely, and from the lumbar sac (except in patients with intracranial space-occupying lesions, in whom lumbar puncture is dangerous).

The P_O₂ of CSF is modified as CSF moves along the CSF pathways. In the lateral ventricle, P_O₂ is highest and is much influenced by the P_O₂ of arterial blood due to oxygen transfer at the vascular choroid plexuses. In moving from the ventricle to the cisterna magna, the CSF comes into close contact with brain-tissue extracellular fluid, so that P_O₂ of cisterna magna CSF probably bears the closest relationship to mean brain-tissue oxygen tension of all possible CSF samples. A further reduction in CSF P_O₂ occurs between...
Fig. 6. The pressure–volume curve for the intracranial space. The continuous line is a diagrammatic representation of the changes in ICP that occur as a space-occupying lesion grows within the intracranial space. The relationship between pressure and volume has been divided into three phases: phase I, the compensated phase; phase II, the decompensated phase; phase III, the intermediate phase, where the situation is critically balanced. The peaks in phase I represent the effects of administration of halothane at different stages during the development of intracranial compression. (Reproduced from Scott C. Feldman SA (editors); Scientific Foundations of Anaesthesia. London, Heinemann Medical Books Limited, by permission of the editors and publisher.)

the eisterna magna and the lumbar sac. Similar comments apply to CSF $P_{cv}$, but the changes are in the opposite direction, of course. Cisternal CSF may, therefore, provide an estimate of mean brain tensions of oxygen and carbon dioxide. A low cisternal CSF $P_{cv}$ or a high $P_{cv}$ in relation to the arterial values implies inadequacy of cerebral perfusion.

Indeed, the CSF values may be a truer reflection of brain-tissue conditions than jugular venous blood $P_{jv}$ or $P_{cv}$, because poorly-perfused tissues contribute little blood to venous samples.51,68 Furthermore, in certain conditions diffusion shunts may exist in the brain, i.e., oxygen may diffuse from the arterial end of one capillary to the venous end of an adjacent one, thereby bypassing certain parts of the brain tissue. When such shunting occurs, venous blood $P_{jv}$ gives an erroneously high value for mean brain oxygen tension. This possibility is more likely in circumstances of low perfusion and increased intercapillary distances, as is the case in cerebral edema, especially when $P_{jv}$ is high, since this aids diffusion. Interesting studies related to this point, in which large differences between jugular venous blood $P_{jv}$ and CSF $P_{cv}$ were observed, have been reported by Gordon and Rossana.60,67 These authors ascribed the differences to better equilibration of CSF with brain tissue, compared with blood, in pathologic conditions involving cerebral edema.

The lumbar sac is the commonest site for CSF sampling in clinical practice, but the $P_{cv}$ of lumbar CSF is lower than that of cisternal CSF and the $P_{cv}$ higher. Furthermore, there are considerable delays in the transfer of alterations of $P_{cv}$ or $P_{cv}$ to the lumbar CSF. i.e., lumbar CSF $P_{cv}$ lasts 10–20 min behind a change in the cisternal value.53 Nonetheless, under steady-state conditions lumbar CSF $P_{cv}$ and $P_{cv}$ may relate to conditions in the brain, but such steady-state conditions would rarely occur in critically-ill patients.

Probably the most valuable measurements to be made on CSF samples are those relating to non-respiratory acid–base status, including lactate and lactate–pyruvate measurements. CSF is obviously on the brain side of the blood–brain barrier to hydrogen and lactate ion diffusion, so CSF measurements may give information about brain-tissue oxygenation and perfusion that is not available in venous blood samples. A low CSF bicarbonate, together with a high lactate value, especially when combined with a high lactate: pyruvate ratio, may indicate brain-tissue ischemia. Such deviations in CSF values have been reported to occur in many clinical conditions, including head injury.56–59 In these studies most measurements were made using lumbar CSF samples and the results were interpreted as indicating changes in cerebral perfusion and/or metabolism. Such inferences are probably acceptable in steady-state conditions, but in acutely-ill patients discrepancies between lumbar and cisternal CSF pH's have been observed, thus making it unwise to rely on lumbar CSF measurements as indicators of brain conditions.56,69 Overgaard and Tweed,56 however, have reported CSF acidosis in ventricular CSF following head injury.

Intracranial Pressure

Great interest in intracranial pressure (ICP) measurement has been initiated by the work
of Guillaume and Janny\cite{21} and Lundberg\cite{22} Measurement of intracranial pressure gives information about the state of intracranial compression produced by space-occupying disease states, whether hemorrhage, tumor, or edema. It is also employed in assessment of patients who have abnormalities of CSF formation, absorption or circulation.

To understand the relationship between ICP and intracranial compression, which is not a simple one, it is necessary to understand the intracranial pressure-volume curve, which has been described in many recent publications (e.g., McDowell).\cite{23} A simplified diagram of the relationship is shown in figure 6, which demonstrates the three portions of the curve: an initial compensated portion in which intracranial pressure rises little with expansion of the space-occupying lesion; a terminal phase in which intracranial pressure rises very steeply, with little change in volume of the space-occupying lesion, and an intermediate stage of progression from the compensated to the uncompensated condition. During phase I intracranial compliance progressively decreases, so that a sudden expansion of the volume of any one of the intracranial compartments, blood, brain, or CSF, leads to an increase in ICP that is related to the position in phase I of the pressure-volume curve occupied by the particular patient. This is demonstrated by the superimposed peaks on the diagram. This decreasing compliance of the intracranial space accounts for the accentuation of the ICP-increasing effect of volatile anesthetics in patients who have space-occupying lesions.\cite{24}

Without deliberately testing compliance, the clinician cannot tell where any individual patient is in phase 1 of the pressure-volume curve, since the resting ICP may not be greatly elevated. Miller and colleagues\cite{25} have introduced a standard test for intracranial compliance, in which 1 ml of fluid is quickly added to, or withdrawn from, the ventricular CSF and the ICP change observed. This simple test has some technical problems, however, because of the rapidity with which the resultant ICP changes occur, so that it is easy to miss the peak pressure achieved.

There is one additional important feature of ICP measurement: as the intracranial contents become compressed, abnormal waves of ICP appear on the record. These have been characterized by Lundberg\cite{26} as A, B, and C waves. A waves are large elevations of ICP, commonly to 60–80 mm Hg, of at least 20-min duration; B waves are smaller and occur at frequencies of ½–2 cycles/min, often related to Cheyne-Stokes breathing, and C waves occur at about 6/min, related to variations in blood pressure. The appearance of any of these waves indicates significant intracranial compression, and their early detection may be important for treatment, especially as they are associated with worsened prognosis.\cite{27}

ICP can be measured with a catheter in one lateral ventricle; alternatively, measurements can be made in the surface subarachnoid space, in the subdural space, or in the extradural space. Catheters in these spaces have been used, but they tend to become blocked, so that various types of hollow holst have been used, the thread of the bolt providing a seal with the skull.\cite{28} Thin-walled balloons are very satisfactory for pressure measurements in the surface subarachnoid space, but less so in the extradural space.\cite{29} Transducers have been implanted in the subdural\cite{30} and extradural spaces,\cite{31–38} and in some of them the problems of zero drift and calibration shift, and fluid penetration of the diaphragm, appear to have been solved. The advantages of extradural, compared with ventricular, fluid pressure measurement are compared in table 1.

Of the disadvantages of ventricular measurement, the most serious is the possibility of introducing subarachnoid infection which, according to Lundhag and colleagues,\cite{39} occurs in 1 per cent of cases. In addition, some ventricular catheters cease to give good recordings due to damping, as a result of blockage, or due to movement of the catheter out of the ventricle.

There are two main problems with extradural recordings. The first is that the extradural pressure overreads the ventricular pressure, especially at high intracranial pressures.\cite{32–35} The second applies only where a transducer is inserted into the extradural space, for when its pressure-sensitive diaphragm is not coplanar or parallel to the dural surface dural stretching will affect
the pressure measured. Subdural and surface subarachnoid measurements are reliable with suitably-designed equipment, but they have the same infection hazard as ventricular measurements. There is a place for such measurements, however, when difficulty is experienced in locating the ventricle and the dura has already been opened. Only with the ventricular catheter can CSF samples be obtained for acid-base measurement.

Measurement of ICP is of value in the management of the acute stage of severe head injury, because it gives early warning of edema or intracranial bleeding. It cannot distinguish between the two, but this distinction may in the future be possible using computer-assisted tomography. At present, in many centers differentiation has to depend on cerebral angiography and/or on exploratory burr holes. In the early detection of intracranial bleeding it should be remembered that clinical signs are late in appearance, often resulting in a dramatic last-minute surgical exploration. The combination of ICP measurement and computerized tomography should allow much earlier diagnosis and treatment.

The second major contribution of ICP monitoring is in the management of cerebral edema, by such techniques as hyperventilation, dehydrating therapy, and steroids. It is possible to manage cerebral edema without ICP measurement, just as it is possible to perform cardiac surgery without an intra-arterial line, but no-one would choose to do either having previously experienced the benefits of monitoring. The third advantage is in the general care of the patient. ICP monitoring helps in determining the best pattern of mechanical ventilation, particularly when positive end-expiratory pressure (PEEP) is employed. The optimum head-up tilt can be ascertained, and nursing procedures can be carefully done while referring to the ICP changes produced, e.g., during turning patients with injured limbs, when careless handling can produce sudden increases in blood pressure and ICP. Chest physiotherapy, particularly when done with the patient in the head-down position with intermittent manual hyperventilation of the chest, can markedly increase ICP, but it can also be done with minimal ICP changes if the ICP is continuously displayed, for the physiotherapist can time percussion coughing appropriately. Finally, sedation therapy, aimed at suppressing convulsions, can be logically and safely administered.

Some consideration should be given to the best method of displaying ICP at the bedside. Digital display is preferable to analog presentation of ICP, in my experience, because it is more readily accepted by nursing and physiotherapy staff. The nursing staff should record the ICP from the digital display in the patient's standard record chart; this ensures that the nurse actually reads the ICP value at regular intervals.

This is a satisfactory basic method for incorporating ICP measurement in routine clinical monitoring, but it does not provide all the information that is available from the recording, for ICP waves may be missed and the distribution of ICP is not considered. By distribution I mean the scatter of ICP pressures about the mean, or better, the modal value. In the normal subject the distribution of pressures about the modal value is narrow, showing a "normal" distribution. At an early stage of intracranial compression there is a shift of this distribution, so that it becomes "skewed" to the high-pressure end of the recording, and it may be that this abnormal
displacement of ICP distribution in relation to modal pressure precedes any major change in mean ICP. In order to explore this possibility, several groups have studied the use of frequency histograms of ICP, in which the ICP measurements are divided into class intervals, the frequency of measurements in each class being displayed for a certain period of observation.

The system being assessed in Leeds currently is to record the ICP data on magnetic tape and to transmit the information at regular intervals from the tape to a desk-top calculator, which does a frequency analysis and outputs a frequency histogram to either an X-Y plotter or an oscilloscope screen (fig. 7). The oscilloscope used has sufficient memory capacity to hold the previous four histograms of ICP, each representing 30 min of recording. Thus, a nurse or doctor can study the recent 30-min frequency histogram at any time and, at the press of a button, compare it with previous histograms. Also stored is a normal histogram for comparison. It is hoped that in this way early changes in the distribution of ICP will be detected by relatively inexperienced personnel. The method also shows very clearly the appearance of pressure waves, which appear as a separate group of data points on the frequency histogram.

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