

## Calibration of clinical cerebellar and deep brain stimulation systems

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**SUMMARY** The increasing use of electrical stimulation of the brain for relief of pain, spasticity and epilepsy has introduced unfamiliar techniques into clinical neurological and neurosurgical practice. In view of the evidence that excessive levels of stimulation can damage brain tissue, it is of great importance to monitor the dose of stimulation. A review of recent clinical papers suggests that many centres do not measure the dose accurately, relying on arbitrary dial settings on external transmitters. This paper reviews the factors that affect the dose received by the patient and suggests methods of measuring them, at operation and subsequently, which should routinely be employed by clinicians implanting stimulators.

In the past six years electrical stimulation has been applied to the cerebellum, periaqueductal grey matter, cerebral cortex and basal ganglia in order to treat a variety of clinical disorders. The charge transferred per second is much higher than for cardiac pacing and therefore nearly all the implanted stimulators to date have required an external energy source. This is provided by a battery-powered pocket radiofrequency (RF) transmitter that transmits high-energy RF pulses through the skin to an RF receiver implanted in the patient (fig 1). The transmission is effected by an antenna taped over the skin in a convenient site, usually the anterior chest wall. The implanted receiver is connected by wires to the electrode which is surgically placed on its target in the brain.

The stimulating electrodes consist of a number of platinum-iridium buttons or loops of wire, which can be connected in various combinations to the implanted receiver. The output of most of the receivers is of constant polarity—that is to say, one output wire is the cathode and the other is the anode. This means that the position of the cathode and anode on the tissue is fixed. Initially, all stimulating electrodes were bipolar. The leads to the anode are more prone to corrosion and failure in the body than the leads to the cathode

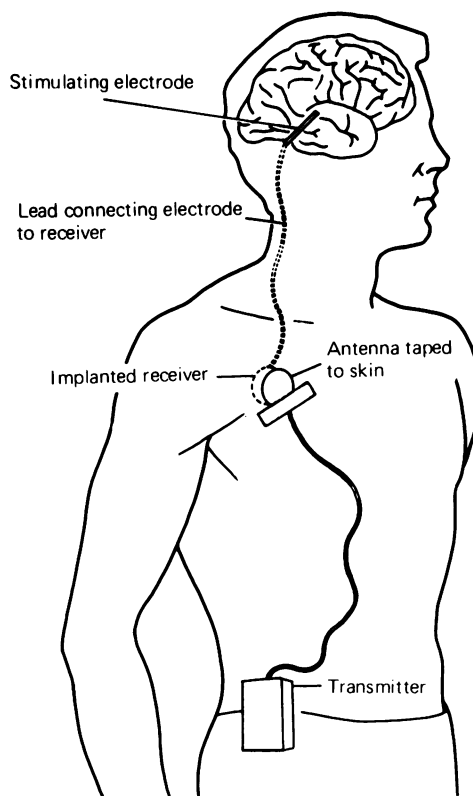


Fig 1 *Diagram of implanted and external components of a brain stimulation system.*

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(Mr R Avery, personal communication). Recently, anode plate electrodes have become available. These are usually implanted near the receiver and the stimulating electrodes on the brain may all then be cathodes. Alternatively, the anode plate may be incorporated into the receiver itself, abolishing the risk of lead failure to the anode. Also available is a receiver that “flip-flops” or alternates the polarity of the pulses given out, so that each pole of the electrode acts as anode and cathode in turn. This facility is a function of the construction of the implanted receiver and it cannot be altered by changing the transmitted radio-frequency signal.

#### FACTORS DETERMINING DOSE OF STIMULATION DELIVERED

The factors that determine the amount of neural tissue stimulated or damaged are the size of the electrode, the electrode current, the charge transferred per stimulation pulse and the precise shape of the stimulus pulse waveform which must not contain a net DC component. All manufacturers use similarly shaped capacitatively-coupled waveforms. If other stimulus generators are used (for example, while calibrating the equipment during implantation), the pulse must be balanced to prevent ionisation and tissue damage at the interface between the electrode and the tissue.

**Electrode current** The peak current flowing during a stimulus pulse is determined by the voltage applied across the electrode and the access resistance of the electrode-tissue combination. If the voltage is held constant and the access resistance falls, which it may do in the months after implantation, then the current will increase. However, implanted receivers now available for brain stimulation do not hold their voltage constant in the face of a changing load or access resistance. Thus, the current change is less than one would expect from a simple calculation using Ohm's Law. The receivers sold for brain stimulation (in contrast to the Avery phrenic nerve system) produce an output that is determined by only two factors—the amplitude of the RF signal they receive and the access resistance of the electrodes to which they are connected. Both these factors have to be measured at the time of implantation since they cannot be measured once the receiver has been implanted.

**Charge density** The other factor that determines the effect of this current is the length of time for which it passes. A pulse of say 50  $\mu$ s is too short to activate most neurones at the current levels used, and the pulse widths that appear most

effective range from 0.2 to 0.5 ms. The degree of tissue damage is determined by the charge per phase, or to be more precise the charge *density* per phase.<sup>1</sup> The charge per phase is the product of the current and the duration of each pulse. The charge *density* takes account of the area over which this charge is distributed and is the charge divided by the surface area of the cathode. Calculations based upon the geometric (measured) surface area may be misleading because the effective surface area of the electrode may be several times bigger due to pitting and irregularity of the surface of the metal from which the electrode is made. It follows that the “dose” or charge density per phase is determined by the surface area of the electrode in contact with neural tissue, the current flowing during the pulse and the duration of the pulse. The duration of the pulse is determined by the duration of the radio-frequency pulse and can be altered by adjusting the transmitter.

**Coupling** The efficiency of “coupling” (transmission from antenna to receiver) alters if there is a change in thickness of the subcutaneous tissue overlying the receiver, if the receiver migrates in the tissue, and particularly if its axis tilts in relation to the plane of the skin. The RF signal reaching the receiver is critically dependent upon correct positioning of the antenna.

**Transmitter function** Even when these factors remain stable, the transmitter itself may not produce an effective RF signal because of a faulty antenna, a flat battery, an internal fault or incorrect adjustment.

#### CALIBRATION OF THE IMPLANTED SYSTEM

The implanted electrodes will, in practice, be driven by the patient's RF transmitter and the first step is therefore to check the calibration of this transmitter.

##### 1 *Standardisation of the transmitter*

The RF signal can itself be monitored by feeding the output to an oscilloscope, but the most convenient method (which provides a concurrent check of antenna function) is to take a spare receiver and use it as a laboratory standard. It can be laid upon a bench top (*not* a metal surface, which will deflect and absorb the RF signal) or embedded in plastic (fig 2), with the antenna placed over it at a fixed distance away. The output of the receiver can now be connected to a known resistance (the present convention is to use 1,000 ohms). The voltage across the known resistance can be measured using an oscilloscope. If

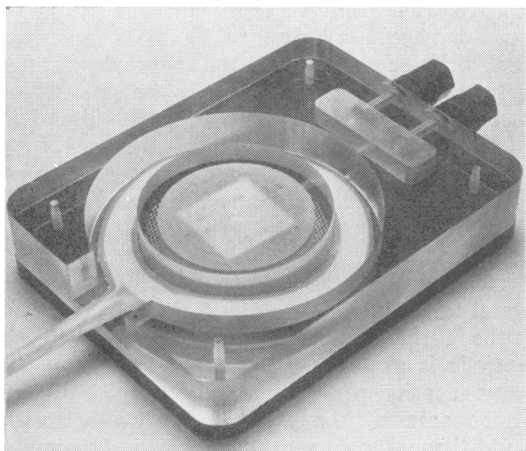


Fig 2 Receiver mounted in a block for calibration of transmitters. The antenna sits in a groove in the surface of the block. The output terminals of the receiver are wired to the sockets at the far end of the block (by courtesy of Avery Laboratories Inc).

RF components obscure the edge of the signal, they can easily be eliminated by connecting a small capacitance (for example 0.02 pF) in parallel with the resistance. The amplitude dial of the transmitter can now be standardised against the bench system and recorded. The frequency and pulse width settings can be checked at the same time. A typical waveform is seen in fig 3.

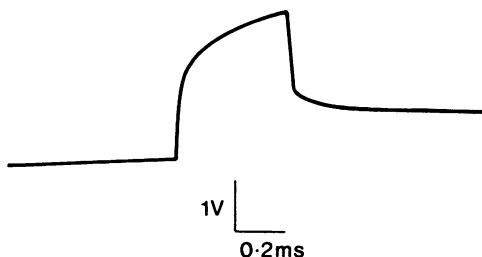


Fig 3 Voltage waveform of a single pulse recorded across the terminals of an electrode pad driven from an implanted receiver. If the peak current is known, the access resistance can be assessed with reasonable accuracy by measuring the voltage drop along the vertical or near-vertical portions of the waveform, in this case approximately 1.8 v.

## 2 Calibration of transmitter in terms of electrode current

In the operating theatre, the electrodes are implanted, the receiver is inserted into its subcutaneous pocket and the interconnecting wires tunnelled between them. Before finally connecting the

electrode to the receiver, a small and accurately known resistance (for example 10 ohms) is temporarily connected in series with one side of the circuit (fig 4). This is conveniently done using

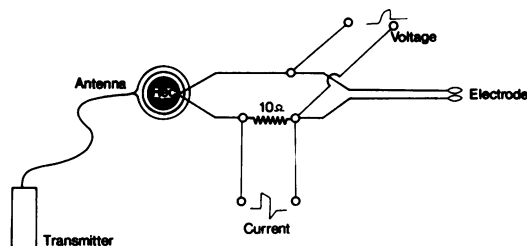


Fig 4 Circuit diagram of the intra-operative calibration system. The inserts show the shapes of the voltage waveforms seen on an oscilloscope across a 10 ohm resistor in series with the electrode (from which the electrode current can be calculated) and the electrodes themselves, from which the access resistance of the electrode-tissue interface can be calculated once the current is known.

sterilised wires with plugs appropriate to the system that is being used. The resistor must be of a specification that allows it to withstand sterilisation, unless it is retained outside the operative field. A sterilised antenna can now be held against the skin directly over the implanted receiver (fig 4) and activated by the transmitter, standardised as above, that the patient will later be using. The voltage drop across the resistor can be measured with an oscilloscope and from this the current can be calculated using Ohm's Law:  $\text{Current} = \text{Voltage} \div \text{Resistance}$ . Because of the risks of current leakage from oscilloscopes, the connection should be made via an optical isolator or micro-ampere circuit breaker. The shape of a typical waveform is shown in fig 5. The dial on the



Fig 5 Voltage waveform of a single pulse recorded across a 10 ohm resistor in series with electrode. The vertical section of the waveform indicates the voltage across the resistor while peak current is flowing, in this case about 18 mV, indicating a peak current of 1.8 mA.

patient's transmitter can now be calibrated in terms of electrode current for that particular electrode.

### 3 Measurement of access resistance of the electrode-tissue combination

Knowledge of the access resistance can provide useful confirmation of a satisfactory contact between the electrode surface and neural tissue. Access resistance varies from approximately 350 ohms for the Avery 8-button plate electrode to approximately 750 ohms for the Medtronic deep brain electrode. Much lower values than those shown imply short-circuiting of the current, while much higher values suggest breakage of a lead wire.

Measurements of the potential across the electrode itself (fig 4) gives a "voltage waveform." When determining the access resistance, the sharply rising or sharply falling phase of the waveform is used for measuring the voltage applied across the electrode (fig 3). The current is already known (Step 2, above) and the access resistance can thus be calculated using Ohm's Law. For the reasons given above, the oscilloscope must not be connected directly across the patient's electrode. Electrical isolation or another appropriate safety device is required.

It should be noted that the true access resistance of monopolar electrodes, driven by a receiver with an integral anode plate, cannot be measured because the anode half of the circuit is sealed. In this case only the electrode current can be measured directly. An approximation to the effective access resistance can nevertheless be obtained by activating the monopolar electrode during implantation using an independent power source with a separate anode.

This sequence of tests will provide measurement of electrode access resistance, and full calibration of the transmitter in terms of electrode current. It will also have confirmed that the implanted equipment is fully functional, for if a wire has been broken during implantation the appropriate waveforms will not be obtained.

## MONITORING THE FUNCTION OF THE STIMULATING SYSTEM FOLLOWING IMPLANTATION

### 1 X-ray

It is our practice after implantation to obtain a radiograph of the entire implanted system. This helps to detect subsequent displacement of the electrode or receiver and facilitates the identification of any subsequent breaks in the lead wires.

### 2 Measurement of field potentials arising from activation of the electrode

Monitoring the level of stimulation of the cerebellum is more difficult than monitoring stimulation of the spinal cord or peripheral nerves because most patients cannot detect the onset of stimulation. The therapeutic results that accrue are occasionally noted within hours but more often in weeks or even months. Charges could therefore be delivered to brain tissue (especially cerebellar cortex where higher currents tend to be used) at levels that might damage the tissue. This makes the initial operative calibration all the more important. During follow-up, some kind of external measurement system has to be applied to confirm that the transmitted RF signal has been demodulated by the implanted receiver and transmitted to the electrodes. Activation of the electrodes produces a field potential which can be recorded at convenient sites in the body. We have chosen the nasion and the pre-auricular points which give satisfactory signals but these sites are arbitrary; the important fact is that reliable measurements can be made repeatedly from the same sites. Using silver-chloride disc electrodes (of the type routinely used for EEG recordings) potentials are obtained having a waveform similar to that of the current waveform shown in fig 5. It is essential to check the impedance of these electrodes before measurements of field potentials are made. The recording amplifier must have a high-impedance, low-capacitance input in order to reproduce the waveform without distortion.

One factor that may complicate this measurement is an RF artefact derived from the transmitted signal itself. This is rarely a source of error with receivers producing pulses of alternating polarity because the RF artefact has a constant polarity but with monopolar receivers, careful scrutiny of the oscilloscope signal may be required to detect the artefact, since it is exactly superimposed upon the electrode field potential. The presence of an artefact can be demonstrated by relocating the antenna over distant tissue. Any signal recorded cannot then be due to activation of the implanted electrode. If the artefact persists despite good skin contact with the recording electrodes, the high frequencies may need to be filtered from the recorded signal, taking care not to distort the shape or amplitude of the signal by excessive filtering.

### 3 Mapping

This term was introduced by Sedgwick and

Renouf<sup>3</sup> to describe the process by which current leakage may be detected and located when a subcutaneous lead wire fractures. Although their technique is described in relation to spinal cord stimulators, the principles are exactly the same when applied to brain stimulators. Difficulty may be experienced with deep brain stimulators because the applied voltages are eight to 10 times smaller than with cerebellar stimulation, thus producing field potentials that may be considerably smaller than the RF artefact.

#### ROUTINE TESTING BY THE PATIENT

Most transmitter systems include an antenna testing circuit. Alternatively, the antenna may be held near a transistor radio and buzzing interference is heard when the transmitter is turned on. However, intermittent faults are often missed by these means. Any evidence of corrosion (green staining) of the antenna cable means that the antenna should be discarded, even if it appears to be functioning. The practice of testing the system by turning up the strength of stimulation until headache develops is strongly to be deprecated.

#### BIOCALIBRATION

This term was introduced by Upton and Cooper<sup>4</sup> who suggested that stimulation produced certain physiological changes that could be used to calibrate the charge delivered. Bursts of cerebellar stimulation may alter the amplitude of electromyographically recorded reflexes and of somatosensory or auditory evoked potentials. This attractive idea has proved disappointing in use, because many patients do not show these physiological changes. Furthermore, patients who initially show them may later fail to do so, even when their equipment is working normally and the therapeutic effects of stimulation are being maintained. No proof has yet been presented of any relationship between the amplitude of stimulation needed to produce immediate physiological effects and the amplitude of stimulation needed to control symptoms. It is very likely that different mechanisms are involved in these two processes, since the time course of clinical changes tends to be very much longer.<sup>5</sup>

The charge levels originally used by Cooper's group were of the order of 10–15  $\mu\text{Coul}/\text{cm}^2/\text{phase}$ . Bipolar 8-button electrode pads with a current path at right angles to the long axis of the electrode were employed. More recently, Davis's group has claimed equally good results with monopolar cathodal stimulation using charge levels of approximately 0.8  $\mu\text{Coul}/\text{cm}^2/\text{phase}$ ; charge levels of approximately 4–5  $\mu\text{Coul}$  are said

to be *less* effective in their system.<sup>6</sup> Unfortunately, these are ex-cathedra statements unsupported by objective evidence or by controlled trial. Experimental evidence to date indicates that the threshold for tissue damage produced by stimulation (as opposed to that produced by the presence of the electrode in the brain) is a charge density of 20–40  $\mu\text{Coul}/\text{cm}^2/\text{phase}$ .<sup>1</sup>

#### Conclusion

Electrical stimulation of the brain is now taking place in several thousand patients throughout the world but any reference to operative calibration in published papers is exceptional. The long-term effects of brain stimulation in man are entirely unknown and it will be essential, during the continuing evaluation of the therapeutic and unwanted effects of the technique, to correlate these effects with the dose of stimulation that has been given. Only time and careful measurement will tell whether these levels are safe for use in humans over the many years for which electrical therapy is likely to be applied.

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