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## Efficacy and Safety of Induced Seizures (EST) in Man

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Delphicus: Science, Socrates, is the discovery of truth for its own sake, and it seeks it only in matters which are measurable, and usually by applying to such material the matters of experiment.

Socrates: Does that explain, then, why medicine is not regarded as a science?

Delphicus: Yes, indeed, for much of medicine deals with such things which are not accurately measurable, and even when they are, the truth about them is not pursued for its own sake, but in order to prevent or cure disease . . . . Indeed, on the whole I should prefer to call medicine an art rather than a science.\*

**T**HE USE of induced seizures (EST, ECT, convulsive therapy) in clinical psychiatry is limited by concerns about its efficacy and safety, its empiric nature, and the ethical issues of informed consent. Such concerns have led to the proscription of EST and legal restrictions in some jurisdictions and to its very uneven use in different populations.<sup>1-3</sup>

Since seizure therapy was first introduced in 1934, the treatment process has undergone many changes that complicate its evaluation. Electrical induction, pretreatment sedation, and anesthesia are generally accepted; muscle relaxants, hyperoxygenation, special electrical currents, and anticholinergic drugs are used by some and not by others; the unilateral placement of electrodes and multiple monitored treatments are used only occasionally.

The principal clinical studies of EST were done during the first decades of the treatment's use, and extrapolation of those clinical results may have limited relevance today. Few meet present standards for the evaluation of therapeutic efficacy; most are case studies, with little description of the previous or concurrent therapy, and without a follow-up adequate to assess the therapeutic results. They particularly lack control or comparison groups.<sup>4</sup>

The complications of EST, particularly the neurologic and psychologic sequelae, were described in greater detail when treatments differed from our

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\*Anonymous: *The purity of science, in Socrates on the Health Service*. Bedford, England, Sidney Press, 1960, pp 73-74

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present practice. For example, amnesia and cyanosis were once believed to be part of the therapeutic process, and, instead of avoiding hypoxia, it was encouraged.

The diagnostic criteria, selection of patients, methods of evaluation, and concurrent treatments also differ. Our present classifications depend largely on behavioral, historical, familial, and genetic factors, and less on the psychodynamic formulations that were current at the time EST was introduced. Populations labeled “schizophrenic” may have included patients now labeled “manic” or “acute confusional psychosis,” leading to clinical results different from those we may find today. Today’s widespread use of antidepressant and antipsychotic drugs, minor tranquilizers, and lithium leave the nonresponsive patients for EST.

Despite these significant caveats, the EST experience is reviewed, with particular emphasis on its therapeutic benefits and its principal risks and complications.

### EFFICACY

The benefits of EST are directly related to clinical diagnosis. EST is most effective in psychotic-depressive syndromes and in mania where success rates of 60%–90% of treated cases are reported. While EST is recommended in acute and chronic schizophrenia, the data in these populations are much less compelling.

#### Depression and Mania

The principal indication for EST is a depressive psychosis, almost regardless of subtype. Thus, patients with diagnoses of bipolar depression, unipolar depression, involuntal depression, and depression in the elderly are rapidly responsive, usually requiring 2–4 seizures spaced at 48-hour intervals to elicit an elevation of mood, the relief of suicidal preoccupation and agitation, and a reversal of the symptoms of hypothalamic dysfunction.<sup>4–9</sup> In most instances 6–8 seizures have been given, and this number seems constant regardless of whether seizures are induced electrically (using bilateral or unilateral electrode placements) or induced by flurothyl.<sup>10–14</sup> Increasing the frequency of seizures, as in multiple monitored seizures,<sup>15</sup> is reported to reduce the time needed for a therapeutic response. This result is only occasionally seen, and at some additional risk to the subject.<sup>16–18</sup>

While most comparative studies are weakened by poor descriptions of the treatments administered, the criteria used to assess improvement, or the duration of remissions,<sup>4</sup> many studies clearly define an efficacy for EST in depressive illnesses. Patients receiving EST show greater reduction in symptom scores, better discharge evaluations, and shorter periods of hospitalization than do those treated with placebo,<sup>19–23</sup> psychotherapy,<sup>24,25</sup> or simulated EST or subconvulsive treatments.<sup>23,26–28</sup> In comparisons with antidepressant drugs, EST is more or equally as effective as thymoleptics,<sup>19,21–23,29–33</sup> and more effective than the monoamine oxidase inhibitors phenelzine,<sup>22,32,34,35</sup> iproniazid,<sup>20</sup> and isocarboxazid.<sup>36,37</sup> In their assessment of the studies of the clinical efficacy of various antidepressants, Cole and Davis<sup>38</sup> report six studies comparing EST and imipramine: three studies in which EST is more effective than imipramine; three in which the effects are equal; and none in which EST was less effective than imipramine.

When EST is combined with imipramine<sup>23,39,40</sup> or amitriptyline,<sup>41</sup> there is no

difference in the number of seizures used to effect clinical improvement, but follow-up results are better<sup>42</sup> or equivalent<sup>23,40</sup> for the combination compared to EST alone. Similarly, EST plus phenelzine is equivalent to EST plus imipramine,<sup>39</sup> but EST plus amitriptyline is superior to EST plus diazepam.<sup>41</sup> EST and chlorpromazine was not superior to EST alone in the treatment of depression.<sup>43</sup> Subsequent treatment with antidepressant drugs sustains improvement better than treatment with sedative drugs<sup>41</sup> or when no maintenance drugs are given.<sup>39,40</sup> While such combinations are commonly used, their relative efficacy remains poorly defined.

Depressed patients have a higher death rate than the general population, both from suicide and nonsuicide causes,<sup>44</sup> and this rate is reduced by EST. Huston and Locher<sup>25</sup> and Ziskind et al.<sup>45</sup> found suicide to be less frequent in EST treated patients compared with those treated by psychotherapy alone. Ziskind et al.<sup>45</sup> reported 9 deaths in 109 patients treated by psychotherapy compared to 1 death in 88 patients treated with EST. Mortality from nonsuicide causes is also reduced. In a careful 3-year follow-up study of 519 depressed patients treated in 1959–1969 by EST alone, by antidepressants in adequate or inadequate dosage or by neither EST nor antidepressants, Avery and Winokur<sup>41</sup> found a lower fatality rate for the EST-treated group compared to the drug-treated or the patients treated by neither drug nor EST. Their findings support the clinical observation that EST is effective in reducing mortality and morbidity due to agitation, exhaustion, inanition, fever, infections, or cardiotoxicity in depressed patients.

Some depressed patients who do not respond to antidepressant drugs do respond to EST. In a recent report, Glassman et al.<sup>46</sup> found that depressed patients with delusions were markedly unresponsive to tricyclic drugs—10 of 13 so treated failed. When these were retreated with EST, 9 of the 10 failures had a dramatic and sustained response.

EST is also effective in the treatment of mania.<sup>47</sup> The sedating action of EST is often used to reduce excitement and agitated states. Ziskind et al.<sup>45</sup> found greater improvement in follow-up for manic patients treated with EST compared to psychotherapy controls. McCabe<sup>48</sup> reviewed the records of patients treated with EST in 1945–1949 and found shorter hospitalization, greater per cent improvement, and better follow-up results for EST than for controls. Kalinowsky,<sup>13</sup> Epstein,<sup>49</sup> and Bianchi and Chiarello<sup>50</sup> found improvement rates for EST treated manic-depressive patients to be equivalent in depressed and manic phases. Ebaugh and Johnson<sup>51</sup> reported 100% social recovery for five manic patients treated with pentylenetetrazol; Thorpe<sup>52</sup> and Kino and Thorpe<sup>53</sup> described the efficacy of multiple daily treatments in acute mania. Comparisons of the clinical efficacy of lithium and EST, alone or combined, in the treatment of acute and recurrent mania are not available.

The efficacy of seizure therapies in depressive illnesses may also be seen in comparisons of different methods of inducing the seizure. Studies comparing EST using unilateral or bilateral electrode placements find the two methods effective in reducing symptoms and shortening hospitalization.<sup>12,54,55</sup> D'Elia and Raotma<sup>55</sup> examined 29 studies in which the results of unilateral electrode placements were compared to bilateral placements. In 14 the results were equal, in 13 bilateral was more effective, and in 2 unilateral placements were more effective. Comparisons of seizures induced electrically with those induced by the inhalant flurothyl also

found the results equivalent.<sup>14,56</sup> The efficacy of EST is related more to clinical diagnosis than to the mode of seizure induction.<sup>5, 13, 26, 57-59</sup>

### Schizophrenia

EST is widely used in the treatment of acute and chronic schizophrenia.<sup>7,8,60-62</sup> Its efficacy is greater with shorter durations of illness<sup>63-65</sup> and with a greater number and increased frequency of seizures.<sup>13,63,66</sup> The efficacy in illnesses of less than two years duration and acute onset is well defined, but in illnesses of longer duration with slow, insidious onset, the results are proportional to the length and severity of the illness<sup>13,63,67-70</sup> and the intensity of the treatment.<sup>63,64,66,71-74</sup> Efficacy is also greater in patients exhibiting some depressive features such as mood disorder, feelings of hopelessness and guilt, or thoughts of suicide.<sup>75</sup>

Behavioral changes after EST occur more slowly in schizophrenic than in depressed patients. A clinical response may not be seen until after 10-15 seizures. The delay in clinical effects parallels the development of persistent EEG slowing,<sup>5</sup> activation by barbiturates,<sup>76</sup> and changes in memory, psychomotor, and perceptual tests.<sup>26</sup> The same time course is seen after inductions with the inhalant convulsant, flurothyl.<sup>14,56,77</sup> In comparative studies, EST and flurothyl are usually found equivalent in clinical efficacy and in physiologic and psychologic tests.

### *Acute Schizophrenia*

In the early uncontrolled clinical studies, EST improvement rates averaged 75% of cases treated, based on a reduction in symptoms and shorter hospitalization.<sup>53,63-65,78-80</sup> Zeifert<sup>65</sup> reported improvement rates of 84% with pentylene-tetrazol (Metrazol; Knoll Pharmaceutical, Whippany, N.J.) and 80% with EST. In comparisons of EST with psychotherapy, milieu therapy, and sedatives, EST-treated samples showed better discharge rates, improved symptom evaluations, and fewer relapses than the other treated samples.<sup>81-85</sup> In studies using a historical control, EST-treated patients exhibited a 50%-70% improvement rate compared with a 10%-30% rate for the earlier period.<sup>58,86-89</sup> Two reports found no advantage for EST.<sup>6,9</sup> In a follow-up of 317 hospitalized patients treated by psychotherapy, EST, or insulin coma therapy, Rachlin et al.<sup>90</sup> found shorter hospitalization periods and better discharge rates for EST.

With the advent of psychotropic drugs, the interest in assessments was mainly in comparisons of EST and drug therapy, either alone<sup>78,91-96</sup> or combined.<sup>91,97,98</sup> In the controlled comparisons of EST and phenothiazines in first admission or acute schizophrenic patients, the treatments are equivalent in short term results.<sup>4,78,91-94,97</sup> Where patients received 12-20 EST and chlorpromazine 300-1200 mg/day, the reduction in symptom ratings by "blind" raters, nurses' ward observations, and discharge evaluations were equivalent.<sup>92,93,96</sup> Two studies find the duration of hospitalization for EST longer<sup>92,93</sup> and one finds it shorter than for psychotropic drugs.<sup>96</sup>

Two studies compared the efficacy of the combination of EST and phenothiazines with EST alone.<sup>91,98</sup> Childers<sup>91</sup> found no difference between EST alone and chlorpromazine with EST in changes in symptom ratings, but in comparisons between EST (without or without chlorpromazine) with fluphenazine (20 mg/day) or chlorpromazine (1 g/day) alone, the EST-treated group showed significantly

more improvement than drug treatment alone. Smith et al.<sup>98</sup> found greater short-term (1, 3 week) improvement scores for patients treated by EST plus chlorpromazine (400 mg/day) than EST alone; in later assessments (6 weeks, 6 months, 1 year) the therapies were equivalent.

The use of antipsychotic drugs with EST is complicated by questions of toxicity. Controlled trials are lacking, but the incidental reports of fatalities when EST is combined with chlorpromazine<sup>85,99,100</sup> and reserpine,<sup>101–103</sup> or severe hypotension when EST is combined with chlorpromazine<sup>104</sup> suggest that the combination should be used cautiously until better assessments are made.

### *Chronic Schizophrenia.*

Open clinical studies find EST effective in improving discharge rates from the hospital in 10%–20% of the long-term mentally ill.<sup>13,105,106</sup> Symptom reduction is often described, particularly reductions in aggressiveness and in the need for restraints. In comparisons of EST with milieu and insulin coma (ICT) therapies, few differences between the treatments are reported.<sup>88,107–111</sup> Neither EST nor histamine evinced any advantage in short-term efficacy.<sup>107,110</sup> A comparison of EST, ICT, and psychotherapy found no differences in short-term evaluations of improvement,<sup>88</sup> while a follow-up study showed better clinical results for EST than for insulin coma or psychotherapy alone.<sup>70</sup>

Controlled clinical trials are few, and these also fail to define differences among the treatments.<sup>4,31</sup> Miller et al.<sup>68</sup> compared the effects of EST, anesthesia alone, EST and anesthesia, and subconvulsive currents in chronic mentally ill and found them equally ineffective. Brill et al.<sup>67</sup> failed to find any differences in long-term hospitalized veterans treated by EST alone, EST and succinylcholine, EST and thiopental, thiopental alone, or nitrous oxide. May and his coworkers assigned “middle prognosis” schizophrenic patients, many of whom were readmissions, to EST, milieu therapy, psychotherapy, psychotropic drugs, or psychotherapy and psychotropic drugs.<sup>94–96</sup> The short-term results for both drug therapies were superior to EST and other therapies, but patients treated with EST or drug therapies had shorter stays in the hospital before discharge, and shorter rehospitalization periods after their initial release.<sup>95,96</sup>

The number and rate of treatments and the duration of illness affect the outcome of EST in chronic schizophrenia. The longer the duration, the poorer the therapeutic results, and the greater the number of treatments needed for symptom relief. Relief is estimated as 50%–70% in patients who have been ill for less than a year, but less than 20% in patients who have been ill for more than 3 years.<sup>7,13,63,64,67–70,84</sup> Treatment with less than 20 seizures is usually less effective than longer courses.<sup>64,66,71–74</sup> Baker et al.<sup>66</sup> compared the efficacy of 12 EST with 20 EST and found greater benefits for 20 treatments. Others find improved efficacy when treatments are given as frequently as a few times a day.<sup>71,72,112</sup> In uncontrolled studies, the efficacy rates were greater for patients treated with multiple treatments (“regressive EST”) than for those treated 3 times a week.<sup>63,71</sup> The success of antipsychotic drugs led to the disuse of regressive EST, although recently, Murillo and Exner<sup>74,113</sup> examined the efficacy of intensive EST and found it superior in the long-term indices of work record, number and duration of rehospitalizations, and need for further treatment, compared to drug therapy or standard courses of EST.

### Other Disorders

EST has been tried in many clinical conditions. The studies are mainly uncontrolled single case reports. EST has been reported to be effective in the treatment of hysterical personality, anorexia nervosa, drug dependence, alcoholism, obsessional neurosis, epilepsy, porphyria, intractable skin disease, and causalgia, to name a few.<sup>6-8,60,114</sup> But the absence of controlled studies makes judgment impossible.

The use of EST in children and adolescents presents special problems. Studies in children are few, and none are controlled<sup>115-119</sup> Bender reviewed her experience, and despite early optimistic reports, found little long-term benefit.<sup>115,116</sup> Heuyer et al.<sup>120</sup> found EST symptomatically helpful in depressed, manic, or confusional syndromes in children, but without sustained benefits. Hift, Hift, and Spiel<sup>121</sup> found no successes in EST treatment of 23 psychotic children after 2 years. Despite this melancholy record, a recent survey found EST to be used frequently in childhood disorders in Massachusetts.<sup>122</sup>

EST is also used as a prophylactic or in maintenance therapy. Stevenson and Geohegan<sup>123,124</sup> observed 13 manic-depressive patients who received monthly treatments for 5 years after a course of EST. In 3 years, there were no rehospitalizations in this group, compared to 11 readmissions among 11 patients who did not agree to receive prophylactic treatments.<sup>124</sup> In the next 2 years, two of the 13 were readmitted despite continued treatment.<sup>123</sup> Karliner and Wehrheim<sup>125</sup> offered maintenance treatment to 210 patients; fifty-seven accepted and received an average of one treatment a month, and of these, 12% relapsed. In 153 patients who received no maintenance treatments, 79% relapsed within a 6-year observation period. Barton et al.<sup>10</sup> compared the effects of two extra treatments to those who ended a course as soon as improvement was established. They found no additional benefit for two extra treatments at 2-, 6-, and 12-week evaluations. Similar observations are reported by others.<sup>126-128</sup>

### SAFETY

The risks and complications of EST are derived from many sources: the direct effects of the seizure, the convulsion, the anesthesia, and the mode of induction of the seizure (whether by electricity or by flurothyl); anxiety and fear of "shock therapy"; the social stigma of having received "shock therapy." The principal complications of EST are death, brain damage, memory impairment, and spontaneous seizure. These complications are similar to those seen after head trauma, with which EST has been compared.<sup>129</sup> In addition, fracture (particularly of the spine), fear and panic, headache, and skin burns are reported with sufficient frequency to be considered risks of treatment.

#### Death

Of studies reporting death rates with EST, the incidence varies from none in 8500 treatments in 870 patients<sup>9</sup> to 0.04%, 0.06%, 0.08%, 0.3%, and 0.8% of patients treated.<sup>7,130-133</sup> Death is usually ascribed to cardiac complications, frequently occurring after the seizure, during the recovery period.

Death rates are lower in the more recent studies than in the older. Perhaps, the difference in incidence may be related to the use of curare as a muscle relaxant



and the frequency of “missed seizures” in the earlier treatments. Curare is a natural botanical product of indefinite purity and activity with effects that were often unpredictable. Both overdosage and underdosage were common, so that seizures were irregularly modified, with patients having complete paralysis and apnea on one occasion and a fully unmodified seizure on the next.

“Missed” or “incomplete” seizures occur when a current passes between the scalp electrodes without inducing a seizure and its associated amnesia. Patients experience pain, fear, and panic, and can rarely be induced to have another treatment following such an experience. Missed seizures occur frequently, but are most damaging in patients treated without anesthesia. The panic and terror of patients subjected to a “missed seizure” provide conditions for the precipitation of a cardiac death. In a recent editorial, Engel<sup>134</sup> notes that psychologic factors may be potent contributors to instantaneous death, and unmodified missed seizure provides a suitable medium for such an event. In some of the pathologic reports, deaths were associated with missed seizures.<sup>36, 42, 135, 136</sup> The use of an anesthetic is a clear prophylactic for this complication.

### Brain Damage

The evidence for sustained pathologic changes with repeated seizures comes from the examination of brain tissues from patients who died after EST; tissues from epileptic patients who died in status epilepticus; tissues from animals subjected to experimentally induced seizures; and the psychologic and physiologic tests which are usually interpreted as measures of brain function in man.<sup>137</sup>

#### *Human Brain Tissue.*

Study of the pathology of seizures is complicated by the time between EST and the time of death. Some tissues are examined under conditions in which seizures are clearly proximal to the death, while in some EST was a distant event. With this caveat, brain tissues have been reported to show increased gliosis,<sup>138</sup> diffuse degeneration,<sup>139</sup> petechial hemorrhages in the midbrain and evidence of fat embolism,<sup>140</sup> and edema and subarachnoid hemorrhage.<sup>112, 141, 142</sup> Will et al.<sup>136</sup> reported the brain of a patient who died 15 minutes after the twelfth EST to be swollen and edematous with neuronal damage and increased lipofuscin pigmentation. Madow<sup>42</sup> reported autopsy data in four subjects, finding one case with intraventricular hemorrhage and three who died of cardiovascular disease.

#### *Animal Experimental Data*

After experimental seizures in animals, punctate hemorrhages and subarachnoid bleeding are seen.<sup>143, 144</sup> Monkeys subjected to 4–18 seizures at a rate of 3 per week show a reversible degeneration of cerebral cells and gliosis.<sup>145</sup> Follow-up studies at 30 min–18 months in monkeys receiving an extensive course of 32–100 seizures, showed gliosis and cellular degeneration within days after treatment, but none after months.<sup>146</sup> Hartelius<sup>147</sup> examined the effects of seizures in cats and noted disintegration of nerve cells, neuronal loss, and glial reactions which were not extensive and which were related to the age of the animal and the number of seizures. Other workers, carrying out equally extensive studies, failed to find either vascular or glial reactions to repeated seizures.<sup>148–151</sup>

### *Effects of Status Epilepticus*

Another field of study is the pathology after spontaneous seizures in humans. A frequent finding is sclerosis of the pyramidal cell layer of Ammon's horn,<sup>152</sup> and diffuse necrosis, neurophagia, and gliosis.<sup>59,153</sup> Norman et al.<sup>154</sup> suggest that repeated seizures lead to impaired blood and oxygen supply, and that the sequence of pathologic changes are secondary to hypoxia.

In experimental studies, baboons were subjected to seizures at varying rates, and biochemical and pathologic changes in brain function were measured.<sup>155,156</sup> Repeated and sustained seizures over 1½ hours without muscle paralysis and 3 hours with muscle paralysis were required to produce measurable ischemic cellular changes. The authors compared these findings with 30–60 minutes of febrile convulsions in children required to produce cerebral pathology. Six hours or more of seizures were required in adults for the same pathology. In these studies, cerebral changes were transient unless hypoglycemia or hypoxia supervened.

The effect on the developing fetus of seizures given to the mother has been studied. ECT has been given during pregnancy without precipitating labor<sup>118,157</sup> or without measurable deficits in the fetus.<sup>157,158,159</sup>

### *Physiologic Indices*

Psychologic tests (particularly of memory), psychomotor performance tests, and electrophysiologic measures (particularly the resting EEG) are measures of brain dysfunction frequently studied in EST.

*Memory dysfunction.* The most widely known hazard of EST is difficulty in recollecting the events surrounding the immediate illness and each treatment.<sup>160–163</sup> There is amnesia for each seizure, and for the immediate postseizure period. Retrograde amnesia occurs and may extend for hours and occasionally days before EST. Tasks given patients before treatment are particularly sensitive to loss of recall. Some patients also complain of a disturbance in the clarity of their recollections, and have difficulty in recognizing events or subjects that occurred or were shown to them in proximity to the treatments.<sup>160,161,164</sup>

In memory and psychologic performance tests, performance decays progressively with successive seizures.<sup>161,164</sup> Like the physiologic (EEG) measures, the decrements rebound after each treatment. Two weeks after the last treatment, performance on memory tests is equal to or better than performance before EST. Within the few months of the last EST treatment, memory functions reach pre-illness levels for the recall of life events.<sup>164</sup> These evaluations are confounded by the depressive illness that, even in the absence of EST, is associated with measurable amnesia for the period of illness.<sup>165</sup>

*EEG.* Repeated seizures result in increased EEG slow wave activity, appearing in bursts and runs, and more prominent in the frontal and temporal leads.<sup>5</sup> The degree of slowing, the increase in amplitude, the duration of burst activity, and the persistence of these changes after the last treatment are directly related to the number and the frequency of seizure inductions. After the last seizure, slow waves rapidly decrease in amount and prominence, amplitudes decrease, and the mean frequency increases. Within 2 weeks of the last treatment, the EEG is filled with regular, rhythmic alpha activity, usually in amounts greater than before EST. Oc-



asionally, slow waves persist for a number of weeks and may be recorded 4–6 weeks after the last treatment.<sup>58,84,129,166,167</sup> These EEG changes are similar to those seen in patients with reversible organic mental syndromes.

Some authors find the EEG changes to have prognostic significance. Hoagland et al.<sup>168</sup> reported that the reduction in fast beta EEG activity was a favorable sign in the EST treatment of agitated depression—a finding confirmed by Fink and Kahn<sup>5</sup> and Kurland et al.<sup>169</sup> Roth<sup>76</sup> found the early and sustained appearance of beta activity after thiopental to be a favorable prognostic sign; this was confirmed by EEG and language studies.<sup>26,57</sup> When careful quantitative measures are applied, the relationship between improvement and degree of EEG change becomes blurred, but the EEG changes do not have negative prognostic implications.<sup>167</sup>

### Spontaneous Seizures

Spontaneous seizures have been reported in some patients weeks after the last treatment.<sup>170,171</sup> Fifty-one cases were reported up to 1955, when Blumenthal<sup>135</sup> added 12 cases. Many authors were able to elicit a prior history or a family history of seizures, and they described the seizures as examples of spontaneous epilepsy, unrelated to the EST process.<sup>7</sup> Blumenthal<sup>135</sup> estimated the incidence of spontaneous seizures after EST as 0.5%, similar to that recorded for epilepsy in the population.

Karliner<sup>172</sup> reported six examples of spontaneous seizures in patients without a history of epilepsy. The seizures remitted within 3 years, and he viewed their appearance as evidence of persistent brain dysfunction after EST.

Assael, Halperin, and Alpern<sup>173</sup> reported a single illustrative case of a 30-year-old woman admitted to the hospital in a catatonic stupor. Her EEG was normal. After four EST, she remitted and returned home. Within a fortnight she had a typical grand mal convulsion, which recurred once or twice weekly until anticonvulsant drugs were given. The EEG showed a typical epileptic pattern, and the authors concluded that this epileptic process was the result of a brain stem lesion secondary to EST.

Do spontaneous seizures result from the experimental “kindling” of epileptic foci?<sup>174</sup> Kindling occurs when the threshold for a spontaneous seizure is lowered after small electric currents are passed through implanted electrodes in the brain stem.<sup>175</sup> Kindling is associated with a lowering of the cerebral threshold, so that brain tissues fire with low, incidental brain currents. In EST, however, the cerebral threshold for seizures rises.<sup>137,176</sup> The current necessary to elicit a grand mal seizure rose in 24 of 39 cases, showed no change in fifteen cases, and in no case did it fall.<sup>176</sup> The difference between EST and the animal studies<sup>175</sup> may be in the use of implanted electrodes, the depth or absence of anesthesia, the amplitude of currents, and the frequency with which the brain is stimulated to elicit kindling.

Another persistent brain effect of EST may be inferred from the unreplicated report by Uhrbrand and Faurbye<sup>177</sup> that tardive dyskinesia may occur after extensive courses of EST.

### Other Complications

Psychoses may be exacerbated with EST. Some authors find an organic type psychosis to occur early in the course of EST, and suggest that such occurrences

may herald the existence of unanticipated brain pathology, such as brain tumor.<sup>7, 178, 179</sup>

Fractures, particularly of the spine, occurred in up to 40% of examined cases when convulsions were unmodified. Since the introduction of succinylcholine for muscle paralysis, the incidence of fractures has become negligible, occurring only in seizures that are unmodified either by neglect or when muscle relaxants are contraindicated by medical considerations in high risk patients.<sup>7</sup>

Prolonged apnea is a rare complication of the failure to degrade succinylcholine (Anectine; Burroughs Wellcome, Research Triangle Park, N.C.) enzymatically in individuals with abnormal low levels of pseudocholinesterase.

Panic and fear reactions are reduced by the routine use of pretreatment sedation and general anesthesia.<sup>62</sup> Missed seizures, in which patients experience large electric currents or the panic associated with pentylenetetrazol, are no longer a feature of properly applied treatment modified by anesthesia.

The psychologic hazards of EST persist. The use of the term "shock therapy" by physicians and the laity elicits an image of unmodified EST. The stigma of having received "shock therapy" remains a social and political liability.

Patients receiving EST may also suffer postseizure headache and nausea, skin irritations or burns at the site of electrode placement, or extravasated blood at the sites of injection. These risks are now rare in institutions in which trained therapists administer the treatment.

#### RISK/BENEFIT RATIO

These diverse observations of efficacy and complications of the EST process provide the basis for a risk/benefit analysis. There is evidence that EST is very useful in depressive psychosis, with an efficacy that is at least equal and often superior to pharmacotherapy and other therapies. The reduction in mortality from suicide is a particularly compelling observation, making suicide risk an important indication for EST.

In acute schizophrenia there is symptomatic benefit, particularly in the relief of hyperactivity, delusions, confusion, and impulsivity, approximately equivalent to that obtained with psychotropic drugs. In chronic schizophrenia, the data are less impressive, indicating that EST is no more effective nor more hazardous than other minimally effective treatments.

For other psychiatric conditions, the evidence of efficacy is limited, and the use of EST must properly be considered within the framework of a research inquiry in which the rules of consent, controls, and peer review need apply. There is a particular problem in the use of EST in children and adolescents, where the evidence for clinical efficacy is poor, the long-term risks unresolved, and proper consent ill-defined.

EST is a procedure with some risk. Death may occur with an incidence of 1/10,000 treatments. Much of the risk may be that associated with anesthesia, but the EST death rate is less than that for general anesthesia alone.\* Most reported deaths occurred early in the history of EST, when procedures were less well de-

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\*Deaths from anesthesia alone are reported from 3.3 to 37/10,000 general inductions.<sup>180-183</sup> The incidence was less (37/10,000) in the decade 1963-72 than in 1953-62, when the rate was 209/10,000. The incidence is clearly age related, rising with increasing age.<sup>183</sup>

fined. A consequence of the relative safety of the procedure is the rarity of pathologic material, leaving the issue of persistent brain damage unresolved.

Memory dysfunction, disturbances in physiologic and psychologic tests, and spontaneous seizures are persistent risks and the principal hazards of EST. The post-EST organic mental syndrome seems to persist in 1/200 cases, and may be a long-term liability. Fracture, panic, pain, and fear are no longer significant features when the full range of modifications of EST are used.

These risks and benefits of EST need to be compared to those of the alternate treatments. In depressive psychosis, EST is either superior or equal to antidepressants. The risks of antidepressants are extensive. Toxicity of tricyclic drugs includes anticholinergic symptoms, cardiovascular complications, and the risk of overdose.<sup>92</sup> The use of MAOI is restricted by hypertensive crises, cardiovascular and hepatic toxicity and their interactions with common foodstuffs, tricyclics, and some drugs used in medical practice.<sup>184</sup> In depressed patients treated by psychotherapy or milieu therapy, the risks of suicide and prolonged illness must be considered.

In mania, lithium and phenothiazines are widely used. Mortality, organic psychosis, and neurologic sequelae are complications of their use.<sup>47</sup> In very excited patients, parenteral doses of chlorpromazine or haloperidol may be combined with lithium and elicit significant neurologic sequelae.<sup>47, 185, 186</sup>

In schizophrenia, the efficacy of EST is poorly defined. Treatment results seem best with greater numbers and higher frequencies of induced seizures, increasing the probability of a persistent organic mental syndrome, memory deficits, and spontaneous seizures. The efficacy of antipsychotic drugs is well defined, but the hazards of tardive dyskinesia, hepatic dysfunction, and lenticular opacities are being recognized with increasing frequency.<sup>184</sup> Despite the risks, pharmacotherapy has significant advantages over EST in chronic cases, particularly since maintenance therapy is more readily provided by antipsychotic drugs.

#### COMMENTS

The EST process, despite its empiric origins, remains a viable treatment, and when properly applied, is safer than the records testify. The principal hazards of death, fracture, panic, fear, prolonged apnea, postseizure headache, nausea, skin irritations, and burns at electrode locations are preventable hazards. Even the persistent organic mental syndrome can be prevented, or its incidence reduced by careful attention to sedation, the use of minimal electrode currents, the location of electrodes, and mature doctor-patient relationships. EST is a major treatment in medicine, and its use by inexperienced therapists or unsupervised trainees is unacceptable. In their text, Sargent and Slater<sup>8</sup> state:

It can hardly be sufficiently emphasized that convulsion therapy is a surgical treatment in psychiatry, and the general rules governing the admissibility of surgical intervention apply. While operation should not be necessarily delayed, it should not be undertaken in a lighthearted spirit, and should never be employed as a mere placebo. The decision when operation is necessary requires a refined clinical sense, and the opinion of an expert in the treatment should be sought when available. When operation is decided on the patient should be carefully examined to exclude exceptional dangers, the position should be explained both to him and his relatives, and the permission of both sought. Finally, when the treatment is eventually carried out, every method should be used to minimize the risks which can never be entirely excluded.

The profession should assume a greater role in monitoring clinical practice. The survey of EST use in Massachusetts<sup>122</sup> provided a basis for regulations regarding the reporting of the use of EST in institutions. In a follow-up report,<sup>2</sup> fewer patients received more than 35 treatments in a year, and the use of EST in children and adolescents was less. The voluntary regulation of EST in Massachusetts is a more commendable model than the repugnant statutory regulations recently issued in California.

EST deserves greater academic attention to better define the limits of its use. EST reversibly affects mental performance and thus provides a special research technique which has only occasionally been explored.<sup>58</sup> Research should be encouraged, rather than suppressed for fear of political criticism. The efficacy of EST in chronic schizophrenia is related to the number and frequency of seizures induced, and the proper use and efficacy of multiple (regressive) EST needs more study.<sup>13,74</sup> Multiple monitored EST may shorten a course of treatment with fewer anesthetic inductions, and this assertion requires verification.<sup>15-18</sup> The efficacy in mania has been suggested,<sup>47</sup> but a prospective comparison with lithium is lacking.<sup>48</sup> While many therapists use maintenance treatments, their indications are not well defined. The many studies of psychologic, behavioral, and physiologic predictors for EST selection and outcome should be integrated and applied in clinical practice. We need ways to define the number and frequency of seizures for different illnesses. Considering the prevailing practice of using tricyclic drugs first in cases of depressive psychosis, better assessments of the risks inherent in the delayed onset of their effect, their cardiovascular effects, and their mortality are needed. Phenothiazines and antidepressants are often combined with EST, although the safety of these combinations is not defined.

More fundamental questions provide outstanding opportunities to explore the role of brain functions in behavior, and ways to prevent and treat depression: the persistent cerebral effects of seizures, particularly the changes in neuroendocrine and neurohumoral relations; the effects on cerebral metabolism and particularly the blood-brain barrier; and the psychologic, linguistic, and behavioral consequences of seizures. Such studies may replace the complexity and inelegance of EST by a simpler, more precise, and more effective therapy.

#### SUMMARY

A review of the EST process finds its efficacy and safety in the treatment of psychotic depressive states and mania to be well-documented. In acute schizophrenia, EST is symptomatic and its usefulness is equivalent to psychotropic drugs. In chronic schizophrenia, the effects of EST and other therapies are equally poor; but the principal studies are faulted by inadequate numbers of EST treatments. In all other conditions, including the use in children and adolescents, the data are insecure and additional studies are needed.

The principal risks of EST have been reduced by improved treatment methods. Fracture, panic, spontaneous seizures, and death are no longer prominent. Persistent deficits in memory and the psychologic stigma of having had "shock therapy" are the principal costs of therapy today. Suggestions to reduce these risks are made.

For depression, mania, and acute schizophrenia, EST has a risk/benefit ratio equal to or better than other available treatments. Further study of the relative

efficacy and safety of these treatments are needed; as are controlled studies for other conditions where its use has been recommended.

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