

Animals Used in these Published Studies on CES

Clark, Nancy, Mills, Daniel, Marchant, Jeremy. Evaluation of the potential efficacy of the Alpha-Stim SCS in the Horse. DeMontfort University Equestrian Centre and Field Station, Caythorpe, Lincolnshire, United Kingdom. 2002. (Publication in process)

After completing a successful pilot study of the stress reduction effects of the Alpha-Stim SCS in a 6 horse pilot study, a double-blind study was completed with 8 thoroughbred horses (2 fillies, 3 mares, 3 geldings) at the De Montfort University Equestrian Centre and Field Station at Caythorpe, Lincolnshire, United Kingdom. Alpha-Stim AS-Trode brand self adhesive electrodes were attached to shaved areas on each side of the neck beneath the collar. Alpha-Stim SCS devices were set to provide 0.5 Hz biphasic stimulation at 200 microamperes, or sham stimulation. Heart rate measurements (HR) were provided by an attached Polar Horse Trainer transmitter belt and a Polar Vantage receiver.

Observers blind to the treatment condition recorded duration of behaviors of body locomotion, head motion, ear position, oral behavior and the state of the lower lip at 15 second intervals for 15 seconds duration. Four trials were carried out each day for a total of 8 days (4 testing days per week). The frequency of each behavior was calculated and divided by the total number of observations for statistical analysis. The time standing alert decreased significantly from trial 1 to trial 4 ($p < 0.05$). The time spent standing alert also continued to decrease after the stimulation had stopped, suggesting an ongoing effect of CES following the period of actual stimulation. The horses spent significantly more time standing dozing between trials 1 and 4 ($p < 0.05$), less time with lower lip tense between trials 1 and 2 ($p < 0.05$), had less ear flicking from trial 1 to 3 ($p < 0.05$), increased head wobbling between phases 1 and 4 ($p < 0.05$), less time vocalizing between phase 1 and 4 ($p < 0.05$), and less time shaking the head between phases 1 and 3 ($p < 0.05$). All of these changes were highly intercorrelated and strongly indicated a reduction in the horses' state of arousal following treatment but not sham treatment with Alpha-Stim CES. Finally, although not significant, there was a trend in which the variation in mean HR values decreased from the first to the latter phases of the study. HR fell more in the three horses with the highest mean HR going into the study.



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The authors concluded that taken together these results are consistent with potentially beneficial effects using the Alpha-Stim SCS for horses. Effects were seen on the behaviors of greatest relevance to assessing anxious arousal in the given circumstances, namely time

spent alert and dozing, and a number of other parameters consistent with relaxation. Specifically, there was no significant increase in any parameter associated with excitement nor is there any evidence that Alpha-Stim has any detrimental effects on the horse's wellbeing. A number of parameters, which may also be indication of relaxation, were not significantly effected by the Alpha-Stim SCS but this could be explained by their rarity. The results further suggest that CES effects extend beyond the period of immediate stimulation.

Other CES Device Reports

Culp, L.P., Skarda, R.T. and Muir, W.W. Comparisons of the effects of acupuncture, electroacupuncture, and transcutaneous cranial electrical stimulation on the minimum alveolar concentration of isoflurane in dogs. *Am J Vet Res.* 66(8):1364-70, 2005.

This study at the College of Veterinary Medicine, Ohio State University, Columbus, compared the effects of acupuncture (AP), electroacupuncture (EA), and CES with high-frequency intermittent currents on the minimum alveolar concentration (MAC) of isoflurane and associated cardiovascular variables in dogs. 8 healthy adult female Beagles were anesthetized with isoflurane on 4 occasions, allowing a minimum of 10 days between experiments. Isoflurane MAC values were determined for each dog without treatment (controls) and after treatment with AP and EA (AP points included LI 4, LU 7, GV 20, GV 14, San Tai and Baihui) and CES. Isoflurane MAC values were determined by use of noxious electrical buccal stimulation. Heart rate, mean arterial blood pressure (MAP), arterial blood oxygen saturation (SpO₂) measured by use of pulse oximetry, esophageal body temperature, inspired and expired end-tidal isoflurane concentrations, end-tidal carbon dioxide concentration, and bispectral index (BIS) were monitored. Blood samples were collected for determination of plasma cortisol concentration. Mean +/- SD baseline MAC of isoflurane was 1.19 +/- 0.1%. Acupuncture did not significantly change MAC of isoflurane. Treatments with EA and CES significantly lowered the MAC of isoflurane by 10.1% and 13.4%, respectively. The SpO₂, heart rate, MAP, BIS, esophageal body temperature, and plasma cortisol concentration were not significantly different after AP, EA, CES, and control treatments at any time interval. The authors concluded that the use of EA and CES decreased MAC of isoflurane in dogs without inducing adverse hemodynamic effects. However, the reduction in isoflurane MAC by EA and CES treatments was not considered clinically relevant.

Robert, Claude, Limoge, Aymé and Stinus, Luis. Transcranial electrical stimulation (Limoge's currents) potentiates the inhibition of righting reflex induced by droperidol in rats. *Brain Research.* 822(10-2):132-141, 1999. (France)

The effects of CES on droperidol-treated rats were evaluated using the righting reflex latency (RRL) test. CES was shown to potentiate the inhibition of righting reflex induced by droperidol. This potentiation was found to depend on the dose of the drug, the characteristics of the current delivered and the duration of stimulation. The author's also observed that CES-induced potentiation of inhibition of righting reflex produced by droperidol injection was not reversed after naltrexone administration, or when measures were performed on p-chlorophenylalanine (pCPA)-treated animals. These results suggest that, under the experimental conditions: (i) CES does not interact with endogenous opioids to potentiate droperidol effects, (ii) the effect of CES on dopaminergic system prevails against CES action

on serotonergic system. Though these findings enlarge the comprehension of CES effects on the central nervous system, further investigations are necessary to elucidate CES mechanisms.

Little, Bert and Patterson, Margaret A. Embryofetal effects of neuroelectric therapy (NET). *Electro and Magnetobiology*. 15(1):1-8, 1996.

After obtaining IRB approval by the University of Texas Southwestern Medical Center, virgin Sprague-Dawley female rats were mated with Sprague-Dawley male rats. All rats were fitted with 2 ear identification tags, including controls who did not receive any CES, to provide equal nociception and stress. All rats were permitted to move freely within their cages. The treated rats were divided into 3 groups and given CES 1 hour daily throughout their pregnancy at either 10, 100, or 1,000 Hz, 1 volt, 0.125 mA, at a 0.22 mS pulse width via alligator clips attached to the ear tags. On day 18 of pregnancy, the dams were killed by guillotine or with ether, and cesarean section was performed immediately. Fetuses were counted and the uteri were examined for evidence of embryo resorption. The fetuses were immediately placed in 10% formalin. Xeroradiographic surveys of posteroanterior and lateral views of each fetus were taken and evaluated for cranial, rib, vertebral, or long bone abnormalities. After thorough external examination, autopsies were performed under a dissecting microscope to evaluate the palate, heart and major vessels, lungs, liver, kidneys, ureters, and bladder. Statistical analysis included the use of χ^2 , analysis of variance, and Newman-Keuls multiple group comparisons test. 844 fetal rats were evaluated.

The detailed external examinations under light microscopy revealed no obvious neural tube defects, limb reduction deformities, or anterior abdominal wall abnormalities in the controls or any of the treatment groups. Skeletal surveys of the fetal rats revealed no vertebral column, rib, or long bone deformities. Comparison between groups revealed more pregnancy resorptions and fewer offspring in all treatment groups as compared to the control group, with the difference reaching significance in the 1,000 Hz treatment group. Average fetal weights were inversely proportional to frequency and were significantly different among groups. Fetal brain weight followed a similar pattern of reduction, except that weights were not significantly different between the medium and highest frequency treatment groups.

In their discussion, the authors stated that while the incidence of congenital anomalies was zero, the reason pregnancy resorptions were increased may be due to the CES treated rats being more complacent. Their behavior resembled the effects of CES in humans, even in this aggressive population well known for their violence. The treated rats were not as active as the controls, accordingly it is possible that food intake was lowered in the treatment group, a reasonable implication given the reduction in fetal weights. The authors concluded that CES may be embryolethal in the very early stages of pregnancy in the rat and might cause some miscarriages, but there is no evidence of fetotoxic effects. The relevance of these findings to humans is unknown.

Mantz, J., Azerad, J., Limoge, A. and Desmots, J.M. Transcranial electrical stimulation with Limoge's currents decreases halothane requirements in rats. Evidence for the involvement of endogenous opioids. *Anesthesiology*. 76:253-60, 1992.

CES has been shown to facilitate anesthesia/analgesia in surgical patients. However, the neurobiologic substrate of this effect remains unknown. The present study was designed

to analyze the influence of CES on halothane requirements in rats and the contribution of the central endogenous opioid, alpha 2-adrenergic and 5-hydroxytryptamine (5-HT1 and 5-HT2) serotonergic systems to this effect. The influence of CES on the MAC of halothane (MACH) and its reversibility by a subcutaneous 2 mg/kg naloxone injection were first determined in 20 rats using a randomized blinded protocol. MACH was decreased markedly in stimulated animals (CES, N = 10) in comparison with sham-operated nonstimulated rats (controls, N = 10): MACH = 0.60 ± 0.15 , mean \pm SD, versus 1.07 ± 0.05 vol%, $P < .001$. In CES animals, naloxone administration restored MACH values to the levels of controls but failed to affect MACH in controls. The influence of the duration of CES applied prior to MACH determination was further investigated in 30 animals. The magnitude of MACH reduction was significantly increased with the cumulative duration of stimulation. For each duration of stimulation tested, administration of a 5-micrograms intracerebroventricular (icv) dose of the enkephalinase inhibitor thiorphan significantly enhanced CES effects ($P < .05$). Finally, the icv administration of a 15-micrograms naloxone dose appeared to completely reverse the MACH reduction elicited by CES (N = 8, $P < .01$).

Krupisky, E.M., Katznelson, Ya.S., Lebedev, V.P., Flood, N.V., Patterson, M.A., Lipton, J.M. and Kozlowski, G.P. Transcranial electrostimulation (TES) of brain opioid structures (BOS): experimental treatment of alcohol withdrawal syndrome (AWS) and clinical application. Presented at the Society for Neuroscience Annual Meeting, New Orleans, November 10-15, 1991.

Alcohol withdrawal syndrome (AWS) was induced in rats. Noninvasive CES increased the β -endorphin level in rat cerebrospinal fluid from 15.93 ± 2.17 to 53.25 ± 6.1 pmol/ml and met-enkephalin from 3.61 ± 1.39 to 7.86 ± 0.94 pmol/ml. Marked therapeutic effect of CES was also demonstrated in this animal model. Clinical double-blind placebo-controlled studies showed that CES was an effective method in the treatment of AWS in patients. After the CES treatment in AWS patients, the β -endorphin concentration in plasma rose from 5.86 ± 0.72 to 10.66 ± 0.65 pmol/L. There was a threefold increase in β -endorphin concentration after just 1 CES treatment.

Dougherty, P.M., Dong, W.Q., Faillace, L.A. and Dafny, N. Transcranial electrical stimulation attenuates abrupt morphine withdrawal in rats assayed by remote computerized quantification of multiple motor behavior indices. *Eur J Pharmacol.* 175:187-95, 1990. (Netherlands)

The goal of the present study was to assess the effects of CES on the behavioral signs of the abrupt withdrawal syndrome of rats. However, this goal also necessitated the introduction of an experimental model measuring animal behavior for prolonged periods of time using a computerized animal activity monitoring system to quantify spontaneous motor activities associated with abstinence behavior. Comparable withdrawal severity was obtained by both the activity monitoring system and investigator observation of motor signs of abstinence behavior. Moreover, using this system we demonstrate a time-dependent effect of electrical stimulation in reducing the severity of various indices of motor hyperactivity associated with abrupt morphine withdrawal in rats.

Stinus, Louis, Auriacombe, Marc, Tignol, Jean, Limoge, Aimé and Le Moal, Michel. Transcranial electrical stimulation with high frequency intermittent current (Limoge's) potentiates opiate-induced analgesia: blind studies. *Pain*. 42(3):351-363, 1990.

CES with high frequency (166 kHz) intermittent current (100 Hz: 2 μ S positive and 4 μ S negative pulses, 100 mA peak-to-peak current corresponding to 17.5 mA effective current, "Limoge" current) has been used for several years in cardiac, thoracic, abdominal, urological and micro-surgery in France. The main benefits are a reduced requirement for analgesic drugs, especially opiates, and a long-lasting postoperative analgesia. This study confirmed these clinical observations using an Anesthelec MPO3 device with 213 male Sprague-Dawley rats using the tail-flick latency (TFL) test to measure pain threshold. CES was not found to modify the pain threshold in drug-free rats, but it potentiated morphine-induced analgesia (systemic injection). To obtain a maximal effect, the stimulation must be initiated 3 hours before the drug injection and be maintained throughout the duration of its pharmacological action. CES potentiation was found to depend on the dose of the drug, the intensity of the current and the polarity of electrodes. Blind tests of the efficiency of CES on several opiate analgesic drugs currently used in human surgery (morphine, fentanyl, alfentanil and dextromoramide) confirmed these findings. The analgesic effect of these 4 opiates (TFL as % of baseline without or with CES) were respectively: 174%, 306%; 176%, 336%; 160%, 215%; and 267%, 392%. The results were obtained not only after systemic opiate treatment, but also after intracerebroventricular injection of morphine (10 micrograms; analgesic effect 152%, 207% with CES) suggesting that CES potentiation of opiate-induced analgesia is centrally mediated. These findings confirm clinical observations on the potentiation of the analgesic properties of opiates by CES.

Non-quantitative observations indicated that CES did not affect the behavior of the rats. They ate, drank, and slept as well as the control rats. Under 100 mA CES, the rats moved normally in the cages, during handling they seemed reactive, motor strength and movements were not affected, catalepsy and sedation were absent and their tail-flick reaction was vigorous. This observation suggests the asymptomatic nature of CES, which can be applied for several days without causing any adverse reactions.

Warner, R., Hudson-Howard, L., Johnston, C. and Skolnick, M. Serotonin involvement in analgesia induced by transcranial electrostimulation. *Life Sciences*. 46:1131-8, 1990.

The experiments described here were intended to investigate whether serotonin (5HT) may be involved in analgesia induced by low current CES. The CES stimulus is a 10 μ A, 10 Hz, pulsed current transmitted via electrodes in the pinnae. Combinations of the following were given as intraperitoneal injections: 300 mg/kg p-chlorophenylalanine (pCPA) 48 hours before testing, 100 mg/kg 5-hydroxytryptophan (5HTP) 30 minutes before testing and the saline vehicle for these drugs. Rats were tested prior to and 30 minutes after CES or sham CES. Testing for analgesia consisted of putting progressively increasing pressure on the rat tail 1/4 inch from the tip with a pneumatically driven, right angle wedge. The amount of pressure at which the rat moved its tail was measured both before and after CES, or sham CES, and recorded as the difference in tolerated peak pressure (DTPP). CES produced analgesia as manifested by a 613% increase in DTPP compared with sham CES treatment values. Among CES treated rats, pretreatment with pCPA decreased DTPP 91.5% compared with saline control values, indicating 5HT involvement. 5HTP restored CES induced

analgesia in pCPA treated rats to the level of saline treated control animals, confirming 5HT involvement.

Wilson, O.B., Hamilton, R.F., Warner, R.L., Johnston, C.M., deFriece, R., Harter, L., Schweitzer, C., Talaverra, J., Hymel, C.M. and Skolnick, M.H. The influence of electrical variables on analgesia produced by low current transcranial electrostimulation of rats. *Anesth Analg.* 68:673-81, 1989.

Pulsed low current CES has been shown to induce analgesia in rats as measured by the wet tail flick test. This study investigates the effect of varying stimulus frequency, pulse width, charge balance and polarity, as well as the influence of electrode placement and time of day at which stimulus occurred. A biphasic, charge balanced waveform with a first phase duration of 2 mS, 10 μ A and 10 Hz was found to induce maximum tail flick latency changes. The effects of morning or nighttime stimulation were statistically indistinguishable, as were the differences between monophasic and biphasic stimulation. Analgesia was maximized when a positive first phase was delivered into the right ears of the rats, but monolateral stimulation with both electrodes on either the left or the right ear produced no measurable effect. Examination of CES responses in sham and stimulated populations reveals normal response distributions with the stimulated group skewed toward a positive effect.

Capel, I.D., Pinnock, M.H., Withey, N.J., Williams, D.C. and Patterson, M.A. The effect of electrostimulation on barbiturate-induced sleeping times in rats. *Drug Development Research*, 2:73-79, 1982.

This study was conducted to determine the biochemical basis by which CES might induce drug detoxification. The time taken to regain righting reflex following barbiturate anesthesia (sleeping time) was investigated as a means to provide an in vivo estimate of hepatic function. Naloxone was administered prior to CES to determine whether the effects on barbiturate anesthesia was mediated by endorphins. Female rats were anesthetized by intraperitoneal administration of either hexobarbital (100 mg/kg), thiopentone (56 mg/kg), or quinalbarbitone/amylobarbitone (25 mg/kg). Electrodes were attached to the rats ear via alligator clips to Michaels suture clips inserted through each pinna. Treated animals were stimulated until they regained their righting reflex with 1 volt at a 0.22 mS pulse width. A control group of rats were sham treated via the same connections without the CES device being turned on.

CES treated rats regained their righting reflex more rapidly than sham-treated controls following administration of anesthetics. The most effective frequencies in decreasing hexobarbital-induced sleeping time was 10 Hz ($P < .001$) or 500 Hz ($P < .001$). The treatment produced no significant difference in microsomal protein or cytochrome P450 levels. Paradoxically, two mixed function oxidase enzyme activities investigated, aminopyrine N-demethylase and aniline hydroxylase, were significantly lower ($P < .001$) in the CES treated rats than in the sham treated littermates.

Pretreatment with naloxone increased the hexobarbital-induced sleeping times of the non-CES rats. CES at 10 Hz was far less effective in reducing sleeping time following pretreatment with naloxone, whereas the reduction of sleeping time was greatly enhanced ($P < .001$) at 500 Hz.

Rats receiving CES at 10 Hz had significantly lower ($P<.002$) and those treated at 500 Hz had significantly higher ($P<.025$) serum cortisol levels than the sham treated controls.

Capel, I.D., Williams, D.C., Davey, R.W. and Patterson, M.A.. Amelioration of restraint stress by electrostimulation. *IRCS Medical Science: Biochemistry, Environmental Biology and Medicine, Nervous System, Pharmacology, Psychology and Psychiatry.* 7:634, 1979.

Device: 100 Hz, pulse width 0.22 mS, mean voltage of 9 to 11 V.

Two groups of 6 male Sprague-Dawley rats of body weight 250 +/- 20 g were housed 6 per cage in standard high density polypropylene cages on sawdust bedding. Each ear was pierced by insertion of a Michel suture clip. 24 hours after insertion of the ear clips the rats were placed in individual restraining cages. Electric current was passed from the CES device through the ear clip electrodes via alligator clips attached to the sutures. Sham treated animals were connected in the same way, but no electricity was passed. Both sets of animals remained in their restraining cages for 3 hours. Plasma cortisol levels were significantly lower ($P<0.001$) in the CES treated rats (70 +/-32 ng/ml) compared with the sham (162 +/- 22 ng/ml). There was no significant change in liver weight or microsomal protein in either CES or sham treated rats. Aryl hydrocarbon hydroxylase ($P<0.001$), nitroanisole demethylase ($P<0.05$) and uridine diphosphoglucuronic acid transferase ($P<0.05$) of the CES treated animals were significantly higher than those of the sham treated controls. Paradoxically, the activity of the mixed function oxidases was increased by CES despite the decreased cortisol levels. The authors concluded that further work is necessary to elucidate the mechanisms by which CES enhances hepatic enzyme activity.

Hornstein, S.R., Filho, R.A., Toledo, M. and Spirck, C.N. Preliminary data on a new method for lithium therapy. *Rev Bras Pesqui Med Biol.* 10:249-54, 1977. (Brazil)

Lithium therapy was assessed using CES on two dogs. Cotton swabs soaked in an aqueous isotonic lithium chloride solution were placed over the eyes and mastoids of the dogs, and connected to the CES apparatus. In 2 minutes, sleep was induced in both dogs, at 500 μ A on the intensity scale (which runs 1 to 9 mA). After 2 hours, the apparatus was turned off. One of the dogs was put under continuous observation, and the other one was sacrificed. Parts of it's cortex, subcortex, and cerebellum were processed and fragments were assayed spectrophotometrically for Lithium. Lithium was found in all the material examined. These results suggest a possible technique for Lithium therapy using CES, the ion being carried directly to the CNS, avoiding systemic toxicity caused by oral administration.

Jordan, Eric J. and Morris, David. Evaluation of the electrosleep machine. *Diseases of the Nervous System.* 36(12):661-665, 1975.

9 littermate-male Beagle dogs were given 13 daily 1 hour treatments under anesthesia with eye to occipital electrodes and measured with EEG's, ERG's, blood pressure, temperature, respiration, blood and urine analysis. Photic stimulation was applied in addition to the CES. 3 dogs were given "normal" levels of 1 mA AC and .33 mA DC, another 3 received "high" levels of 5 mA AC and 1.33 mA DC, the third group of 3 had sham treatment.

After the course of treatment, the dogs were sacrificed and examined. 2 dogs suffered direct trauma from the cisternal puncture, causing spinal cord lesions. No neurologic signs were noted from the CES. It was noted that CES may cause mild EEG slowing. Suspicious findings were found in the striate cortex, caudate nucleus, and septum. Except for 1 case, these were small and of questionable significance. There were no changes that were unequivocally pathological. No acute or chronic changes were noted in BP, EKG, temperature or respiration. The authors concluded that evidence of CES-induced pathology is inconclusive.

Richter, Ward R., Zouhar, Raymond L., Tatsuno, Jiro, Smith, Robert H. and Cullen, Stuart C. Electron microscopy of the macaca mulatta brain after repeated applications of electric current. *Anesthesiology*. 36(4):374-377, 1972.

2 immature Rhesus monkeys and a control were studied to assess safety of electric currents applied to the brain. 1 monkey received only sine wave current up to 50 mA, another received only square wave, up to 13 mA. They received 10, 1 hour treatments. Following the course of treatment, the monkeys were sacrificed and brain tissue was analyzed. They examined neurons, neuroglia, myelinated and nonmyelinated fibers, capillaries and nearby astrocytes, synaptic endings and the general architecture of the neurophil. Special attention was given to the structure of the synapse and the size, location, and distribution of synaptic vesicles. The authors concluded that all of these structures were within normal limits, that there is no generalized evidence of injury, and that they have greatly increased their confidence in the safety of repeated application of electric currents.

Reigel, D.H., Larson, Sanford J., Sances Jr., Anthony, Christman, Norbert, Dallmann, Donald and Henschel, Ernest O. Effects of electrosleep currents on gastric physiology. In Reynolds, David V. and Sjoberg, Anita (Eds.) *Neuroelectric Research*. Springfield, Charles Thomas. 24:226-229, 1971.

Gastric cannulas were placed in the dependent portion of the stomach of seven stump-tailed monkeys. After recovery from surgery, CES currents of 20 to 100 μ A, 2.5 to 70 Hz, were applied between the nasion andinion for periods of 1 hour. The maximal change in gastric secretion occurred during the last half of the 60 minute period of CES. The mean volume decreased 28.3%, the mean concentration decreased 38%, and acid production decreased 60%. Acid production returned to normal within 1 to 2 hours after CES. The authors found that nocturnal gastric acid levels without CES were similar to those during application of CES or during in-depth stimulation of various limbic structures, and concluded that these two types of stimulation may affect similar structures.

Pozos, Robert S., Richardson, Alfred W. and Kaplan, Harold M. Electroanesthesia: A proposed physiologic mechanism. In Reynolds, David V. and Anita Sjoberg (Eds.) *Neuro-electric Research*. Charles Thomas, Springfield, Pp. 110-113, 1971.

The authors used both electroanesthesia and CES current levels along with reserpine, anoxia, L-dopa, atropine and physostigmine in mongrel dogs to elucidate the mechanisms of action from electrical stimulation to the head. Their findings suggested that CES releases dopamine in the basal ganglia, and that the overall physiological effects appear to be

anticholinergic and catecholamine-like in action, and that some form of acidosis or a concomitant of this state is implicated in the mechanism of action.

Singh, Baldev, Chhina, G.S., Anand, B.K., Bopari, M.S. and Neki, J.S. Sleep and consciousness mechanism with special reference to electrosleep. *Armed Forces Medical Journal India (New Delhi)*. 27(3):292-297, 1971.

4 normal human subjects showed increased alpha index on EEG immediately following CES (30 to 45 minutes), which culminated in spindle and slow sleep after a variable interval. In 6 patients suffering from subjective insomnia the passage of current resulted in increased alpha activity and a subjective feeling of well-being but was not accompanied by either slow or paradoxical sleep. No side effects were reported.

In 10 monkeys with electrodes implanted in the brain the results showed that the cortical EEG activity either had increased spindle or it gave high voltage slow wave paroxysmal activity following CES induction. The increased slowing was also observed in the periaqueductal grey of the brain stem and lateral geniculate nucleus of the thalamus. The caudate, intralaminar thalamic nuclei and hippocampus showed no consistent changes. The tentative conclusion drawn by the authors was: 1) The EEG record tends to show more alpha activity after CES in human subjects, 2) Monkeys go into slow sleep showing sleep spindles and slow waves, 3) No paradoxical sleep has been recorded in animals. The authors also stated that the depth electrodes in monkeys seem to favor the contention that CES has an initial effect on the periaqueductal region and then it spreads to other regions of the brain.

Zuperku, E.J., Hosek, R.S., Larson, Sanford J., Reigel, D.H., Sances Jr, Anthony and Henschel, Ernest O. Studies during electrotherapeutic sleep. In Reynolds, David V. and Anita Sjöberg (Eds.) *Neuroelectric Research*. Charles Thomas, Springfield, Pp. 235-241, 1971.

CES currents from 2.5 to 80 Hz, with amplitudes from 20 μ A to 1.5 mA were applied to stump-tail macaque and squirrel monkeys and various physiological recordings made. It was found that visual and somatosensory evoked potentials were not significantly altered during and after CES. A reduction in EMG amplitude occurred during CES, and the EEG showed a greater tendency toward slower, high-voltage activity. Respiration and EKG were stable.

Austen, Burton G. Current distribution in subcortical regions of the cat's brain during electrosleep. In Reynolds, David V. and Anita Sjöberg (Eds), *Neuroelectric Research*. Springfield, Charles Thomas. 28:262-266, 1971.

Following up on earlier researchers who said that when the hypothalamus was electrically stimulated "natural sleep" resulted, the author stimulated the caudate nucleus and the preoptic region of the hypothalamus in 5 adult female cats. The stimulus was a 15 second train of rectangular pulses, each with a width of 0.3 mS, frequency of 5 Hz, and an amplitude of between 0.1 and 2 V. The resulting current density and distribution in the cats' brain was discussed.

Pozos, Robert S., Strack, L.E., White, R.K. and Richardson, Alfred W. Electrosleep versus electroconvulsive therapy. In Reynolds, David V. and Sjöberg, Anita E. (Eds), Neuroelectric Research. Charles Thomas: Springfield, 23:221-225, 1971.

This is a report of a series of 5 studies that involved a complex examination of physiologic changes in pharmacologically altered experimental animals (dogs), 20 experimental and 20 controls. The animals were prepared with 0.2 mg/kg reserpine intramuscularly. After 1 hour those given either CES, electroconvulsive stimulation or lithium chloride, developed Parkinson-like symptoms. Dogs given electroconvulsive levels of stimulation while in the Parkinson-like state experienced evoked hypersynchrony persisting for 3 - 7 minutes, while stimulated controls showed a discharge pattern lasting for only 20 - 40 seconds. The evoked hypersynchrony in the electroconvulsively stimulated animals could be returned to the duration of hypersynchrony found in the control dogs by giving them atropine (0.4 mg/kg), L-dopa (2.5 mg/kg), or CES.

The authors conclude: "It is proposed that CES, electroconvulsive stimulation, and lithium salts may share a common mechanism... Based on this study alone, the net effects of CES stimulation and electroconvulsive stimulation seem quite similar."

Jarzemski, William B., Larson, Sanford J. and Sances Jr, Anthony. Evaluation of specific cerebral impedance and cerebral current density. *Annals of the New York Academy of Sciences*. 170:476-490, 1970.

Sensor electrodes were chronically implanted in the sagittal planes in the region of the medial thalamus and in sagittal and coronal planes in the region of the motor cortex of the brains of 30 monkeys. Electrodes were placed externally at the nasion andinion. Currents varying from 0.1 to 100 mA were generated with frequencies ranging from 10 to 5,000 Hz. They found that the current densities in the brain at all frequencies tested were linearly proportional to the applied currents, but with the thalamic current density slightly higher than the cortical current density. Calculations indicated that from 42% to 46% of the total applied current entered the brain.

Reigel, D.H., Dallmann, D.E., Christman, N.T., Hamilton, L.H., Zuperku, E.J., Henschel, E.O., Larson, S.J., and Sances Jr, A. Physiological effects of electrotherapeutic currents in the primate and man. In Wageneder, F.M., and St. Schuy (Eds.), *Electrotherapeutic Sleep and Electroanesthesia*. Vol. II, Amsterdam, Excerpta Medica, Pp. 158-165, 1970.

Studies were completed on squirrel monkeys, macaque monkeys and 15 human volunteers. Measures studied were somatosensory evoked potentials, visual evoked potentials, electroretinograms, electrocorticograms, electromyographic potentials, electrocardiograms, respiratory rate, and gastric acid. For the animal studies pulse type currents from 2.5 to 80 Hz were used. For the human studies, pulsed currents of 100 - 200 μ A intensity and 5 Hz were used. They summarized: "Neurophysiologic, cardiorespiratory and gastric secretory physiology was observed in man and primate during CES. Visual and somatosensory evoked potentials were not significantly altered during and after CES in the primates. The EMG and ECG suggested changes compatible with relaxation in the primates. Respiration and EKG remained stable in both humans and primates. Total gastric acid output

in primates is significantly reduced by CES. These studies suggest that CES may be of therapeutic value."

Tatsuno, Jiro, Marsoner, Hermann J. and Fukuda, Hiroshi. The effects of diffuse currents on focal epileptic discharges. In Wageneder, F.M. and St. Schuy (Eds.) Electrotherapeutic Sleep and Electroanesthesia. Vol. II, Amsterdam, Excerpta Medica, Pp. 93-101, 1970.

In a study using 15 rabbits in which the skull was exposed via a burr hole and focal discharges engendered by painting the exposed brain surface with penicillin solution, the authors found that no currents of CES intensity were effective in suppressing epileptic activity, but some evidence was obtained which suggested that the more intense currents (30 mA, 1,000 Hz) altered the frequency of firing in the epileptic focus. They noted that while no CES study had found problems in grand mal epilepsy patients with CES (often finding positive results instead), this study suggested that focal epilepsy may react differently to CES, though the authors admit that "from the intensity of the currents used in this experiment it was not possible to conclude that the current in the CES therapy has such effects on the seizure activity of the epileptic patients." Abstract courtesy of Ray B. Smith, Ph.D., M.P.A.

Wulfsohn, N.L. and Waldron, L. The importance of trains of current producing electrosleep. In Wageneder, F. M. and St. Schuy (Eds.), Electrotherapeutic Sleep and Electroanesthesia. Vol. II, Excerpta Medica, Amsterdam, Pp. 212-216, 1970.

In an early attempt to see what parameters of CES would more likely yield sleep in subjects, 5 cats were implanted subdurally, bitemporally and occipito-frontally. The researchers applied numerous stimulation parameters, and concluded that EEG modulated trains produced better sleep effects than non-modulated trains, and were better than EEG modulated current without trains when compared with controls.

Wilson, A.S., Reigel, D., Unger, G.F., Larson, S.J. and Sances Jr., A. Gastric secretion before and after electrotherapeutic sleep in executive monkeys. In Wageneder, F.M. and St. Schuy (Eds.), Electrotherapeutic Sleep and Electroanesthesia. Vol. II, Amsterdam, Excerpta Medica, Pp. 198-206, 1970.

The authors produced a demonstrable increase in gastric acid secretion as a result of learned avoidance behavior in 6 stump-tailed macaques. CES (100 μ A, 15 Hz) markedly reduced gastric hypersecretion (50% - 75%) associated with shock avoidance behavior in these animals. The authors concluded that CES may be of clinical importance in acid hypersecretion in humans. There was no alteration in efficient behavioral performance during or after CES in these animals.

Sommer, H. and Kriebel, J. Neuropathological investigations of electrosleep in animal experiments (Rabbits). In Wageneder, F.M. and St. Schuy (Eds.) Electrotherapeutic Sleep and Electroanesthesia. Vol. II, Amsterdam, Excerpta Medica, Pp. 169-174, 1970.

Finding that the electrical parameters indicated for CES in humans did not produce sleep in rabbits, they gave 700 Hz square wave pulses with a pulse width of 0.4 mS, an average current of 0.5 mA, with a peak value of 4 mA. The animals were put into a sleep-like state 5 times per week for 15, 30, 45, or 60 minutes. Histological sections of the brains were made after 20 sessions. They found numerous pathological changes that were related to intensity of stimulation. One discussant noted that he had found such pathological changes in cats following CES experiments. At the end of the conference discussion, the authors stated that these results cannot be extrapolated to humans because these current parameters are not usually used in humans, and the conditions within the human brain are quite different from those encountered in the rabbit brain. No control animals were used.

Titaeva, M.A. Changes in the functional state of the central nervous system under the influence of a pulse current as used in electrosleep. In Wageneder, F.M. and St. Schuy (Eds.) Electrotherapeutic Sleep and Electroanaesthesia. International Congress Series, No. 136. Excerpta Medica Foundation, Amsterdam, Pp. 175-180, 1967.

This was an uncontrolled set of clinical observations of 110 patients, including 85 with schizophrenia and 25 with "asthenohypochondriacal syndromes of varied etiology." For CES they used a pulsed current of 5 - 10 Hz, and duration of 0.2 msec, at an unspecified amperage. Treatment lasted from 40 minutes to 2 hours and continued for 16 - 25 days. They deduced that their observations indicated that the principal changes arising during CES can be attributed most probably to its direct action on the brain.

They then did a series of 35 experiments on 9 rabbits with the same pulse characteristics but with 0.7 to 2.0 V. Again they concluded that their observations indicated that CES has its effects via stimulation of the nonspecific structures of the subcortex and brain stem.

Siegesmund, K.A., Sances Jr, A. and Larson, S.J. The effects of electrical currents on synaptic vesicles in monkey cortex. In Wageneder, F.M. and St. Schuy (Eds.), Electrotherapeutic Sleep and Electroanaesthesia. International Congress Series No. 136. Excerpta Medica Foundation, Amsterdam, Pp. 31-33, 1967.

Biased rectangular current pulses of 2.5 mS duration, 75 Hz, and 5 mA were delivered through electrodes on the nasion and inion of 4 squirrel monkeys. Electron photomicrographs were made of neural tissue biopsies prior to, during, and post stimulation and the number of synaptic vesicles in close apposition to the presynaptic membranes were counted for at least 200 synapses in each group. They found that in the control specimen 65% of the presynaptic terminals contained 14 ± 2 vesicles near the cleft. Shortly after maximum stimulation was reached, there was an increase of terminals with less than 9 vesicles and corresponding decrease in those with 14. After 5 minutes at an applied current of 5 mA, a further decrease in terminals with 14 vesicles and a corresponding increase in terminals with more than 24 vesicles were found. Shortly after discontinuation of stimulation, the number of terminals with 24 or more vesicles returned to control levels while the number with 9 vesicles or less remained at a higher level than in the controls.

Pocta, J., Lebl, M. and Hanka, R. The autonomic and stress reactions during electrosleep. In Wageneder, F.M and St. Schuy (Eds) Electrotherapeutic Sleep and Electroanaesthesia. International Congress series, No. 136. Excerpta Medica Foundation, Amsterdam, Pp. 342-344, 1967.

The authors completed 45 experiments in dogs, saying that dogs are known to respond to exogenous stimuli by developing disturbances of the autonomic system. The oculocardiac reflex, the carotid sinus reflex, the solar plexus reflex, leukocyte count, hemoglobin, hematocrit, segmented cells, and eosinophil count were obtained. They found that CES elicited firm and reliable stabilization of the organism. No features of instability of the autonomic nervous system were observed.

Geddes, L.A., Hoff, H.E. and McCrady, J.D. Electroanesthesia in the horse. In Wageneder, F.M. and St. Schuy (Eds). Electrotherapeutic Sleep and Electroanaesthesia. International Congress Series No. 136. Excerpta Medica Foundation, Amsterdam, Pp. 73-80, 1967.

The authors demonstrated the parameters of electrode size and current density necessary to produce burns via electrical stimulation of the skin. With electrodes similar to or smaller than those of most CES electrodes and with much greater current loads across the skin, they observed no burns. The discussion centered on the heat dissipation to be expected from polarized impedances when constant or controlled current sources are used.