April 26, 1966

Dear Dr.

The program to evaluate various electrical combinations for their potential for producing anesthesia has been designed and is enclosed. An effort has been made to include as many of the parameters we previously discussed and work out the details as soon as possible. After your review of the program, deletions or additions can be made if necessary.

This study does not go into the specific details of the basic principles as much as I would like to investigate at some time. I think it best to look at that phase of study after we complete this study and know the current combination that gives the best results. I would anticipate doing some microelectrode work for more specific information on the amount of current in specific brain areas at a later date.

I will complete my training program at | This will work very well with you July 1 - June 30 fiscal year. I had anticipated being committed until September 1, but have been able to arrange to start on this program July 1st instead.

One part of the budget was somewhat uncertain. This is in regard to the institutional overhead. After checking with the people at | I find that the overhead charges are 20% on N. I. H. or N. S. F. type grants or 40% of salaries on other types. Since you mentioned a number of groups in Washington were interested in the program, I have assumed that all involved fit into the same bracket.

Our plans are to devote full time to this program. The only exception to this for which I would like approval is to spend 9-12 days per year to provide the necessary surgical and anesthetic procedures for the kidney transplant program at the

Electroanesthesia is used in these procedures on twin calves and the very valuable data on electroanesthesia in twins of known compatibility would be included in the reports. No grant funds from the program would be used in the kidney program.

In discussing the anesthesia program with Dr. it was of considerable interest to note the suggested possibility of human application after completion of the animal program. I felt you would like to know of this in the event it is desirable to co-ordinate a human experimental program at a later date.

Let me know if I need to make any changes in the program enclosed. I am looking forward to getting started on our program and see if we can't find out what the potential of electroanesthesia really is.

Thank you for your continued interest.

Yours truly,

Enclosure

Dr. The program here is ready except for the final front office approval for which we expect no problems. Also Dr. and his secretary have security clearance so this will be no problem. Part of the items in this letter were discussed by phone after I hear from you we will make

PROJECT PROPOSAL

Title: "Effects of Combinations of Waveforms and Frequencies of Electrical Currents Applied to the Head to Produce Anesthesia"

Investigator:

Department and Location:

Director:

Objectives and Procedures:

I. Determination of the most effective combinations of electrical current producing anesthesia

A. Combinations of sine, saw tooth, square, triangle, white noise, pulse D.C. and D.C. signals will be employed in combinations to achieve this objective. Both two and three wave combinations will be employed with variable frequencies. Based on the published experience of others and my own personal experience, it is not anticipated that anesthesia will be produced by all currents. Some will produce convulsions, tonic muscle spasms, and/or respiratory-cardiac distress without anesthesia. From published data, these complications have been more evident with certain waveforms and current combinations than with others. This study proposes to determine in a systematic fashion which wave-forms and frequency combinations produce acceptable anesthesia with minimal undesirable side effects. The equipment has been designed to permit investigation of over two hundred combinations of waveforms and frequencies which will be rated according to desirable and undesirable characteristics produced.

B. Combination waves will be applied to the head by two techniques:

1. Summation of the current before it enters the head. (Two electrodes-American technique)

2. Summation of the current in the head. (Four and six electrode combinations with separate leads to the generators producing the combination-Russian technique).

Combinations of waveforms and frequencies which are obviously not satisfactory due to severe respiratory or circulatory distress, convulsions, cardiac difficulties or other unforeseen problems will be recorded as such, and will not be evaluated more extensively.

Combinations which show promise for anesthesia will be evaluated further as outlined in objective II.

II. The effect of anesthetic currents on respiration, circulation and depth of anesthesia

When a combination of electrical currents appears to have potential as an anesthetic agent. the following procedures will be followed. Pre-anesthetic measurement of all pertinent parameters will be made (see typical experiment below). The cardiac and respiratory alterations will be monitored during and after induction. If successful, a surgical procedure will be carried out to evaluate the effectiveness of the combination of current to produce anesthesia and muscle relaxation. Since it is possible with electrical current to produce satisfactory anesthesia in portions of the body while inadequate in others, six locations will be considered for surgical procedures (simple cut down). These are head, neck, limbs, bones or skin, thoracic, urogenital, superficial abdominal, and deep abdominal. Monitoring will continue during surgical procedures. After operation, current will be shut off and the recovery behavior noted. Blood samples will be drawn before, during and after anesthesia and the recovery pattern of cardiac and respiratory changes will be followed for 24 hours. Blood pressure measurement will be made by direct cannulation of the femoral artery and this will permit monitoring of heart rate as well. Respiration will be measured by pneumograph and Lead II of the electrocardiogram will be monitored before and after application of the current.

Dogs will not receive muscle relaxants nor oxygen nor will they be intubated. These will be deliberately avoided so that muscle activity and respiratory depression may be observed, when they occur. This also allows a full response to pain during surgery if there is insufficient anesthesia.

III. Determination of the total amperage of each combination and correlation with effectiveness in producing anesthesia

This will be done to determine the combination requiring minimal current for anesthesia. The current and voltage will be measured with a milliammeter and a true r.m.s. voltmeter. The waveforms will be monitored with an oscilliscope and the waveform combinations will be photographed from the scope to record them accurately. Measurement equipment will be attached to the anesthesia generator output.

IV. Determination of the "shape" of the electrical field produced by the Current combination

This will be determined by connecting the recording equipment to implanted macroelectrodes and is designed to indicate the distribution of the current within the brain and its intensity. For this study, six chronic electrodes will be placed in selected locations within the brain. Dogs will then be subjected to currents of waveform and frequency combinations known to produce anesthesia. Recordings will be made using the same equipment required in Section III.

These dogs will be used only to measure the shape of the electrical field. Since these dogs can be used repeatedly, we plan to keep five dogs with chronically implanted electrodes at all times. The use of these same animals for several combinations of currents will reduce the error in measurement between animals.

These dogs will be prepared early during the period required to obtain the necessary equipment and personnel to initiate the other aspects of the project. Metallic-nylon electrodes will be implanted through small trephines in the skull during general anesthesia. The micromanipulator will be used for positioning electrodes with neurosurgical assistance.

V. Typical Experiment: Planned technique for evaluation of each combination

A. Waveform combination and frequency will be selected and equipment adjusted for operation.

B. The following measurements will be made on normal animals:

1. Heart rate and ECG.
2. Respiratory rate.
3. Rectal temperature.
4. Arterial blood gases (pCO_2, pO_2) and pH.
5. Notation of general physical condition, activity and alertness.

C. Animal will then be prepared for application of current.

1. Preparation of electrode sites (Bitemporal or frontal-occipital).
2. Cannulation of femoral artery with local anesthesia.
3. Placement of electrodes (electrode will be needle or plate depending on D.C. or A.C. operation).

D. Connect leads and apply current.

1. Record response (muscle movements, struggling, excitement, salivation, etc.).
2. Monitor blood pressure, cardiac rate and respiratory rate.
3. Sample arterial blood for PCO_2, PO_2, pH when induction is completed or abandoned.

E. Determine depth of anesthesia by tail clamping, corneal reflexes, swallowing reflexes. If no anesthesia, abandon.

F. If anesthesia present, proceed to cut downs at various sites. Monitoring will continue throughout operation. Responses to incision in various areas and manipulation will be noted.

G. Response to removal of current from the head will be recorded and all parameters remeasured.

H. Twelve and 24-hour post-operative observations will be made.

I. Determination of the current and voltage levels will be made after induction, during operation, and just prior to termination of current application.

J. If satisfactory anesthesia obtained, shape of electrical field will be determined in dogs with chronically implanted electrodes.

The number of combinations of currents and waveforms to be evaluated and the need for numbers of animals sufficient for proper statistical analysis make it necessary to use a large number of dogs. Each dog will be used as extensively as possible and yet yield accurate results. It is anticipated that some losses by death will occur, especially since many current combinations have never before been attempted. When possible, dogs will be reused as often as practical. To obtain a definitive answer for each current we believe 4 dogs must be studied before abandoning the combination. Combinations which give promise of satisfactory anesthesia will be studied more extensively whenever indicated.

Responses noted during the entire procedure will be recorded in terms of depth of anesthesia and duration of current application.

The investigator and technicians will spend full time on the project and will have no other activities. A two-year period is considered the minimal time to complete the program. It is anticipated that two months will be required to assemble the equipment and personnel necessary for full scale operation.

Illustration of the Method of Determining Waveform Combinations

Waveforms

A. Sine
B. Square
C. Triangle
D. Saw Tooth
E. Random or White Noise
F. D.C.
G. D.C. pulse

Combinations

A+A	B+B	C+C	D+D	E+E	F+F	G+G
A+B	B+C	C+D	D+E	E+F	F+G	
A+C	B+D	C+E	D+F	E+G		
A+D	B+E	C+F	D+G			
A+E	B+F	C+G				
A+F	B+G					
A+G						

Combinations will be summated before and after entering head. Frequencies will also be varied. The same system will be used for determining triple waveform combinations.

BUDGET

PERSONNEL SALARIES

Investigator.............Full Time.............. $
Technicians (2)
1. Assisting with animal procedures
   Anesthesia and Surgery
2. Laboratory Analysis
   (Blood gases, etc.)
Secretary - part time (50%)
Total $

ANIMALS

500 dogs @) each $
Board - 5 dogs for 365 days @ .60/day
500 dogs for average of 3.5 days @ .60/day
Total $

EQUIPMENT

Components for Anesthesia Apparatus:
(1) Harrison Lab. Model 865 C for D.C. $
(2) Universal Dynamics Electro-Thesis D.C. pulse generator
(3) Hewlett-Packard Model #3380B Sine Wave
(4) Hewlett-Packard Model 3300A/3304 Function generator for triangle & sawtooth
(5) General Radio Model 1390-B - (a component for random noise)
(6) Krohn-Hite Model 310-C - Tuneable filter for producing ranges of random noise
(7) Interconnecting cables, leads from generators to animals, connected hardware, etc.
Sub Total $

Recording Components:
(1) Oscilliscope - To monitor waveforms and observe electrical field in head. Hewlett-Packard Model 141 A with Differential Amplifier (1403A), Time base 1420 A or equivalent $
(2) Oscilliscope Camera for recording waveforms for records

(3) Milliameter - To measure the current applied to head and also in brain $

(4) True R. M. S. Voltmeter - To measure the true R. M. S. current. Gives information needed for true electrical power applied to the head.

(5) Connections, shipping

Sub Total $

Micromanipulator for positioning electrodes $

Electrodes

Blood Gas Analysis Equipment:

(1) Instrumentation Labs. Micro Analysis System recommended $

(2) Gases for Analysis Equipment

Surgical Supply Charges:

(Includes instruments, drapes, suture, related surgical supplies.) Charges are $ /set per day. It is planned to complete series procedures on days of surgery for more efficiency and economy. We are capable of performing 12-14 surgical procedures for the purpose of evaluation of anesthetic levels in the various regions of the body/day. Surgery is planned for 170 days. $

Total $

MISCELLANEOUS

Photography $
Travel
Tubing, catheters, drugs

Total $

INSTITUTIONAL OVERHEAD

40% of Salaries $

Grand Total - 1st Year $

BUDGET - 2nd Year

PERSONNEL SALARIES

Investigator	$
Technicians	
1.	
2.	
Secretarial Service - 50% of Time	
Total	$

ANIMALS

600 dogs @	$
Board -	
Total	$

EQUIPMENT

Replacements, extra components for anesthesia equipment	$
Electrodes	
Blood gas equipment, electrodes and gases	
Surgical Supply Charges	
Total	$

MISCELLANEOUS

Photography	$
Travel	
Drugs, tubing, small equipment	
Total	$

INSTITUTIONAL OVERHEAD

40% of Salaries	$
Grand Total - 2nd Year	$

INTRODUCTION

A wide range of electrical waveforms have been used on many species of animals and on man since Le Duc[1] made his attempts to produce electro-anesthesia in 1902. The most common types of current used were either direct current with DC pulses, square, triangle, sawtooth, or sine waveforms, or combinations of these. White noise was also introduced in attempts to produce better anesthesia. The principal responses detected by a number of investigators during the past few years are included. Examples of both desirable and undesirable reactions observed are included.

Fabian[2] and Hardy[7-9] did extensive animal studies and then attempted human applications. They used 700 cycle per second sine wave and characteristically produced strong tonic muscle contractions. The most conspicuous cardiovascular reaction was hypertension and tachycardia. This was associated with a rise in plasma catechol amine levels. Prolonged electro-anesthesia had little effect on the blood oxygen if the animal was well ventilated. A hyperglycemic response was recorded in animals subjected to electro-anesthesia.

Geddes[3,4] reported on results in dogs and horses. Direct current with DC pulses was used and hypertension and poor muscle relaxation were characteristics. He observed cardiac and respiratory arrest in all cases. This was temporary in most cases if the current levels were properly adjusted. However, in his report on applications in horses, there was a 14 per cent mortality rate due to permanent respiratory arrest. Salivation and hyperthermia were also observed as undesirable side effects in dogs.

Gowing[5,6] reported no abnormalities in the electrocardiogram during electro-anesthesia by DC-square wave current in dogs.

Herin[10] evaluated the responses and current requirements in dogs using sine, square and triangle waveforms. He concluded that sine wave applications gave the least amount of unwanted side effects. The hypertension during induction subsided as anesthesia progressed. Hematologic studies before, during and after electro-anesthesia revealed no significant differences in blood clotting time, packed cell volume, sedimentation rate, hemoglobin or differential white blood cell count.

Klemm[11,12] used square wave currents at frequencies up to 1100 c.p.s. A relationship between the amount of current required and the frequency of the current was observed in applications to cats.

Knutson[13-16] conducted most of his work with 700-1500 cycle per second sine wave currents in dogs and man. Hyperglycemia occurred during the passage of electrical currents. Knutson found no evidence of brain damage from the current levels used in his experiments, but cites work done by other investigators with higher voltage levels which produced hemorrhages in the brain. At the lower levels of current application, the principal danger of brain cell damage was from inadequate oxygen, due to depression of the respiration by physical interference from muscle contractions. Knutson controlled convulsions by the use of muscle relaxants or by adjustments in the current applied to the head.

Knutson found that serum potassium, calcium, chloride and sodium did not change during three hours of continuous electro-anesthesia. Blood urea nitrogen levels indicated a decrease in kidney function.

By using techniques of modern anesthesia, Knutson was able to eliminate or modify the complications of cyanosis, bradycardia, cardiac irregularities and severe muscle contractions.

Price[17] reported muscle spasms, elevation in blood pressure and tachycardia as the principal disadvantages. His experience indicated that children and elderly patients tolerated electro-anesthesia especially well. The responses to electro-anesthesia could indicate potential use in patients with low blood pressure or bronchial infections, according to Price. The wave form used was sine wave at 700 cycles per second.

Powers[18, 44] reported diverse effects he observed in dogs using 700 c.p.s. since wave current. Current of 100 milliamperes for one-half hour produced increases in the hematocrit unless dogs were splenectomized. A significant increase in the myocardial contractile force was recorded using a Walton-Brodie strain gauge sutured to the right ventricle and recorded on a Model 5c Grass polygraph.

Sances[19-26] used rectangular electrical waves and made studies on conduction over cortical pathways. Evoked potentials were recorded in Macaque monkeys during electro-anesthesia. With electrical stimulation of the sciatic nerve, the evoked response recorded from the medial lemniscus was minimally affected, that recorded from the nucleus ventralis posterior was moderately reduced in amplitude, while the evoked potential recorded from the post central gyrus was abolished.

Smith[32-36] used a number of different currents in his research. In dogs subjected to 20 milliamperes of DC and 20-30 milliamperes of square wave AC, there was a temporary but consistent change in amplitude and frequency of the EEG. The post-electro-anesthesia EEG pattern returned to normal within 30 minutes.

Histo-pathology studies revealed no neuronal changes other than agonal swelling, without areas of hemorrhage or necrosis in the eight brains evaluated.

In clinical studies on dogs, respiration was slowed, but the arterial oxygen saturation did not fall below 91 per cent. The pCO_2 levels did not rise above normal. Body temperature rises were detected, but could be reduced if the animal was not intubated and had the tongue exposed to the air.

Turbes[37-39] used a variety of currents and studied the effects on the EEG, reflexes, pain and maintance of electro-anesthesia. Slow induction was found to give a more acceptable physiological state and thus give more reliable results for all parameters evaluated. Fast inductions gave cardio-pulmonary difficulties which were fatal if not treated promptly.

Van Harreveld[40-43] using 60 cycle currents observed respiratory arrest during induction with 300 milliamperes of current. After this initial period, he reduced the current sufficient to restore respiration. No mention was made of the number of animals that had permanent respiratory arrest. Increases in blood pressure were observed. The material published by Van Harreveld indicated respiratory difficulties were present throughout his procedures.

Many of the difficulties reported with the use of electro-anesthesia can be controlled by the application of proper principles, as Knutson indicates. Cardiac and respiratory difficulties will frequently occur if these are not observed.

The two most important principles of safe anesthesia which should be observed during electro-anesthesia are the maintenance of respiration and circulation. Most of the problems encountered are related to one or both of these systems. Maintaining proper ventilation for appropriate oxygen supply to the cells, adequate elimination of carbon dioxide and normal blood pH is essential. Equally important is the maintenance of a safe blood pressure, sufficient cardiac output, and a proper blood supply to all vital body tissues.

It is important to consider the comfort of the patient and avoid undue stress, injury and discomfort. The anesthesia should be controlled to assure adequate depth for the surgical procedures that are to be performed.

The conscientious anesthesiologist never relinquishes the immediate care of his patient until he is certain that he is no longer needed for the support of the patient's normal physiological state. He is responsible, from the administration of the preanesthetic drugs until the completion of the post-anesthetic care, for the needs of his patient. The investigator in electro-anesthesia should be expected to maintain the same degree of responsibility. He must maintain a physiological state that is as near normal as possible throughout the application of the electrical currents for anesthesia.

Proper attention to the principles of anesthesiology in the calf and other animals has made it possible to produce adequate anesthesia for surgery without cardiac and respiratory arrest and related difficulties. Higher frequencies are needed to eliminate these problems and applications need to be made with a slower induction than routinely used by many investigators.

Investigations at Oak Ridge, Tennessee[27-31] proved it was not necessary to use techniques which interfer with the normal function of the animal. These applications of electrical anesthesia were sufficient to produce anesthesia for surgery. Later the same results were accomplished in other environments.

PURPOSE OF THE PROPOSED RESEARCH PROGRAM

Numerous investigators since 1902 have attempted to produce anesthesia with the use of electrical currents. Many types of current and methods of applying them have been tried. Some of these have been moderately successful in producing an anesthetic state. Even with successful applications, however, unwanted side-effects were usually present and resulted from the application of electrical current to the brain as a whole. Indiscriminate application of electrical currents to the head accounted for the severe unwanted actions.

It is not known if electrical currents sufficient to produce anesthesia can be directed to specific areas of the brain through external electrodes. Neither do we know if this would eliminate all unwanted side-effects. There is also a lack of sufficient evidence to distinguish between anesthesia and paralysis produced by electrical currents in animals.

The understanding of the mechanisms by which electro-anesthesia is produced could make it possible for this method of anesthesia to become clinically acceptable. Therefore, the proposed program to determine the information necessary to justify the extension of the use of electrical current for clinical anesthesia is submitted.

OBJECTIVES OF THE PROPOSED RESEARCH PROGRAM

The objectives of this proposal are to answer three major questions.

1. Where does the current go when it is applied to the cranium?
2. When is anesthesia present and at what depth?
3. What are the undesirable side effects of various currents and can they be eliminated?

PROPOSED STUDIES TO ACHIEVE OBJECTIVES

I. Electrical Mechanisms

   A. Determination of the frequency response curves and the external impedance levels of cranium.

   B. Determination of the degrees of linearity of these electrical responses.

   C. Determination of the impedance of the tissues of the brain.

   D. Determination of tissue voltage levels in the brain.

   E. Determination of the distribution of total electrical current in the cranium.

F. Determination of the convolution of dual electrical currents in the brain.

G. Determination of the role of the cerebral spinal fluid as a conductor of electrical currents.

H. Determination of the effects of induced brain lesions on the capability to produce electro-anesthesia.

I. Determination of methods to focus current to specific locations in the brain.

II. Biological Responses

A. Determination of the level of anesthesia.

B. Determination of the effect of electro-anesthesia on blood gases and blood pH.

C. Determination of the effect of electro-anesthesia on the circulatory system, including blood glucose levels.

METHODS

I. Animals to be Used

A. Calves.

B. Primates.

The calf has been selected as the experimental animal in the initial studies. Primates will be used after the evaluations are complete in the calf. For this purpose, the Rheus monkey and the Chimpanzee have been selected.

In vitro studies will be done on cadaver heads of calves, primates and humans in a related sequence to the in vivo studies.

C. Justification of Animal Selection.

The most repeatable results and the most stable level of anesthesia from the use of electrical currents have been achieved during bovine applications. There are specific problems associated with each of the other species as experienced by this investigator in studies on horses, sheep, pigs, dogs, cats, rabbits, rats, goats, and monkeys. The most accurate information on the mechanisms of electro-anesthesia can be obtained from animals that respond most favorable to electrical currents. Therefore, the calf was selected as the experimental animal for the first phase of the program.

Calves are available in adequate numbers and the facilities for handling them are adequate. Calves of a 175-200 pound weight range would be used. Twenty-five calves per year would be needed.

Primates are considered essential to the program, after completion of calf studies, since the anatomical structure of the head and the reactions to electro-anesthesia more closely resembles those of the human. Thus a link between bovine and human applications is formed to more clearly define the mechanisms involved.

II. Currents to be Used

A. Pulsed direct current with variable pulse duration, frequency of pulse and amplitude.

B. Sinusoidal alternating current with variable frequency and amplitude.

C. Dual sinusoidal with summation in the generator.

D. Dual sinusoidal with summation in the head.

E. Justification of Current Selections.

The review of the literature reveals that hypertension, cardiac and respiratory arrest and strong muscle contractions can occur. The cardiac and respiratory arrest can be permanent if the electrical currents are not properly applied.

1. Sinusoidal currents can be varied to produce a wide range of responses in the animal. These include electro-sleep with high-frequency-low amperage, electro-anesthesia with mid-frequency and amperage, and electro-convulsion with low-frequency-high amperage application. Thus by adjustment of the relationships between current amplitude and frequency, the differences in responses of the electrobiological parameters can be evaluated for the corresponding states of consciousness.

2. The sinusoidal waveform is a clean electrical wave unlike a number of other types, such as square and triangle waves which are composed of a number of sinusoidal waves at various frequencies in the harmonic mechanism. Therefore, less distortion should occur in sinusoidal applications.

3. Dual sinusoidal with summation in the generator produces superficial analgesia without sufficient depth in the deep tissues. It has the reverse effect of single sinusoidal, therefore the response of the mechanisms involved are changed.

4. Dual sinusoidal with summation in the head is a technique that opens new approaches to electroanesthesia. As the two currents are brought together inside the head, a number of possibilities exist which affects the response to current. If the phase angles are the same, the currents will combine in a true summation. However, variations in the relationship of phase angles of the applied currents can cause summation at locations in the brain and cancellations of the current in other areas. Thus if we can learn how to control this

mechanism to focus the current to specific locations in the brain rather than total brain stimulation, many of the unwanted side effects could possibly be eliminated.

III. Methods to be used in each Proposed Study

A. General Statement for All Studies:

Statistical consultation will be obtained for aid in the design of experiments and in the evaluation of data generated.

B. Specific Studies (Electrical)

1. Determination of the frequency response curves and external impedance levels of the cranium. In vitro studies will be made in cadaver calf heads and in vivo studies in calves of same size. The technique to be used consists of:

   a. Applying electrodes to the head of the calf for current application. Both bitemporal and anterior-posterior types are to be used.

   b. Placement of recording electrode by sterotoxic adjustment into the tissues of the cranium.

Electrodes can be adjusted for depth and location in the tissues from skin levels to the dura mater. Trephine openings in the skull will be made.

c. Connect anesthesia-current generator in series with animal head and impedance bridge for input.

d. Connect output of impedance bridge and recording electrode in head in series to the oscilliscope.

e. Current is applied through the head at designated frequencies and amperage and recorded on oscilliscope. The same current is applied through the impedance bridge and it is adjusted to give same output to the scope. The impedance levels on the bridge then correspond to those of the animals head. Thus the total impedance met by the current applied through external electrodes is determined.

f. By determining the impedance of the head and knowing the current input to the head, the current flow in the brain can be determined.

g. By adjusting the frequencies and amplitude in an interval method, the response curves can be determined. Five milliampere and 100 cycles per second or pulses per second intervals will be used at ranges up to 2000 cycles per second. Above this, 500 cycles per second intervals will be used.

2. Determination of the degree of linearity of these electrical responses. This study is closely associated with Study A. It does not require additional measurements, but a mathamatical analysis and graphing of the responses exhibited for frequency and impedance to determine the degree of linearity of the system.

3. Determination of the impedance of the tissues of the brain.

   a. Theory: Investigations by Adrey[54, 55], Nicholson[56], Rall[57], Ranch[58, 59, 60], and van Harreveld[62] illustrate the variations in impedance levels in the segments of the brain and changes that take place under changing behavior patterns. Willenkin[65] found that the impedance levels in the brain stem changed in relation to the level of anesthesia from methoxyflurane. Since the brain and surrounding tissues behave like a series of parallel resistors and capicators, it is reasonable to theorize that the impedance responses will vary in relation to the frequency of current applied to the brain.

b. Method of Conducting Study - This study will follow the frequency response curve and external impedance study. The same equipment and procedures are used. The primary difference is in the tissues to be studied. This study evaluates the impedance levels at varying frequencies in the brain tissue. Areas of the brain to be studied are:

1) Cerebral Cortex
2) Thalmus
3) Hypothalmus
4) Brain Stem
5) Cerebellum

c. Special Techniques - The study of external impedance required a maximum depth to the dura for recording electrodes. In this study, the electrodes must be placed in specific locations of the brain. Electrodes will be of minimum size to prevent excess damage to the brain tissue and will have a 1 m.m. uninsulated point for recording. The insulation will be non-metallic to prevent error in results. Metallic coating produces extra capacitance values. The principal investigator has placed acute and chronic electrodes in the brain of large animals. Problems encountered will be solved by consultation with neuroanatomy and neurosurgery staff personnel.

4. Determination of tissue voltage levels in the brain.

   a. Theory: The various types of brain cells and nerve fibers have specific voltage potentials. It is also known that the voltage changes with the state of the cells, i. e. resting, during depolarization or re-polarization.[64, 65] It is reasonable to predict that the induction of additional voltage of electrical currents into the brain will interfer with the normal voltage potentials of the cells, thus affecting their usual function.

   b. Method to Complete Study.

      1) Equipment -

         a) Electro-anesthesia generators.

         b) Oscilliscope with differential amplifier.

         c) Double recording electrodes with 1 m. m. non-insulated tips 1 m. m. apart.

         d) Electrodes controlled by sterotoxic adjustment.

      2) Procedures -

         a) Cadaver heads will be used to perfect techniques and then live calves.

         b) Electrodes will be worked through trephine openings in the skull.

         c) Readings will be made in the major segments of the brain at selected frequencies and amplitudes of input current.

3) Brain Areas to be Studied -

a) Cerebral Cortex

b) Thalmus

c) Hypothalmus

d) Brain Stem

e) Cerebellum

5. Determination of the distribution of total electrical current in the cranium.

a. Object: How much of the total current applied to the head actually reaches the brain? This is an in vitro study on cadaver heads.

b. Procedure: Calf heads will be opened sufficiently for the brain to be aspirated. Recording electrodes will be placed in the cerebral cavity and it will be refilled with physiological saline. Electrical currents will be applied to the head in the normal manner for anesthesia and the current amplitude in the homologus solution will be calculated from the oscilliscope readings. This value substracted from the generator output should give the amount of current dissipated in the skin, muscle and bone of the head.[53]

6. Determination of the convolution of dual electrical currents in the brain.

a. Theory: The observed responses of experimental animals under the influence of dual electrical currents indicate that the effect on the central nervous system is not the same as single wave induced currents. The responses are of a sleep-like nature rather than anesthesia if the combination is summated in the generator, but indicates deeper anesthesia if the summation is in the head. Since summation of two currents in a system does not necessarily follow a numerically adding effect, it is logical to believe that the currents applied to the head from two sources are convoluting (passing one another) in such form that the phase angles determine if they are adding or cancelling in a particular segment of the brain. Therefore, the determination of this theory would indicate the possibility of focusing current to specific locations of the brain.

b. Animals -

   1) in vitro studies in cadaver calf heads.

   2) in vivo studies in calves.

c. Instrumentation -

   1) Current Generators.

   2) Oscilliscope.

   3) Recording electrodes and sterotaxic equipment.

d. Procedure -

1) Electrodes would be surgically placed in select locations in the cerebral cortex, thalmus, hypothalmus, brain stem, and cerebellum.

2) External currents for anesthesia would be applied through external electrodes.

3) Reading will be made on the oscilliscope.

4) Using known input and observed output, the convolution of current in the system (brain) will be mathematically determined.

7. Determination of the role of the cerebral spinal fluid as a conductor of electrical currents.

a. Since the impedance of CSF is so little compared to the tissue of the head, there is evidence that this may be the medium through which much of the current flows.

b. An in vitro study is proposed in which the head and neck of calves would be used as the container for the fluids. Currents will be applied to the head in the normal fashion for electro-anesthesia. Recording electrodes will be placed in the brain and connected to an oscilliscope. After recordings of the voltage and current to the brain, the CSF will be replaced by electrolyte solutions and H_2O. The conductance through each of these media will be determined for correlation. Thus the role of conductance through the CSF can be made.

8. Determination of the effects of induced brain lesions on the capability to produce electro-anesthesia.

   a. To provide additional evidence that specific areas in the brain are involved with the mechanism of electro-anesthesia, lesions will be produced in live animals in select areas of the thalmus, hypothalmus, and cerebral cortex and their effects on the capability to produce electro-anesthesia determined.

   b. Lesions will be surgically produced and consultation with the staff neurosurgeons at will be made in perfecting techniques. Current frequency and amperage requirements will be compared with those of normal brains.

   c. The bradykinin test will be made to determine depth of anesthesia.

9. Determination of the methods to focus current to specific locations in the brain.

a. Although this study is listed last it is one of the most important studies. However, the preceeding studies must be made to make it possible.

b. Theory: It is desirable to only have the current in the brain where stimulation to specific sites will produce anesthesia, thus reducing the unwanted side effects. The question to be answered is, "Can this be controlled by applying currents at selected phase angles from specific locations on the skull to allow cancellation of current in all areas of the brain except those that need to be affected?"

c. In this study, the multiple inducing electrodes would be placed in specific locations enabling the phase angle to be controlled, giving the proper level of current in various areas of the brain. In the initial studies, the electrodes would be placed through the bone of the skull by surgical technique, thus eliminating the deflection of current by the bone. After determination of the proper effect by this technique, attempts to produce the same effect with electrodes outside the skull would be made.

d. Thus determination can be made by recording from the specific locations of the brain, the amount of current present.

C. Specific Studies (Biological)

1. Determination of the level of anesthesia.

a. The bradykinin test as described by Lim, et al[45-52] will be used as an index to depth of anesthesia. Either intra-arterial or intra-peritoneal injection of bradykinin evokes a response if pain is perceived. There is no tissue damage by bradykinin, and the pain responses can be recorded in terms of blood pressure elevation. The test can be repeated frequently. Pain is perceived 15 seconds after injection and lasts 30-40 seconds.

b. By using this test at each of the frequency and amplitude levels for the four types of current to be studied, the depth of anesthesia and at what current levels it occurs can be determined.

c. By correlating response to bradykinin with the other physiological changes, an outline of the signs of various levels of anesthesia can be drawn up for electro-anesthesia.

d. Recordings of responses will be made with a physiological recorder with blood pressure, ECG, and impedance pneumograph transducers and pre-amplifiers. Blood pressure measurements will be made by direct cannulation of the external maxillary artery.

2. Determination of the effect of electro-anesthesia on blood gases and blood pH.

   a. Since proper oxygen supply to the brain cells must be maintained to prevent cell damage, the effects of the various types of current on these parameters must be made.

   b. High amplitude currents at low frequencies produce definite respiratory distress. It is, therefore, important to know at what levels there is sufficient disturbance of the blood gases and pH to be hazardous.

   c. Determination before, during, and after anesthesia will be done for all four types of current at 100 cycles per second and 5 milliamperage intervals. The range will extend from no detectable respiratory distress to obvious disturbance.

   d. Arterial samples will be collected through an implanted carotid catheter and results determined immediately after sampling. Samples will be collected at 15 minute intervals and continue until the response is stable.

e. The instrument to be used is the blood gas and pH equipment produced by Instrumentation Labs of Boston, Massachusetts.

3. Determination of the effect of electro-anesthesia on the circulatory system, including blood glucose levels.

a. Cardiac arrest can be produced by electro-anesthesia. It is usually not fatal if the current is reduced promptly, allowing the heart to resume function. Cardiac arrest is not produced if higher frequencies of current are used. Therefore, it is important to know the range of currents which will produce cardiac difficulties.

b. Three circulatory parameters that are known to be affected by electro-anesthesia will be studied.

1) Blood Pressure.

2) ECG for heart rate and arrhythmias.

3) Blood Glucose.

c. All four types of current to be studied at the frequency and amplitudes ranges previously indicated.

d. Equipment -

1) Physiological recording equipment with transducers and preamplifiers for blood pressure and ECG.

2) Bausch and Lomb Spectrometer for blood glucose determination will be used.

ANTICIPATED PROGRESS

In vitro studies can start two weeks after funding. It is anticipated that the first four electrical studies for the four types of current and the biological studies for two of the four types of current could be completed the first year.

PERSONNEL

I.

II.

III.

IV. To be named.

Will spend minimum of 50% time on project.

V. Animal Assistant - Full time.

VI. Technician for lab analysis - Full time.

VII. Secretary - 50% of time.

VIII. Neurosurgery)

IX. Neurophysiology)

X. Neuroanatomy)

XI. Radiology)

Assistance available in advisory capacity from these departments

BUDGET FIRST YEAR

PERSONNEL SALARIES

Investigator . . . . . Full time $

Technicians (2)
1. Assisting with animal procedures
2. Laboratory analysis

Secretary . . . part time (50%)

Engineering (systems electronics)

Consulting (Electronics, Neurosurgery, Neuroanatomey, Neurophysiology)

$

ANIMALS

25 calves @ $60 each $

Board.* $4.00/day for 330 days

$

* Plan to reuse each animal as much as possible. Number on hand at a given time will be two thus reducing board.

EQUIPMENT

1. Tektronix Model R293 DC pulse generator and power supply. $

2. Hewlett-Packard Model 3380 B Sine wave generator (can be used in both sine wave analysis and external summation analysis, one sine wave generator is already available for use in dual wave convolution studies).

3. General Radio Impedance Bridge for measuring brain impedance levels, Model 1608-A $

4. Motor drive unit for exact rate of current application in all cases

5. Simpson Voltmeter Model 312

6. Blood gas analysis equipment. Instrumentation Labs. Micro-analysis system

   Gasses for caliberation of above

7. Bausch and Lomb Sepectrometer Model 20 for blood glucose determinations

8. Oscilliscope for monitoring waveform, rise time, distortion of waves, voltage levels and time intervals

   The Tektronix Model 561A with needed components lists for $1,780.00. The Hewlett-Packard Model 141A with similar components is $2,075.00. There is one advantage of the H-P model in that information can be stored on the screen. This would enable one to record frequency responses, rise time, voltage levels, etc., on the screen at specific intervals and get direct comparisons. Thus more accuracy can be obtained. The work can be done with either. More accuracy is preferred but can be sacrificed in this case if needed for budget purposes.

9. Oscilliscope camera for permanent records of readings (will work with either of the oscilliscope models listed).

10. Sterotoxic apparatus by Universal:

    610101 "H" stand with adjustable horizontal bar

    610102 Horizontal rider

    610103 Carrier housing

610104 Micrometer carrier	$
613001 Micrometer	
613510 Chuck, insulated	
	$

Base plate and head holder will be constructed to fit needs. The equipment listed can be used in either micro or macro-electrode applications.

11. Electrodes, connecting cables and electrical probes	$
TOTAL EQUIPMENT	$

SURGERY CHARGES

These charges are for surgical instruments, suture, operating room charges. Since animals are to be reused the procedures will be made using aseptic techniques.

50 days of surgery @ /day	$

MISCELLANEOUS

Physiological recording instrument paper	$
Photography	
Travel	
Tubing, catheters, drugs, chemicals	
Computor time in data analysis	
	$

Institutional Overhead:

40% of Salaries	$
Total First Year	$

Reductions in equipment cost the second year should offset any increases in other items for a second year budget of $. Detailed budgets for time periods after the initial year will be submitted at the requested time.

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