Part I

Scientific and experimental bases of electroconvulsive therapy

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Electricity and electroconvulsive therapy

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Information about electricity helps ensure electroconvulsive therapy (ECT) safety and efficacy and limit side effects. It bears on seizure generation, stimulus dose, and stimulus efficiency. Efficiency refers to how stimuli of the same dose differ in generating seizures or side effects. Although electricity specific to ECT is our focus, regular safety practices should be used. Do not use frayed cables or electrical equipment that is or was wet, do not pull on wires, and avoid becoming part of an electrical circuit by contacting the patient at more than one place during the stimulus.

Basic electrical facts and safety

Electricity, the flow of electrons, is basically specified by its current and voltage, and how they vary with time. "Current" is the number of electrons flowing per second. Amperes ("amps") are electrons per second multiplied by a conversion factor. "Voltage" is the electrical force that pushes these electrons to flow. "Charge" is the number of electrons passing during the period of interest; if current is constant, charge equals current multiplied by time. In an analogy between electron flow (electricity) and water flow, current is analogous to water volume flowing per second, voltage is analogous to water pressure, and charge is analogous to total water volume passing during the period of interest. Greater pressure or voltage produces proportionately greater current. For electricity, the proportionality constant between voltage and current is impedance, that is, voltage equals current times impedance. The famous "Ohm's law" is the special case in which all impedance is resistance.

Just as it takes energy to pump water, energy is carried in electric current. All energy in the ECT stimulus is eventually converted into heat, and the amount of energy is described in the same units used for heat. Risk from electricity comes from temperature increases that correspond to the rate of heat liberation. A separate safety issue is that electricity applied near the heart can cause arrhythmias, but we avoid this problem at ECT by applying electricity only on the head.

Electrical energy is the product of voltage, current, impedance, and time; the electric company charges us for this product. Just as with a tank of gasoline, energy has no built-in time rate; you can use a particular amount quickly or slowly. In contrast, power has a time factor, power is the rate of energy use, and power corresponds to temperature changes. For an ECT stimulus that we plan to apply, we can know in advance only the current or the voltage (but not both) because we do not know the patient's impedance to the stimulus before it is delivered. After the stimulus, when we know the current we can use the relationship that energy equals the product of current squared, impedance, and time. When we know the voltage we can use energy equals voltage squared multiplied by time and divided by impedance.

These basic facts apply to ECT in several ways. There are three types of ECT stimulus generators ("ECT machines"): constant current, constant voltage, and fixed charge. All commercially available modern stimulus generators supply a constant (and therefore limited) current. This means that voltage increases with impedance because current remains fixed. This is generally safer than constant voltage because of the possibility of a short circuit between the electrodes (as from sweat, gel, water, or if electrodes are too near each other). With constant current, a short circuit produces impedance near zero and thereby a voltage near zero. No burn can occur because the rate of energy release is low, as it equals impedance times current squared. In this circumstance impedance is low and current does not change, so their multiplication product is low.

In contrast, with a constant-voltage stimulus the rate of energy release equals voltage squared divided by impedance. This means that low impedance increases the rate of energy release and thereby the risk of skin burn. Indeed, a study that placed electrodes only 5 cm apart with constant-voltage stimuli produced unacceptable skin burns (Abrams and Taylor, 1973). This is one reason why constant-voltage ECT devices are obsolete.

Fixed-charge devices gradually build up ("fully charge") a large capacitor; the stimulus is then delivered from the capacitor. Cardiac defibrillators are fixed-charge devices. Before they can deliver a shock, a "charge-up" button must be pressed, and there is a wait for the capacitor to fill with electrons. Defibrillators are notorious for skin burns that result because their current is not limited. Fixed-charge ECT stimulus generators are not currently commercially available.

Skin burns can occur with constant-current ECT. This can happen in the circumstance that is the opposite of a short circuit: extremely high impedance between the two electrodes. In practice, this occurs only when there is poor contact between the electrode and the skin or between the electrode and the ECT instrument itself. Poor contact means high impedance. There is a one-to-one relationship between high impedance and high heat release. If higher impedance is present where the

stimulus electrode meets the skin, a higher temperature will surely develop there. Conversely, a skin burn occurring during an ECT stimulus specifically indicates that high impedance was present where the burn occurred. In one situation in which I used a rubber head strap with steel plate electrodes, after the stimulus I noticed that one of the electrodes had slipped onto its edge. Under the electrode edge I saw a thin straight red line – a mild burn. It healed quickly but left me a mental picture of the need to keep impedance down.

The energy in constant-current ECT stimuli is far too small to produce a burn anywhere but where the electrode meets the skin. Even if all the electrical current were to enter the brain and liberate 100 joules in its path, brain tissue temperature would increase by less than 0.1°C (Swartz, 1989). However, only about 1% of the electrical current crosses the bony skull into the brain because skull impedance is about 100 times higher than skin impedance (Weaver et al., 1976). That is, about 99% is shunted through the scalp and the skin and never enters the brain, and 99% of the stimulus energy is dissipated as heat in the skin and scalp. Accordingly, brain temperature increases by less than 0.001°C. Still, a skin burn can occur, but only if the connection between the electrode and the skin is not good, that is, the impedance of the connection is high. The clinician can act to lower the impedance of the skin, the electrode, and the connection between them by removing sources of high impedance. These include oils, rust, dirt, cosmetics, skin lotions, crust, and hair. Removing natural skin oils with organic solvents such as alcohol or acetone increases impedance. Salt-containing gels and fluids decrease impedance.

In medication therapy, we are concerned about how close our therapeutic dosage approaches the toxic range. Analogously, how high would an ECT stimulus have to be to cause injury? Electrical injury derives from the heat of electrical energy dissipation. Because 99% of the current is shunted through skin (including scalp), it is the vulnerable site in the electrical path. Troublesome skin injury would occur at far lower stimulus energy than could cause thermal injury inside the skull, as long as the skull is intact. For brief-pulse stimuli, if liquid electrode gel were applied between the electrode and the skin, the heat liberated by each pulse would be conducted into the gel and dispersed through it before the next pulse arrived (Swartz, 1989). If a metal electrode were involved, it would be included in this heat dispersal. This means that no skin burn could occur until the entire gel and metal electrode mass reached scalding temperature, approximately 60°C, about 35°C higher than room temperature. A typical metal electrode weighs 20 g. Assuming a gram of gel, the total weighs 42 grams for two electrodes. Supposing the worst case – all energy dissipation at the skin to electrode junction – each 100-joule stimulus would raise electrode temperature by 0.57°C. Raising the heat of the electrodes to scalding temperature would require 6,100 joules, or 61 maximal brief-pulse ECT stimuli. A very conservative safe upper limit for ECT stimulus

energy regarding the most vulnerable site, the skin, is 10% of this, 610 joules. There are 4.187 joules per calorie; 100 joules = 24 calories.

For the small amount of electric current that passes through the skull and the brain, virtually all energy dissipation occurs within the skull because impedance is far higher through skull than through brain. Brain tissue would not be electrically heated until skull impedance breaks down from heat damage. Before brain tissue would be subject to electrical heating it would be exposed to heat that diffuses from the electrically heated skull. This analysis leads to a useful result: Before brain tissue could be injured by electrical heating, the skull would become painfully hot. Of course in ECT practice skull heating does not occur. Accordingly, no electrical brain injury occurs. If you have wondered why execution by electrocution sometimes does not occur despite massive amounts of electrical energy, now you know. There is more lethality in cardiac arrhythmia.

Before the ECT stimulus dose is applied, some stimulus generators can apply a tiny and impalpable electrical current to examine the electrical connection. The resulting number is the "static impedance." A high impedance risks skin burn. The "dynamic impedance" printed after the treatment results from measuring both the current and voltage of the ECT stimulus. A typical dynamic impedance is 220 ohms, and an ordinary range is 100 to 320 ohms. A higher dynamic impedance indicates poor connection to the patient, for example, an electrode slipped out of place after the static impedance test.

Seizure generation

ECT efficacy derives from the generalized seizure (Ottosson, 1960). Seizure includes both neurotransmitter release and electrical currents, and, because they are inseparable in the seizure, therapeutic benefit corresponds to both. Still, there is a basic difference between the electricity of the seizure and the electrical stimulus. In modern ECT, the electrical stimulus only induces seizure and by itself is not substantially therapeutic.

The process that connects the seizure to the electrical stimulus is the mechanism of seizure induction. The mechanism described here may seem surprising. The purpose of this mechanism is to identify what it is about electricity that represents the ECT stimulus dose. It also provides the opportunity to understand how the ECT seizure develops from the stimulus, but the following dose formula can be clinically used without understanding.

The modern ECT stimulus consists of a series of electron pulses flowing between two electrodes (see Figure 1.1). The pulses strictly alternate in direction. This electron flow is called "bidirectional" or "alternating" current. Each pulse is typically 0.5 to 1 ms in duration. Electrical silence between pulses typically lasts for 6 to 16 ms,

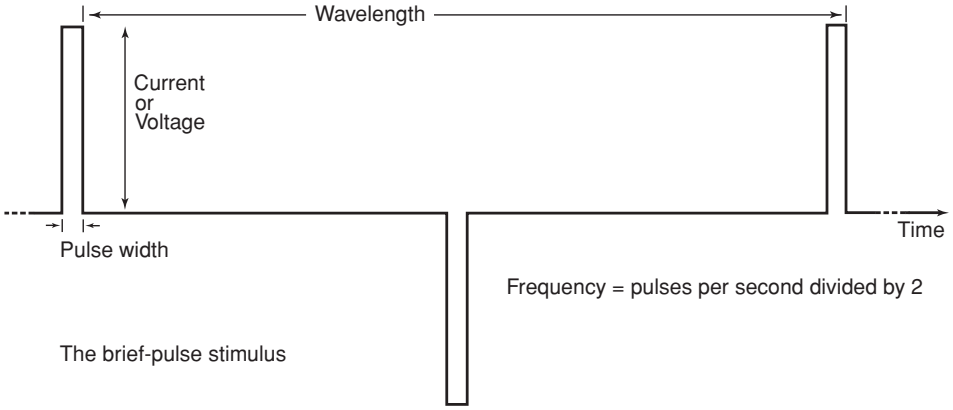

Figure 1.1 The modern ECT stimulus.

about 10 times longer than the pulse. A typical ECT stimulus has 100 to 1,000 pulses and is one to three times as long as the minimum that would generate a seizure, so a single pulse is not strong enough to induce a seizure by itself.

The time that passes between pulses is long enough for any polarization, depolarization, or other directional charge effect induced by a pulse to dissipate before the next pulse. Moreover, this next pulse is in the opposite direction and thereby neutralizes any possible remaining polarization, and any other effect associated with electron flow in a particular direction. Taken together, these basic facts indicate that the modern bidirectional ECT stimulus cannot induce seizure primarily through electrical depolarization.

Traditionally, electrical depolarization has been the stated mechanism for ECT seizure generation. It was rationalized only by analogy to direct-current depolarization of a single neuron (Sackeim et al., 1994). With a single neuron at rest, the inner surface of the cell membrane has a negative voltage relative to the outer surface, by 70 mV. When this polarization is reversed by the current from a small negative electrode applied to the outside of the cell body, the single neuron immediately fires, that is, it immediately transmits a wave of depolarization along its axon that extrudes neurotransmitters onto an adjacent neuron. Analogous firing of many neurons by depolarization has never been proven as the mechanism for seizure with a bidirectionally pulsed stimulus. The analogy is not reasonable because a human brain is 11 orders of magnitude larger than a single neuron. Extrapolating from a mouse to an elephant is much closer, yet lethal (e.g., West et al., 1962).

As an ECT seizure cannot be induced primarily by electrical depolarization, the simplest known remaining possible mechanism is rapid kindling. Kindling means that the seizure threshold progressively decreases with each stimulus pulse. Eventually, it becomes low enough for enough neurons to depolarize to initiate a seizure.

This process is similar to how a seizure is generated by increasing levels of proconvulsant pharmaceuticals, such as stimulant drugs, pentylenetetrazol, and flurothyl. The ECT stimulus pulse evidently disrupts the neuronal cell membrane and the operation of the sodium–potassium exchange pump across it. Normally sodium is actively pumped from the cell; the cell membrane is only slightly permeable to sodium inflow, and the intracellular sodium level remains very low. Presumably, with each ECT stimulus pulse intracellular sodium levels would increase, whether from greater sodium permeability or decreased sodium–potassium pump effectiveness. In turn, this decreases the negative voltage on the inner membrane surface. This is rapid kindling. Eventually, the effects of pulses aggregate into producing neuronal depolarization. The depolarized neurons depolarize adjacent neurons, and a wave of depolarization sweeps through the brain.

If there were no kindling, that is, no decrease in seizure threshold in the brain, and the seizure were generated solely by electrical depolarization, there would be no more than one wave of neuronal depolarization after the end of the ECT stimulus. However, a seizure is much more than a single wave of neuronal depolarization, and it is much more than the depolarization of a single neuron by – and solely during – an applied voltage. Rather, the ECT seizure consists of 2 to 5 waves per second lasting 20 to 60 seconds. In a manner separate from previous discussion, this reasoning also indicates that electrical depolarization of neurons is not the principal means of ECT seizure induction. Rather, the ECT seizure must be built upon rapid kindling. The kindled neurons from which waves of depolarization spread are the seizure foci.

The rapid kindling mechanism applies as well to unidirectional pulse stimuli for the same reasons. It applies because the interval between pulses is long enough to dissipate polarization (or depolarization) effects from any pulse before the next pulse. It applies also because the waves of seizure continue long after the electrical stimulus ceases. If rapid kindling develops only at the anode (the positive electrode), an ECT seizure induced by unidirectional stimuli would begin at one electrode, rather than from both electrodes, as with bidirectional stimuli.

The rapid kindling mechanism implies that the stimulus titration method for measuring seizure threshold embodies a systematic error if two or more stimuli are administered in succession. In this method, progressively higher electrical stimuli are administered until a convulsion develops. If a stimulus is not followed by a convulsion within 20 seconds, another stimulus is administered. However, subconvulsive ECT stimuli contribute to kindling for at least 1 minute (Swartz, 1990). So the "method of limits" measurement of seizure threshold underestimates it more with each additional stimulus administered. Additional internal inconsistencies in using seizure threshold to help set the stimulus dose are discussed elsewhere (Swartz, 2001).

Brief-pulse stimulus dose

This section updates a previous report (Swartz, 2006). Even several times the amount of electrical charge and energy in an ECT stimulus applied to the skin would be impalpable if given over several hours. If it were applied to the head that slowly it would not affect consciousness and certainly it would not generate a seizure because the electrical voltage and current are too small. That is, a certain minimum voltage is needed to induce disruption of the neuronal cell membrane and kindling and eventually produce neuronal depolarization. Using the charge as the stimulus dose ignores the effect of voltage. Expressing stimulus dose as energy (e.g., joules) is similarly inadequate because it represents only the total heat liberated by the electrical stimulus, not even the rate of heat liberation that affects the temperature.

To reflect seizure-inducing capability, the unit of stimulus dose must be related to the desired result, the induction of a generalized brain seizure. That is, the stimulus dose is reflected by the (three-dimensional) volume of seizure foci it produces. The minimum volume of seizure foci that induces a generalized brain seizure is the "seizure threshold." To reach this threshold, the voltage across the electrodes must be high enough to induce kindling and a sufficient number of electrons (that is, charge) must pass between the electrodes.

Modeling real-world phenomena with equations ordinarily begins with identifying reasonable approximations that can be represented by physically meaningful mathematical terms. One such approximation is that the two stimulus electrode sites are far enough apart that the neuronal effects around each are separate from the other site. Another is that each electrode site is small compared with the distance between the electrodes and so can be represented by a point. A third approximation is that the electrical impedance of the brain is uniform. This implies that the voltage drops linearly between the two electrodes. Conversely, a particular voltage drop corresponds to a particular physical distance. A final approximation is that the volume of seizure foci is much smaller than the entire brain, so that the geometry of the skull bordering each electrode can be approximated as a plane.

The approximation of separation is compatible with all three versions of bilateral ECT: bitemporal, bifrontal, and left anterior right temporal (LART). In these placements, the two electrodes are in two widely separated planes. Each electrode site can be considered very small because small differences in electrode placement produce clinically observable changes. In specific, relocating each of the electrodes of bitemporal ECT forward by merely 2.5 cm significantly increased post-ECT cognitive function scores and significantly decreased the variability of these scores. The lower variability indicates that fewer patients had marked cognitive dysfunction.

Consider a voltage *E* as the minimum sufficient to kindle neurons. As noted earlier, a particular voltage corresponds to a particular physical distance. The brain *volume* within a hemisphere of *radius E* around the electrode site is $(2/3)\pi E^3$. The *volume* of kindled brain equals the *volume* within this voltage hemisphere multiplied by the number of voltage carriers, that is, the *charge*. The kindled brain *volume* – which represents the stimulus dose – increases with the cube of the *voltage* multiplied by the *charge*. As voltage increases, this *volume* increases in proportion to *voltage* cubed.

The stimulus dose can be expressed in terms of current instead of voltage by using Ohm's law, *voltage E* equals *current I* times *impedance Z*. Replacing *E* with *I* (current) times *Z* (impedance) indicates that the kindled brain *volume* – that is, the stimulus dose – increases in proportion to the cube of the *current* multiplied by the *charge*.

With bilateral ECT, at the same charge a stimulus of *current I3* has $(I3/I2)^3$ times the seizure-inducing dose as a stimulus of *current I2*. To illustrate, a 900-mA stimulus has 1.42 times the seizure-inducing dose of an 800-mA stimulus at the same charge. This calculation indicates a strong difference between a 900-mA ECT instrument and an 800-mA instrument. Consistent with this 142% calculation, direct randomized comparisons involving 88 patients receiving bitemporal ECT found that 900-mA stimuli had 1.61 times the seizure-inducing effects of stimuli of 800 mA or less at the same charge and a pulse width of 1 ms (Chanpattana, 2001).

Unlike the bilateral placements (bitemporal, bifrontal, LART), the Lancaster right unilateral placement locates the electrodes in the same plane and near each other. In this circumstance the volume of seizure foci increases in two dimensions – rather than three – as the current increases. The stimulus *dose* is then proportional to *charge* times the *current* squared, rather than cubed. In the modern right unilateral placement, with electrodes at the right temple and vertex, there is more separation than in the Lancaster placement but less than in bilateral ECT. Accordingly, the *volume* of seizure foci should increase proportionally to an exponential power of *current* larger than 2 (as for Lancaster) and less than 3 (as for bilateral). As a first approximation, this exponential power is 2.5. Corresponding to this, a 900-mA current would have 1.34 times the dose of an 800-mA current at the same charge.

For bilateral ECT, the result of multiplying *charge* in millicoulombs (mC) by *current* cubed produces an unfamiliar number. For example, a 504-mC charge at 0.9-A current gives 367.4 raw dose units. To have a familiar number as the result, simply use a constant coefficient of 1.372 on the raw dose units to produce foci units, that is, 376.7 times 1.372 equals 504. As another example, a 574-mC charge at 0.8 A is 405 foci units. In other words, by definition, the *charge* and the foci units are the same at 0.9 A; however, they will differ for other at other currents. *Bilateral Dose* (foci units) = 1.372 × *charge* in mC × (*current* in A)^3 and *Unilateral Dose*

(foci units) = 1.372 × *charge* in mC × (*current* in A)$^{2.5}$. Unlike charge alone, these doses are relative, not absolute. In other words, a bilateral dose can be compared only with other bilateral doses, not with a unilateral dose.

Sine wave stimulus dose

The dose of a sine wave stimulus is more complex to express, because its current and voltage constantly vary. *Current* to the third power multiplied by *charge* for the brief-pulse stimulus is basically integration over *time* of *current* to the fourth power. Expressing the sine wave current as $A\ sin(t)$, where A is the peak current and t is the time, and integrating the fourth power of current over one wavelength yields the stimulus dose for one wave as $(3/8)LA^4$, where L is the wavelength. Replacing L with the stimulus duration T gives the dose for an entire sine wave stimulus.

Stating the stimulus dose as the charge alone vastly and incorrectly understates the dose of sine wave stimuli, especially in elderly patients. This understatement is best understood by comparing typical doses of brief-pulse and sine wave stimuli. For a brief-pulse stimulus, the stimulus duration T is calculated as the total time of all pulses. For typical stimuli of 100 to 250 mC at 900 mA, current total time is 0.11 to 0.28 seconds. This range is equivalent to sine wave stimuli of 0.29- to 0.75-seconds duration with the same peak current as the brief-pulse stimuli. Sine wave stimuli of 170 root-mean-square (RMS) volts reach 240 volts at peak. At the average human dynamic impedance of 200 ohms, the peak current is 1200 mA. Corresponding to this peak current, the dose of a 1-second 170-volt sine wave stimulus is 0.78 raw units [that is, $(1.2)^4 \times (3/8) \times 1$]. The current and dose are far higher for patients with lower impedance, specifically elderly patients (Sackeim et al., 1987). At 150 ohms impedance – typical for elderly patients – peak current is 1.6 A and corresponding dose is 2.46 raw units. At 120 ohms – still within normal range – peak current is 2 A and dose is 6 raw units. These much higher doses at low impedance apparently explain why sine wave devices effectively induced seizures in elderly patients. Excessive dose might explain why some patients experienced severe cognitive side effects.

In comparison, maximum doses are 0.37 raw units for a 504-mC brief-pulse device at 900 mA and 0.29 raw units for a 576-mC brief-pulse device at 800 mA. These lower raw unit doses show that sine wave devices delivered far higher maximum stimulus doses than present brief-pulse devices do. Per the previous paragraph illustration, this is 2.1 and 2.7 times the maximum dose at average impedance and 6.6 and 8.5 times the maximum dose for typical elderly patients (150 ohms). The problem with sine wave stimuli was inefficiency. Inefficiency is why sine wave stimuli need high doses to succeed, and it is presumably why they also produce substantially greater cognitive side effects than do brief-pulse stimuli.