JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
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Frederick Tilney, *The Brain in Relation to Behavior;* March 15, 1932
C. Judson Herrick, *Brains as Instruments of Biological Values;* April 6, 1933
D. M. S. Watson, *The Story of Fossil Brains from Fish to Man;* April 24, 1934
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Harry F. Harlow, *The Brain and Learned Behavior;* May 10, 1951
Clinton N. Woolsey, *Sensory and Motor Systems of the Cerebral Cortex;* May 7, 1952
Alfred S. Romer, *Brain Evolution in the Light of Vertebrate History;* May 21, 1953
Horace W. Magoun, *Regulatory Functions of the Brain Stem;* May 5, 1954
Fred A. Mettler, *Culture and the Structural Evolution of the Neural System;* April 21, 1955
Pinckney J. Harman, *Paleoneurologic, Neoneurologic, and Ontogenetic Aspects of Brain Phylogeny;* April 26, 1956
Davenport Hooker, *Evidence of Prenatal Function of the Central Nervous System in Man;* April 25, 1957
David P. C. Lloyd, *The Discrete and the Diffuse in Nervous Action;* May 8, 1958
Charles R. Noback, *The Heritage of the Human Brain;* May 6, 1959
Ernst Scharrer, *Brain Function and the Evolution of Cerebral Vascularization;* May 26, 1960
Paul I. Yakovlev, *Brain, Body and Behavior. Stereodynamic Organization of the Brain and of the Motility-Experience in Man Envisaged as a Biological Action System;* May 16, 1961
H. K. Hartline, *Principles of Neural Interaction in the Retina;* May 29, 1962
Harry Grundfest, *Specialization and Evolution of Bioelectric Activity;* May 28, 1963
Roger W. Sperry, *Problems Outstanding in the Evolution of Brain Function;* June 3, 1964
José M. R. Delgado, *Evolution of Physical Control of the Brain;* May 6, 1965

# EVOLUTION OF PHYSICAL CONTROL OF THE BRAIN

## INTRODUCTION

I would like to express my gratitude for the privilege of addressing this distinguished audience, and also my feeling of responsibility in following so many illustrious predecessors and in honoring the founder of the James Arthur Lectures on the Evolution of the Human Brain. The topics covered by earlier speakers in this series have included behavioral implications derived from cerebral anatomy and physiology, neurophysiological problems, comparative anatomy, embryology, and fossil skulls. In this year's lecture, I would like to project cerebral evolution toward the future without losing touch with the solid ground of experimentation.

The human brain has evolved with a functional asymmetry which may be responsible for some of the conflicts of our present age. Apparently it has been easier for man to direct his attention outward to the environment than inward to deal with the complexity of his own mental structure, and easier to understand and manipulate Nature than to control his own behavior. In prehistoric times, and even today in primitive societies, man was and is at the mercy of the elements. When disaster struck, and floods, pestilence, or hunger desolated the land, the only possible reactions were fatalistic resignation, appeal to supernatural powers, or despair. Modern civilization has progressed so much in the understanding and domination of the physical world, that relations between man and Nature have been completely transformed. Technology is reshaping the face of the earth, but the greatest change has taken place in the human brain which is now filled with new formulas, theories, and knowledge, and empowered with a new attitude of confidence toward natural forces which are no longer the masters but are becoming the servants of man. The expanding sciences have directed most of our present intellectual and economic power toward industry, biology, electronics, atomic energy, outer space, and similar fields of endeavor, while only a minor fraction is devoted to inquiry into the roots of mental faculties. This unbalanced interest has an explanation. When observation and reason were the main tools for the acquisition of knowledge, philosophical speculation flourished. When the discovery of new methods permitted the scientific exploration of Nature, the study of subjects beyond experimental reach was neglected. Certainly, the disciplines of psychology and psychiatry have greatly expanded in our century, but a perusal of the literature shows that until one or two decades ago, the brain was treated as a "black box" which could be reached only through the senses. Psychological investigations analyzed correlations between sensory input and behavioral output, but it was not possible to explore the processes lying in between which were hidden in the mystery of brain physiology.

During the last decade we have reached an historical turning point because of the development of methods which permit the coordination and synthesis of physical, physiological, pharmacological, and psychological research. As will be explained in the following pages, science has developed a new electrical methodology for the study and control of cerebral functions in animals and humans. Learning, emotions, drives, memory, consciousness, and other phenomena which in the past belonged only in the realm of philosophy are now the subjects of neurophysiological experimentation. In the last few years, the scalpel of the brain surgeon has modified psychological reactions and a wealth of wonder drugs has liberated many patients from mental institutions.

I am not so naive as to think that cerebral research holds all the answers to mankind's present problems, but I do believe that an understanding of the biological bases of social and antisocial behavior and of mental activities, which for the first time in history can now be explored in the conscious brain, may be of decisive importance in the search for intelligent solutions to some of our present anxieties, frustrations, and conflicts. Also, it is essential to introduce a balance into the future development of the human mind, and I think that we now have the means to investigate and to influence our own intellect.

In support of these ideas, I shall present a brief outline of the evolution of the physical control of cerebral processes, followed by several examples of our incipient control of behavioral mechanisms, and I will end with a discussion of the principles and implications involved.

## HISTORICAL OUTLINE: THEORETICAL AND METHODOLOGICAL EVOLUTION

### Animal Experimentation

For many centures it was accepted that fluids or "animal spirits" were the cause of muscle contraction (Galen, 130 to *ca.* 200 A.D.), until the famous controversy between the schools of Luigi Galvani (1737–1789) and Alessandro Volta (1745–1827) focused the attention of nineteenth-century scientists and philosophers on the possible physical control of some manifestations of life. Contractions produced in a frog nerve-muscle preparation by touching it with a bimetallic arc were interpreted by Galvani as proof of the existence of animal electricity, while Volta believed that the electrical source was in the contact of two dissimilar metals. This controversy was resolved when Alexander von Humboldt (1769–1859) demonstrated that animal electricity and bimetallic electricity were co-existing phenomena. Leg movements evoked in frogs by the inanimate force of electricity proved that muscle contraction could be induced independently of the "principle of life" which had been considered the essential mover of all biological activities. The discovery that living organs could be influenced by instrumental manipulations directed by the will of a human being brought about a revision of the traditional concepts of vitalism which were challenged at that time by Emil DuBois-Reymond (1818–1896) and other scientists. The romantic mystery of the soul's "animal spirits" which had dominated biology for almost 2000 years now gave place to more prosaic chemical and physical laws, and even nervous activity could be investigated experimentally. DuBois-Reymond not only discovered many basic neurophysiological principles, including action current, polarization, electrogenesis, and propagation of the nerve impulse; he also provided the technical means for study of the two most fundamental processes of neural activity by inventing the galvanometer for the detection of electrical currents and the induction coil for faradic excitation of nervous tissue. At that time, the possibility of exciting the spinal cord and brain stem by other than physiological stimuli was violently debated, and the excitability of the brain was completely denied. Then Fritsch and Hitzig (1870) performed a beautiful series of experiments, applying galvanic stimulations to the exposed cerebral cortex of anesthetized dogs. Excitations of the posterior part of the brain failed to evoke motor effects, but in the anterior region contralateral body and limb movements were elicited. Weak currents induced discrete contractions localized to specified muscle groups, while stronger currents increased the strength and spread of the evoked responses; if the intensity was further augmented, generalized convulsions appeared.

The scientific impact of these studies, and also the successful clinical localization of speech functions by Broca (1824–1880), promoted great interest in cerebral mapping, based on regional ablation and electrical stimulation studies attempting to pin precise functional labels to specific anatomical structures. Fortunately, there was much less speculation and much more experimentation in these studies than in the discredited phrenology, and, in spite of controversial issues, many of the facts discovered in the last century have remained important scientific contributions.

One of the main handicaps in these investigations was the need for opening the skull and exposing the brain. Operations were usually performed under general anesthesia which blocked pain perception but also blocked some of the most important functions of the nervous system. Emotions, consciousness, and intelligence were certainly absent in heavily sedated animals or in the isolated nerves of the squid, and for many years scientists directed their attention to sleeping brains and overlooked the complexity of awake minds. Textbooks of cerebral physiology were concerned with synapses, pathways, reflexes, posture, and movement, while mental functions and behavior were considered to belong to a different discipline.

Some pioneer efforts, however, were directed toward exploration of the waking brain, and techniques were devised for the introduction of wires through the skull in order to apply electrical currents to the brains of conscious animals. In 1898, Ewald had the idea of screwing an ivory cone into the skull of an anesthetized dog, and the following day, when operative anesthesia had worn off, electrodes were inserted into the brain through the ivory piece. A leash around the animal's neck contained stimulating wires, and a small dry-cell battery carried by the observer served as the electrical source. Although the technique and results were primitive, a way had been found to investigate the brain in awake animals. The technique of intracerebral electrodes was dormant for many years until Hess (1932) developed his own method to explore the hypothalamus and other cerebral areas in unanesthetized cats. In a series of brilliant experiments, Hess demonstrated that autonomic functions, posture, equilibrium, movement, sleep, and even fear and aggressiveness may be influenced by electrical stimulation of specific cerebral structures. For the first time, it was revealed that psychological manifestations like rage do not depend exclusively on sensory inputs and physiological stimuli, but can be induced by electrical currents applied directly to the brain. Although these findings did not produce a significant impact on philosophical thinking, in retrospect they may be considered as important as the nineteenth-century demonstration that the contraction of a frog muscle did not depend on circulating spirits and could be controlled by physical instrumentation.

For two decades, the methods of Hess attracted only limited interest among biologists, but in the 1950's, there was a sudden expansion of the new disciplines of psychosurgery, psychosomatic medicine, psychopharmacology, and physiological psychology, and many investigators realized the great research potential of intracerebral methods for the study of behavioral-cerebral correlations in awake animals. With this increased interest, a variety of technical improvements appeared. Electrodes were no longer introduced free-hand into the brain, but were inserted with geometric precision with the aid of micromanipulators and stereotaxic coordinates. Anatomical maps of the depths of the brain were compiled for rats, cats, dogs, and monkeys. Aseptic precautions and instrumental refinements permitted long-term implantation of electrodes, which in some cases lasted for several years. The sight of experimental animals with sockets on top of their heads was exceptional in 1950 but had spread to hundreds of laboratories around the world by 1960. Electrodes were implanted not only in the usual laboratory animals, but also in other species, including crickets, roosters, chimpanzees, dolphins, and brave bulls.

Experiments were generally performed under some restraint. Rats were convenient subjects because of their behavioral simplicity, and they were not disturbed by a light coil of wires connecting their terminal head sockets with the stimulators. In this way, the brain was stimulated in fully conscious rats while they pressed levers, ran mazes, and maneuvered with considerable freedom, being limited only by the length of the leads and the size of the cage. A similar set-up was also used successfully with cats, providing they were peaceful and tame. These studies were often extended for months and were very appropriate for the investigation of autonomic, somatic, and behavioral effects evoked by electrical stimulation of the brain, and also for the analysis of electrical recordings taken during spontaneous or induced activities. The combination of intracerebral electrodes with other physiological and psychological techniques was very fruitful and showed that animals can learn to perform instrumental responses to seek or avoid stimulation of determined cerebral structures. Scientific exploitation of these techniques continues today with universal acceptance, as shown by current scientific literature.

The use of electrodes in monkeys presented a greater challenge because of their destructive skills and restless curiosity. A heavy protection of the connecting leads was necessary when the animal was observed on a testing table. In other cases, the monkey was placed in a special restraining chair where it could manipulate levers and feed itself without being able to reach the terminal sockets on its head. In these situations, conditioning and psychological testing were successfully performed, but spontaneous behavior was naturally curtailed.

The connecting leads trailing behind each animal were a serious handicap for behavioral studies and were unsuitable for use in chronic stimulations or investigations of group activities. The obvious solution was to use remote-controlled instrumentation, with a receiver carried by the animal and activated by induction or by radio. Several stimulators of this type have been proposed in the last 30 years (see bibliography in Delgado, 1963b), but solutions to many of the technical problems involved were not found until recently, when the development of transistors and electronic miniaturization permitted the construction of small, practical, and reliable cerebral radio stimulators (Delgado, 1963b). After a considerable amount of trial and error, and in spite of the primates' genius for destroying any equipment within reach, monkey-proofing of instruments was achieved (figs. 3, 4, 5). The use of radio stimulators allowed the excitation of cerebral structures in completely free animals engaged in normal activities within an established colony and unaware of the scientist's manipulations. In this way, the role of specific areas of the brain in social relations was investigated. At the same time, blood pressure, body temperature, electrical activity of the heart and brain, and other physiological variables could be recorded by radio telemetry. In addition, individual and social behavior have been continuously recorded, day and night, by time-lapse photography. Radio techniques represented an important step toward physical control of the brain, providing an essential tool for behavioral studies, and it may safely be predicted that within a few years telestimulation will spread to most brain research institutes. We can also expect that new developments in micro-electronics, including integrated circuits and thin film techniques, will facilitate the construction of multi-channel radio-activated stimulators reduced in size to a few millimeters. The limits of brain control do not seem to depend on electronic technology but on the biological properties of living neurons.

Among possible physiological handicaps, the presence of electrodes and repeated applications of electricity could be disrupting factors for the normality of the nerve cells. Insertion of electrodes into the brain substance is certainly a traumatic procedure which destroys neural tissue and produces local hemorrhage, followed by inflammation, foreign body reaction, and the formation of a glial capsule 0.1–0.2 mm. thick around the inserted wires. All of this reactive process is limited to a very small area measured in tenths of millimeters, and there is no evidence of functional disturbance in the neighboring neurons. Beyond the electrode tract, the brain appears histologically normal and electrodes seem to be well tolerated, as judged by the absence of abnormal electrical activity, by the reliability of effects evoked by electrical stimulation, and by the consistency of thresholds through months of experimentation (Delgado, 1955b). The longest reported implantation time of electrodes in the brain has been over four years, in a rhesus monkey.

From the functional point of view, two aspects should be considered in implantation experiments. The first is related to fatigability and the second to lasting functional changes. Physiological textbooks state that motor effects produced by electrical stimulation of the cerebral cortex fade away in a few seconds, and that a rest period of about one minute is necessary before the cortex recovers its excitability. If this were true throughout the brain, electricity could not be effectively used for control of cerebral function. However, experimentation has shown that the fatigability of some areas is slow or negligible. In monkeys, the putamen has been stimulated for more than 30 minutes without diminution of the elicited postural changes, and the hypothalamus has been excited for days without fatigue of the evoked pupillary constriction. Red nucleus stimulation repeated every minute for 14 days has evoked reliable and consistent sequential responses. Thus, while a few areas of the brain show quick fatigability, it should be recognized that many others can be stimulated effectively for minutes or even days. The evoked effects generally have lasted only as long as the stimulation, but in some cases enduring aftereffects have been obtained. In the cat, programmed intermittent stimulations of the amygdala for one hour daily evoked bursts of high-voltage fast activity and other signs of increased electrical activity, along with changes in spontaneous behavior which outlasted stimulation periods for many hours and occasionally for days. In other studies, excitation of the basolateral nucleus of the cat's amygdala for only 10 seconds inhibited food intake for minutes, and, in one case, the inhibitory effect persisted for three days (Fonberg and Delgado, 1961). These findings together with extensive experimentation by many authors have demonstrated that intracerebral electrodes are safe and can be tolerated for years, providing an effective tool for sending and recording electrical impulses to and from the brain of unanesthetized animals.

## Electrodes in the Human Brain

With the background of animal experimentation, it was natural that some investigators should contemplate the implantation of electrodes inside the human brain. Neurosurgeons had already proved that the central nervous system is not so delicate as most people believe, and during therapeutic surgery parts of cerebral tissue had been cut, frozen, cauterized, or ablated with negligible adverse effects on the patient. Exploratory introduction of needles into the cerebral ventricles was a well-known and relatively safe clinical procedure, and, as electrodes are smaller in diameter than these needles, their introduction into the brain tissue should be even less traumatic. Implantation of electrodes inside the human brain offered the opportunity for prolonged electrical exploration which could be decisive for several diagnostic and therapeutic procedures. For example, when brain surgery and ablation are contemplated in patients suffering from epileptic attacks, it is essential to identify the focal areas of abnormal electrical activity. Electrodes may remain in place for days or weeks, during which spontaneous seizures can be recorded and detailed exploration repeated as many times as necessary. In other cases, intracerebral electrodes have been used to deliver intermittent stimulations for periods of days or even months (Feindel, 1961; Heath, 1954; King, 1961; Sem-Jacobsen *et al.,* 1956; Walker and Marshall, 1961). Similar procedures have also been used in patients with intractable pain, anxiety neurosis, and involuntary movement. These therapeutic possibilities should be considered rather tentative, but accumulated experience has shown that electrodes are well tolerated by the human brain for periods of at least one year and a half, and that electrical stimulations may induce a variety of responses, including changes in mental functions, as will be explained later. The prospect of leaving wires inside the thinking brain could seem barbaric, uncomfortable, and dangerous, but actually the patients who have undergone this experience have had no ill effects, and they have not been concerned about the idea of being wired or by the existence of leads in their heads.

In some cases, they enjoyed a normal life as out-patients, returning to the clinic for periodic stimulations. Some of the women proved the adaptability of the feminine spirit to all situations by designing pretty hats to conceal their electrical headgear.

The use of electrodes in the human brain is part of the present medical orientation toward activation of physiological mechanisms by electronic instrumentation, which already extends to several organs of the body. The clinical success of electrical driving of cardiac functions in man has been widely acclaimed. In spite of the delicacy and continuous mobility of the heart, stainless steel leads have been sutured to it, and in cases of block in the cardiac conduction system, artificial electronic pacemakers have been able to regulate heart rhythm, saving the lives of many patients. The bladder has been stimulated by implanted electrodes to induce urination in patients with permanent spinal block, and paralyzed limbs have been activated by programmed stimulators. A method has recently been described for placing leads in the auditory nerve to circumvent deafness caused by inner ear damage. Driving malfunctioning organs is simpler than attempting to direct the awake brain where millions of neurons are functioning and firing simultaneously for different purposes, but the expected results in this case are even more interesting. Exploring intracerebral physiology, we are reaching not only the soma but also for the psyche itself. Cerebral functions are usually classified in three groups: autonomic, somatic, and psychic, and in the following pages I shall discuss present experimental evidence for their electrical control.

## TABLE OF HISTORICAL EVOLUTION OF PHYSICAL CONTROL OF THE BRAIN

| Findings | Implications |
| --- | --- |
| Frog muscle contracted when stimulated by electricity. Volta, Galvani, DuBois-Reymond; 1780, 1800, 1848 | "Vital spirits" are not essential for biological activities. Electrical stimuli under man's control can initiate and modify vital processes |
| Electrical stimulation of the brain in anesthetized dog evoked localized body and limb movements. Fritsch and Hitzig, 1870 | The brain is excitable. Electrical stimuli of the cerebral cortex can produce movements |
| Stimulation of the diencephalon in unanesthetized cats evoked well-organized motor effects and emotional reactions. Hess, 1932 | Motor and emotional manifestations may be evoked by electrical stimulation of the brain in awake animals |
| In single animals, learning, conditioning, instrumental responses, pain, and pleasure have been evoked or inhibited by electrical stimulation of the brain in rats, cats, and monkeys. See bibliography in Sheer, 1961 | Psychological phenomena may be controlled by electrical stimulation of specific areas of the brain |
| In colonies of cats and monkeys, aggression, dominance, mounting, and other social interactions have been evoked, modified, or inhibited by radio stimulation of specific cerebral areas. Delgado, 1955a, 1964 | Social behavior may be controlled by radio stimulation of specific areas of the brain |
| In patients, brain stimulations during surgical interventions or with electrodes implanted for days or months have blocked the thinking process, inhibited speech and movement, or in other cases have evoked pleasure, laughter, friendliness, verbal output, hostility, fear, hallucinations, and memories. See bibliography in Ramey and O'Doherty, 1960 | Human mental functions may be influenced by electrical stimulation of specific areas of the brain |

SUMMARY: Autonomic and somatic functions, individual and social behavior, emotional and mental reactions may be evoked, maintained, modified, or inhibited, both in animals and in man, by electrical stimulation of specific cerebral structures. Physical control of many brain functions is a demonstrated fact, but the possibilities and limits of this control are still little known.

## ELECTRICAL CONTROL OF AUTONOMIC FUNCTIONS

Several areas of the brain play important roles in the regulation of visceral activity, and extensive studies have shown that electrical stimulation of the hypothalamus and other cerebral structures can influence vasomotility, blood pressure, heart rate, respiration, thermal regulation, gastric secretion, food intake, and many other functions of the autonomic system. To illustrate the artificial regulation of autonomic reactions by electrical means, I shall discuss pupillary motility because its mechanisms are relatively simple and easy to control.

The areas that participate in the regulation of pupil size are represented on the surface and in the depth of the brain. Cortical zones which have inhibitory effects upon respiration and upon spontaneous movements also produce pupillary dilatation (mydriasis). In cats, dogs, and monkeys, these areas are situated around the sylvian fissure, orbital cortex, temporal tip, cingulate gyrus, insula, rhinal fissure, and hippocampal gyrus. In the depth of the brain, pupillary dilatation may be evoked by stimulation of the basal telencephalon, hypothalamus, septum, midline group of thalamic nuclei, subthalamus, and a large part of the midbrain (Hodes and Magoun, 1942; Kaada, 1951; Showers and Crosby, 1958). Pupillary constriction (miosis) has a more limited representation, localized mainly around the genu of the corpus callosum (Hodes and Magoun, 1942; Kaada, 1951), thalamus, and hypothalamus (Hess, 1954). According to the region stimulated, pupillary responses will be unilateral or bilateral; if bilateral, each eye may respond synergically or antagonically. Most classical studies were performed under anesthesia and with the brain exposed, but recent investigations have been carried out with the use of awake animals equipped with intracerebral electrodes.

In monkeys (Delgado, 1959), electrical stimulation of

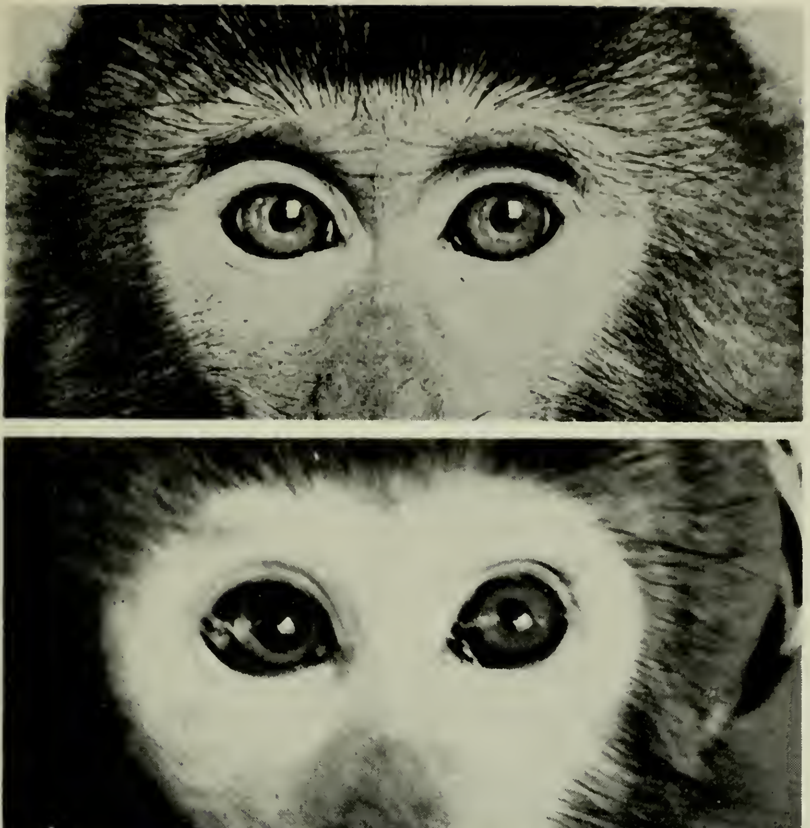

FIG. 1. The diameter of the pupil may be electrically controlled as if it was the diaphragm of a photographic camera. The pictures show normal eyes in a monkey and the dilatation and constriction of the right pupil evoked by stimulation of the hypothalamus. Some of these effects are indefatigable and persist for days as long as stimulation is applied.

the inferior part of the lateral hypothalamus produced marked ipsilateral miosis, while stimulation of another point situated 6 mm. higher in the same tract evoked ipsilateral mydriasis (fig. 1). The magnitude of the effect was proportional to the electrical intensity employed. Stimulation of the inferior point with 0.8 milliampere (mA) produced slight pupillary constriction which increased progressively as the intensity was augmented to 1.5 mA. At this moment, miosis was maximum, and further increase in stimulation did not modify the effect. If the hypothalamic stimulation was slowly decreased in strength, the ipsilateral pupil gradually returned to its normal size. In these experiments, pupil diameter could be controlled precisely like the diaphragm of a camera, by turning the stimulator dials to the left or right. A similar dose-response relation was seen in the higher hypothalamic point where stimulation produced mydriasis. Implantation of electrodes in points with antagonistic pupillary effect made it possible to introduce an artificial conflict by stimulating both areas simultaneously with separate instruments. Results showed that a dynamic equilibrium could be established at different levels of simultaneous antagonistic excitation. With 1.6 foot-candle units of illumination in the laboratory, the initial pupillary diameter of 4 mm. was maintained when the hypothalamic points were stimulated together at similarly increasing intensities up to 4 mA. At any level in this dynamic equilibrium, the pupil constricted if intensity was increased in the inferior or decreased in the higher point. The reverse was also true, and the pupil dilated if stimulation decreased in the inferior or increased in the superior hypothalamic point. To some extent, the effect of excitation of the inferior miotic point could be substituted for a light shone in the eye, illustrating the possibility of algebraic summation of physiological, sensory, and electrical stimuli within the brain. These experiments demonstrated that a regulation of an autonomic function like pupillary size can be effectively maintained by direct stimulation of cerebral structures.

For how long would this regulation be effective? Would the brain fatigue? To answer these questions, long-term experiments were designed. Under continuous hypothalamic excitation, mydriasis lasted for about 30–40 minutes, after which stimulation was ineffective and the pupil gradually returned to its original size, indicating a slow fatigability of the effect. In contrast, pupillary miosis was maintained in several monkeys for as long as stimulation was applied. Each animal was studied while free in a cage and equipped with a portable stimulator connected by subcutaneous leads to the inferior hypothalamic point. Under continuous 24-hour stimulation, the size of the ipsilateral pupil was maintained at less than 1 mm. in diameter, while the other pupil measured a normal 4 mm. As soon as the stimulation was discontinued, a rebound effect appeared and the ipsilateral pupil dilated to about 6 mm. for several hours, and then slowly returned to its normal size. In one monkey, the stimulation was applied for as long as three days, during which pupil constriction was continuous; with cessation of stimulation, a rebound effect appeared which lasted for two days.

In other experiments, when the intensity of hypothalamic stimulation was adjusted to produce only a 20–30 per cent reduction in pupillary size, the reactivity of both pupils to light was preserved, although the stimulated pupil was always smaller than the control. These results demonstrated that a lasting functional "bias" can be introduced in autonomic reactions by the artificial means of electrical stimulation of the brain. The physiological equilibrium was electrically modified, preserving the responses but changing the level of functional adjustment. These results are comparable to the modifications in autonomic reactivity (tuning) induced by injection of sympathetic or parasympathetic agents (Gellhorn, 1957).

In summary, autonomic functions can be controlled by electrical stimulation of the brain. As an example it has been shown that constriction of the pupil evoked by cerebral stimulation is reliable, precise, does not fatigue, can interplay with physiological stimuli, and may provide a functional "bias" to modify the level of physiological responses.

## MOTOR PERFORMANCE UNDER ELECTRONIC COMMAND

The significant nineteenth-century discovery of central nervous system excitability was based on the fact that electrical stimulation of the cerebral cortex produced observable motor responses. Since that discovery, many investigations have been devoted to the analysis of motor representation in different areas of the brain. The evoked effects were usually described as stereotyped tetanic contractions, producing clumsy movements of the body and extremities and lacking the precision and coordination of spontaneous activities. These results were obtained under anesthesia, but it was assumed that because of the complexity of the mechanisms involved, artificial stimulation could never induce, even in awake animals, responses as skillful and well organized as voluntary movements. In spite of this assumption, when stimulation was applied through intracerebral electrodes to completely unrestrained animals, it was evident that motor performance under electronic command could be as complex and precise as spontaneous behavior. Before discussing the reasons for success in the electric driving of behavior, I will describe examples of simple motor responses, complex behavior, and social interaction.

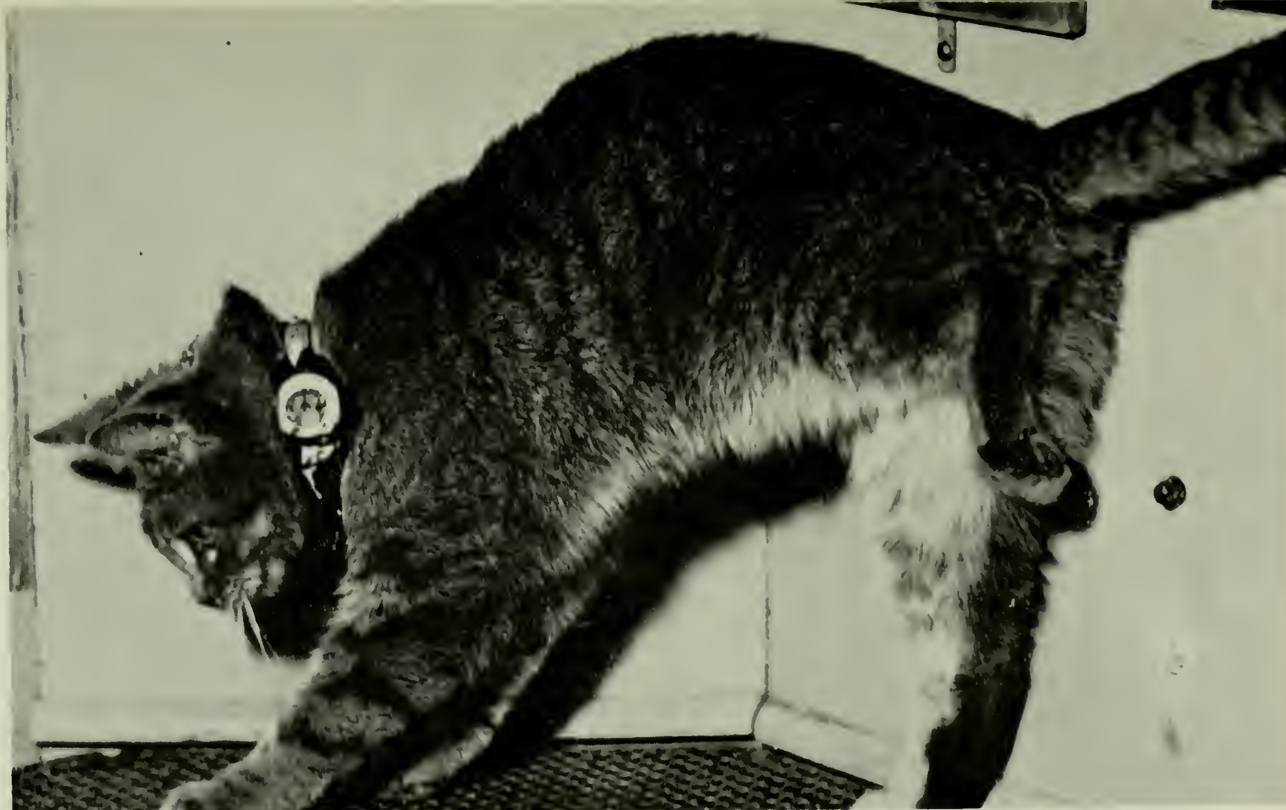

FIG. 2. Flexions of the left hind leg induced in a cat by electrical stimulation of the cruciate sulcus. This evoked effect is not unpleasant for the animal and may interact with spontaneous activities. Observe the good postural adaptations and the peaceful attitude of the cat.

In the cat, electrical stimulation of the right sulcus cruciatus, in the anterior part of the brain, produced flexion of the left hind leg (fig. 2) with an amplitude of movement proportional to stimulation intensity, provided the experimental situation was constant. For example, in a cat standing on all fours, a five-second stimulation of 1.2 mA (monopolar, cathodal, square waves, 0.5 millisecond of pulse duration, 100 cycles per second) evoked a leg flexion barely off the ground. When the intensity was increased up to 1.5 mA, the hind leg rose about 4 centimeters, and when 1.8 mA were applied, the flexion of the leg was complete. The evoked movement usually began slowly, developed smoothly, reached its peak in about two seconds, and lasted until the end of the stimulation. This motor performance could be repeated as many times as desired, and it was accompanied by a postural adjustment of the whole body which included a lowering of the head, raising of the pelvis, and a slight weight shift to the left in order to maintain equilibrium on only three legs. The electrical stimulation did not produce any emotional disturbance, and the cat was as alert and friendly as usual, rubbing its head against the experimenter, seeking to be petted, and purring. However, if we tried to prevent the evoked effect by holding the left hind leg with our hands, the cat stopped purring, struggled to get free, and shook its leg. Apparently the evoked motility was not unpleasant, but attempts to prevent it were disturbing for the animal. The artificial driving of motor activities was accepted in such a natural way by the animal that often there was spontaneous initiative to cooperate with the electrical command. For example, during a moment of precarious balance when all paws were close together, stimulation produced first a postural adjustment, and the cat spread its forelegs to achieve equilibrium by shifting its body weight to the right, and only after this delay did the left hind leg begin to flex. It was evident that the animal was not in a hurry and was taking its time to prepare its position for the induced movement. Preliminary adjustments were not seen if the cat's posture was already adequate for the required motor performance. In other cases, when the animal was lying down with its hind legs already flexed, the stimulation effect was greatly diminished and consisted mainly of increased muscular tension.

In cases of conflict between the free movements of the animal and those elicited by the experimenter, the final result depended on the relative strength of opposing signals. Stimulations of the cruciate sulcus at threshold level of 1.2 mA, which produced a small leg flexion, were ineffective if applied while the cat was walking. To test stronger conflicts, the cat was enticed into jumping off a table to reach food placed on the floor, and, while it was in the air, the cruciate sulcus was electrically stimulated. In this situation, intensities of up to 1.5 mA, which usually evoked a clear motor response, were completely ineffective; physiological activity seemed to override the artificial excitation and the cat landed with perfectly coordinated movements. If the intensity was increased to 2 mA, stimulation effects were prepotent over voluntary activities; leg flexion started during the jump, coordination was disrupted, and the cat landed badly.

A variety of motor effects have been evoked in different species, including cat, dog, bull, and monkey. The animals could be induced to move the legs, raise or lower the body, open or close the mouth, walk or lie still, turn around, and perform a variety of responses with predictable reliability, as if they were electronic toys under human control (see figs. 1–6). Behavior elicited by electrical stimulation was not always comparable to spontaneous activity. In a few experiments, movements beyond the animal's voluntary control were observed, such as the clockwise rotation of the eye. In other cases, abnormal responses, disorganized contractions, and loss of equilibrium have also been induced, depending on the cerebral area and parameters of stimulation.

### Complex Behavior

Normal activities in animals are not confined to simple motor responses such as hind-leg flexion but include a succession of different acts such as body displacement and social interaction. In order to study these complex activities, which require a situation as free and normal as possible, our experimental design included (1) the establishment of a colony with four to six monkeys, (2) the continuous recording of spontaneous and evoked behavior by time-lapse photography, in order to qualify and quantify individual and social actions, and (3) stimulation of the animals by remote control. The behavior of a group of monkeys is an entertaining spectacle, and a few minutes' observation gives the impression that their playing, grooming, chasing, and comic activities are rather unpredictable. Long-term studies, however, have shown that individual and social behavior is predictable within a known range of variability. The study of group behavior is possible precisely because of the recurrence of patterns that can be identified. Every day the monkeys will eat, play, groom, pick, sit, and perform a series of acts which can be analyzed and quantified (Delgado, 1962). After the individual profiles of behavior are established, the responses evoked by electrical stimulation of the brain may be precisely evaluated.

A typical example of complex behavior was observed in a monkey named Ludi while she was forming part of a

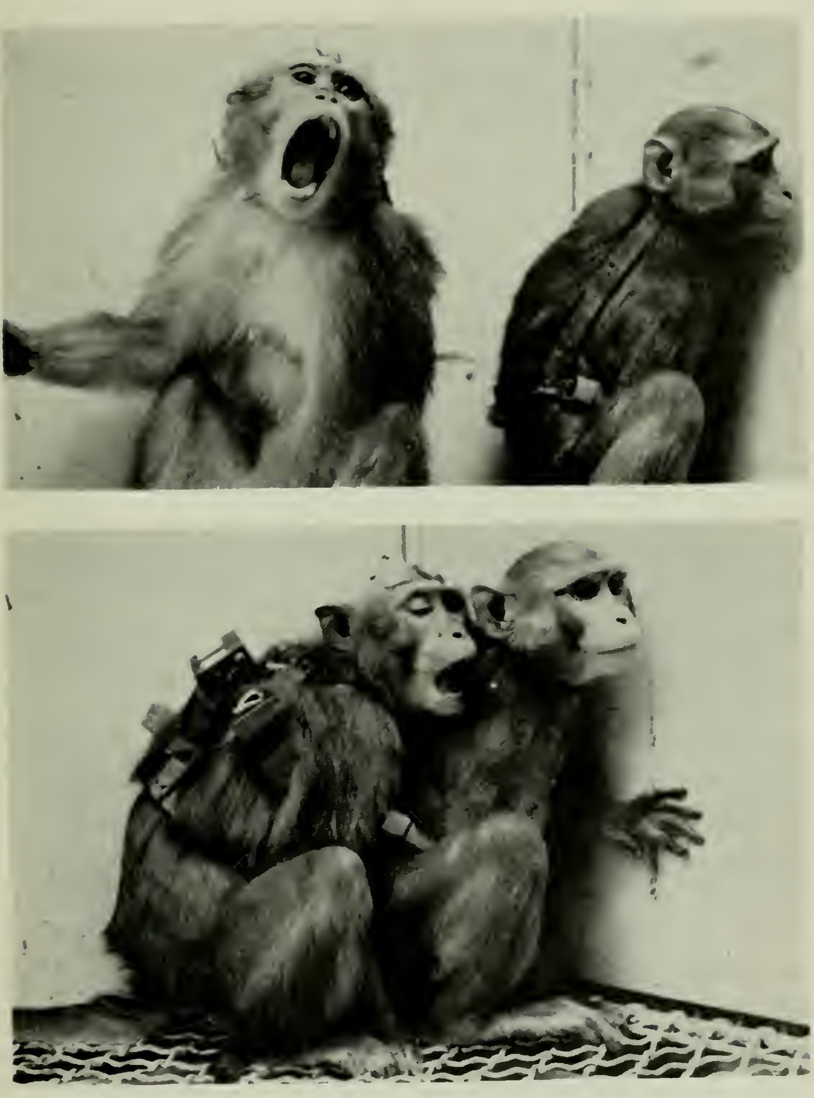

FIG. 3. Yawning evoked in the monkey by radio stimulation of the pars magno cellularis of the red nucleus. Observe the spontaneous qualities of the evoked effect and also the fact that when the monkey is asleep the response diminishes.

colony with two other females and two males. Ludi was an aggressive female who dominated the whole group and exercised the usual prerogatives of being the chief, enjoying greater territoriality and more food, and moving freely around the colony. After different areas of the brain had been studied under restraint, the radio stimulator was strapped to Ludi, and excitations of the rostral part of the red nucleus were started, with the monkey free in her colony. Stimulation produced the following complex sequence of responses (fig. 4): (1) immediate interruption of spontaneous activities, (2) change in facial expression, (3) head turning to the right, (4) standing on two feet, (5) circling to the right, (6) walking on two feet with perfect preservation of equilibrium by balancing the arms, touching the walls of the cage, or grasping the swings, (7) climbing a pole on the back wall of the cage, (8) descending to the floor, (9) low tone vocalization, (10) threatening attitude directed toward subordinate monkeys, (11) changing of attitude and peacefully approaching some other members of the colony, and (12) resumption of the activity interrupted by the stimulation. The whole sequence was repeated again and again, as many times as the red nucleus was stimulated. Responses 1 to 8 developed during the five seconds of stimulation and were followed, as aftereffects, by responses 9 to 12 which lasted from five to 10 seconds. The excitations were repeated every minute for one hour, and results were highly consistent on different days. The responses resembled spontaneous activities, were well organized, and always maintained the described sequence. Climbing followed but never preceded turning of the body; vocalization followed but never preceded walking on two feet; the general pattern was similar in different stimulations, but the details of motor performance varied and were adjusted to existing circumstances. For example, if the stimulation

Fig. 4. As mentioned in the text, a sequence of effects including walking on two feet may be evoked by radiostimulation of the red nucleus.

surprised the animal with one arm around the vertical pole in the cage, the first part of the evoked response was to withdraw the arm in order to make the turn possible. While walking on two feet, the monkey was well oriented and was able to avoid obstacles in its path and to react according to the social situation. In some experiments, three monkeys in the colony were simultaneously radio-stimulated in the red nucleus, and all three performed the full behavioral sequence without interfering with one another. Changes in the experimental situation could modify the evoked response, as shown in the case of external threat to the colony. Waving the catching net or a pair of leather gloves on one side of the home cage induced a precipitous escape of all monkeys to the other side. Red-nucleus stimulation applied at this moment was ineffective and did not interfere with the escape of the animals. In other experiments, after being deprived of food for 24 hours, the animals were offered bananas and oranges which they grabbed and ate voraciously. During this time, Ludi's response to radio stimulation of the red nucleus was completely absent or was reduced to only a short turn. In one long experiment, excitation of the red nucleus was repeated every minute, day and night, for two weeks, with a total of more than 20,000 stimulations. The remarkable reliability of responses was demonstrated throughout the whole period, with the following significant exception. During the day, monkeys take several naps, and during the night they have a long period of sleep which is interrupted by several periods of general activity. Time-lapse recordings showed that, as the stimulated monkey was falling asleep, the evoked responses progressively diminished until only a small head movement remained. As soon as the stimulated animal awoke, the responses reappeared with all of their complexity. This finding indicates that the effects evoked by cerebral stimulation are not inflexible and rigid, but may adapt to changes in the physiological situation. Examples of other patterns of sequential behavior have been evoked by excitation of several diencephalic and mesencephalic structures (Delgado, 1963a, 1964a, 1964b), showing that sequential activities are anatomically represented in several parts of the central nervous system.

## SOCIAL INTERACTION

The social interaction of animals requires continuous mutual adaptation, and activities depend on a variety of factors, including sensory inputs, problem-solving capacity, emotional background, previous experience, conditioning, drives, instincts, and intelligent integration of all these processes. In spite of the extraordinary complexity of these supporting mechanisms, there is experimental evidence that electrical stimulation of specific areas of the brain may influence social interaction such as contactual relations, hierarchical situations, submissive manifestations, sexual activity, aggressive behavior, and social fear. By definition, this type of research requires at least two animals which can interact with each other, but the study of groups is naturally preferable.

In 1928 Hess demonstrated that during electrical stimulation of the periventricular gray matter, cats responded as if threatened by a dog, with dilatation of the pupils, flattening of the ears, piloerection, growling, and well-directed blows with unsheathed claws. Similar offensive-defensive reactions have been described by several authors (see bibliography in Delgado, 1964a), but it was debatable whether the apparently enraged animal was aware of its own behavior and whether the evoked reactions were purposefully oriented; in other words, if the observed phenomena were true or false rage. Today it is known that both types of rage may be elicited, depending on the location of the stimulated points, and we have conclusive evidence that, in cats and monkeys, well-organized behavior may be evoked by stimulation of the amygdala, posteroventral nucleus of the thalamus, fimbria of the fornix, tectal area, central gray, and other cerebral structures. The fact that one animal can be electrically driven to fight against another has been established (Delgado, 1955a). In this experiment, stimulation of the tectal area in a male cat evoked the well-known pattern of offensive-defensive reactions. When this animal was placed on a testing stage in the company of a larger cat, they enjoyed friendly relations, lying close to each other and purring happily until the smaller cat was stimulated in the tectal area. At this moment, it started growling, unsheathed its claws, and launched a fierce attack against the larger animal which flattened its ears, withdrew a few steps, and retaliated with powerful blows. The fight continued as long as the stimulation was applied. The effect could be repeated, and the stimulated cat always took the initiative in spite of the fact that it was smaller and was always overpowered in the battle. After several stimulations, a state of mistrust was created between the two animals, and they watched each other with hostility.

Similar experiments were repeated later in a colony formed by six cats. When one of them was radio-stimulated in the tectal area, it started prowling around looking for fights with the other subordinate animals, but avoiding one of them which was the most powerful of the group. It was evident that brain stimulation had created a state of increased aggressiveness, but it was also clear that the cat directed its hostility intelligently, choosing the enemy and the moment of attack, changing tactics and adapting its motions to the motor reaction of the attacked animal. In this case, brain stimulation seemed to determine the affective state of hostility, but the behavioral performance seemed dependent on the individuality of the stimulated animal, including its learned skills and previous experiences. Stimulation that increased aggressiveness was usually tested for only five to 10 seconds, but, as it was important to determine the fatigability of the effect, a longer experiment was performed by reducing the intensity to a level which did not evoke overt rage. The experimental subject was an affectionate cat which usually sought petting and purred while it was held in the experimenter's arms. When it was introduced into the colony with five other cats, a low-intensity radio stimulation of the amygdala was applied continuously for two hours during which the animal's behavior was affected. It withdrew to a corner of the cage and sat there motionless, uttering barely audible growls from time to time. If any other cat approached, the stimulated animal started hissing and threatening, and, if the experimenter tried to pet him, the growls increased in intensity and the animal often spat and hissed. This hostile attitude disappeared as soon as the stimulation was over, and the cat became as friendly as before. These experiments demonstrated that brain stimulation could modify animals' reactions toward normal sensory perceptions by a modulating of the quality of the responses. The effect was similar to the modifications of spontaneous behavior observed in normal emotional states.

Monkeys offer better opportunities than cats for the study of social interaction because of their more numerous and skillful spontaneous activities. It is well known that these animals form autocratic societies, where one establishes himself as boss of the group, claiming a large amount of the living quarters as his territory, feeding first, and being avoided by the others, which usually express their submissiveness by typical actions such as grimacing, crouching, and presenting. In several of our monkey colonies, we demonstrated that radio stimulation of the posteroventral nucleus of the thalamus and central gray increased the aggressiveness of the stimulated animal and affected the social hierarchy. Stimulation of the boss monkey induced well-directed attacks against the other members of the group, which were chased around and occasionally bitten, but it was evident that the orientation of the evoked response was influenced by previous experiences. During stimulation, the boss usually attacked and chased the male monkeys which represented a challenge to his authority, but he did not threaten the female who was his favorite partner. These results confirmed the finding in cat colonies that aggressiveness induced by cerebral stimulations was not blind and automatic, but selective and intelligently directed.

Rhesus monkeys are destructive and dangerous creatures which do not hesitate to bite anything within reach, including leads, instrumentation, and occasionally the experimenter's hands. Would it be possible to tame these ferocious animals by means of electrical stimulation? To investigate this question, a monkey was strapped to a chair where it made faces and threatened the investigator until the rostral part of the caudate nucleus was electrically stimulated. At this moment, the monkey lost its aggressive expression and did not try to grab or bite the experimenter, who could safely put a finger into its mouth! As soon as stimulation was discontinued, the monkey was as aggressive as before. Later, similar experiments were repeated with the monkeys free inside the colony, and it was evident that their autocratic social structure could be manipulated by radio stimulation. In one case in which the boss monkey was excited in the caudate nucleus with 1.5 mA for five seconds every minute, after several minutes the other mon-

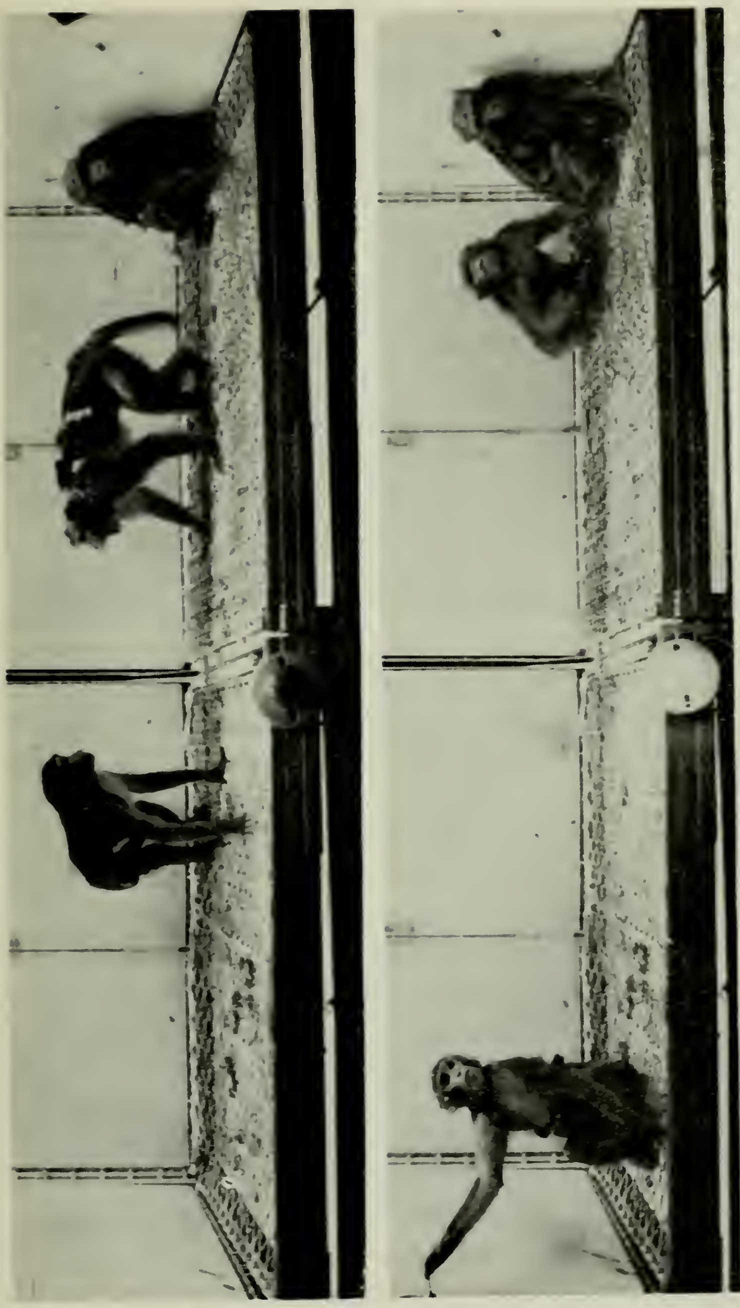

FIG. 5. Monkeys may learn to press a lever in order to stimulate by radio the brain of another aggressive animal and in this way to avoid his attack. Heterostimulation in monkey colonies demonstrates the possibility of instrumental control of social behavior.

keys started to circulate more freely around the cage, often in proximity to the boss, and from time to time they crowded him without fear. The intermittent stimulation continued for one hour, and during this time the territoriality of the boss dropped to zero, his walking time was diminished, and he performed no aggressive acts against the other members of the colony. About 12 minutes after the stimulation hour ended, the boss had reasserted his authority, and his territoriality seemed to be as well established as during the control period. In other experiments, monkeys instead of investigators controlled the activation of radio stimulation. In this situation, subordinate animals learned to press a lever in the cage which triggered stimulation of the boss monkey in the caudate nucleus, inhibiting his aggressive behavior (fig. 5; Delgado, 1963c). Inhibitory effects have been demonstrated in several species including brave bulls, as shown in figure 6 (Delgado, *et al.*, 1964).

A different type of effect was demonstrated in another monkey colony. Radio stimulation of the nucleus medialis dorsalis of the thalamus in a female monkey produced a sequential pattern of behavior characterized by a movement of the head, walking on all fours, jumping to the back wall of the cage for two or three seconds, jumping down to the floor, and walking back to the starting point. At this moment, she was approached by the boss of the colony and she stood on all fours, raised her tail and was grasped and mounted by the boss in a manner indistinguishable from spontaneous mounting. The entire behavioral sequence was repeated once every minute following each stimulation, and a total of 81 mountings was recorded in a 90-minute period, while no other mountings were recorded on the same day. As is natural in social interaction, the evoked responses affected not only the animal with cerebral electrodes, but also other members of the colony.

FIG. 6. A bull in full charge may be suddenly stopped by radio stimulation of the anterior part of the thalamus.

## ANALYSIS OF EVOKED MOTOR BEHAVIOR

The experimental evidence presented in the previous pages clearly demonstrates that electrical stimulation of the brain can induce predictable behavioral performance similar to spontaneous activities. Understanding the significance of these findings requires analysis of the physiological mechanisms involved in voluntary movements. A simple act such as leg flexion requires the precise and progressive contraction of several muscles in which the strength, speed, and amplitude of activation of many motor units are determined by the processing of messages coming from joints and muscle spindles integrated with another vast amount of information circulating through the central nervous system. The complexity of neuronal events is even greater during performance of sequential responses, in which timing and motor correlations must be adjusted to the purpose of the movement and adapted to changes in the environment. Mechanisms responsible for the physiological excitation of spontaneous motility must be highly sophisticated. In contrast, electrical stimulation of the brain is very simple and depends on primitive techniques that apply a train of pulses without modulation, without code, without specific meaning, and without feedback to a group of neurons which by chance are situated within an artificially created field. In view of the complexity of neuronal integrations, it is not surprising that a few authors have downgraded the significance of stimulation effects. How can we explain the contradiction between the crudeness of these excitations and the refinement of the responses that they can elicit?

When considering whether a simple electrical stimulus could be the cause of the many events of a behavioral response, we could ask whether a finger pushing a button to launch a man into orbit is responsible for the complicated machinery or for the sequence of operations. Evidently the finger, like a simple stimulus, is only the trigger of a programmed series of events, and consequently electrical charges applied to the brain cannot be accepted as the direct cause of leg flexion or aggression. The effect of electricity is simply to depolarize some neural membranes and to initiate a chain reaction. We must remember that even at the neuronal level, electrical excitation is not responsible for the many biochemical, enzymatic, thermal, and electrical processes which accompany the evoked action potentials. Evoked effects, like other chain reactions, depend more on the functional properties of the activated structures than on the starter. If electrical stimulation is considered as a non-specific trigger, our discussion must be focused on *what* is triggered. Why do movements start, develop, and end? Which motor mechanisms are involved within the brain? These basic neurophysiological questions are very difficult to answer because of our limited knowledge, but at least we now have some new tools to initiate their study, and experimental hypotheses to guide future research.

A tentative explanation of some of the mechanisms involved in motor activities has been proposed in the theory of fragmental representation of behavior (Delgado, 1964a) which postulates that behavior is organized as fragments which have anatomical and functional reality within the brain, where they can be the subject of experimental analysis. The different fragments may be combined in different sequences like the notes of a melody, resulting in a succession of motor acts which constitute specific behavioral categories such as licking, climbing, or walking. The theory may perhaps be clarified with one example. If I wish to take a cookie from the table, this wish may be considered as a force called *the starter* because it will determine the initiation of a series of motor acts. The starter includes drives, motivations, emotional perceptions, memories, and other processes. To take the cookie it is necessary to organize a motor plan, a mechanical strategy, and to decide among several motor choices, because the cookie may be taken with the left or right hand, directly with the mouth, or even by using the feet if one has simian skills. Choice, strategies, motor planning, and adjustments depend on a set of cerebral structures, *the organizer,* which is different from the set employed by the starter, because the desire for cookies may exist in hungry people or in completely paralyzed patients, and the hands can move and reach the table for many different reasons even if there are no cookies. Finally, the actual contraction of muscles for the performance of the selected movement to reach the cookie—for example, using the right hand—depends on a cerebral set, *the performer,* different from the previous two, because motor representation of hands, mouth, and feet is situated in different areas of the brain, and the choice of muscle group to be activated is under the supervision of a given organizer. Naturally, there is a close correlation among these three basic mechanisms, and also between them and other cerebral functions. The concept of a brain center as a visible anatomical locus is unacceptable in modern physiology, but the participation of a constellation of neuronal groups (a functional set) in a specific act is more in agreement with our present knowledge. The functional set may be formed by the neurons of nuclei far from one another: for instance, in the cerebellum, motor cortex, pallidum, thalamus, and red nucleus, forming a circuit in close mutual dependence, and responsible for a determined act such as picking up a cookie with the right hand.

If we accept the existence of anatomical representation of the three functional sets: starter, organizer, and performer, it is logical that they can be activated by different types of triggers, and that the evoked results will be related to the previous experiences linked to the set. The same set, evoking a similar behavioral response, may be activated by physiological stimuli, such as sensory perceptions and ideations, or by artificial stimuli, such as electrical impulses. Depending on the location of contacts, when we stimulate the brain through implanted electrodes we can activate the starter, the organizer, or the performer of different behavioral reactions, so that natural and artificial stimuli may interplay with one another, as has been experimentally demonstrated.

These theoretical considerations may facilitate the understanding of so-called willful, free, or spontaneous activity. Obviously, the will is not responsible for the chemistry of muscle contraction, for the electrical processes of neural transmission, or even for the intimate organization of movements; these phenomena depend on spindle discharges, cerebellar activation, synaptic junctions, reciprocal inhibitions, and other subconscious mechanisms. Voluntary activity is initiated by a physiological trigger which activates a chain of preformed mechanisms which exist independently inside the brain. The uniqueness of voluntary behavior lies in its wealth of starters, each one of which depends on a vast and unknown integration of past experiences and present receptions. However, the organizers and performers are probably activated in a similar manner by the will and by electrical means, providing the possibility of investigating experimentally some of the basic mechanisms of spontaneous behavior.

One limitation of electrical activation of behavior is the anatomical variability of the brain. Just as there are external physical differences between individuals, there are variations in the shape and size of our cerebral structures which make it impossible to place an electrical contact in exactly the same location in different subjects. Another important limitation is functional variability. The organization of brain physiology depends to a great extent on individual experience which determines the establishment of many temporary or permanent associations among neuronal fields. For example, the sound of a bell is neutral for a naive animal, but will induce secretion of saliva if it has previously been paired with food, and stimulation of the auditory cortex should increase salivary secretion only in the conditioned animal. Anatomical and functional variabilities are the bases for the differences in individual personalities. When we stimulate the motor cortex, we can predict the appearance of a movement but not the details of its performance, indicating that the effects elicited by electrical stimulation of the brain have a statistical but not an individual determination.

## ELECTRICAL DRIVING OF MENTAL FUNCTIONS IN MAN

Elemental psychic phenomena such as hunger and fear can be analyzed in both animal and man, but processes like ideation and imagery that are expressed verbally can be studied only in human beings. The most extensive information on this subject has been obtained by Penfield and his group (see, for instance, Penfield and Jasper, 1954) during surgical operations for epilepsy, tumors, or other illnesses. In these procedures, the brain was exposed under local anesthesia and stimulated electrically under direct visual control. More recently, as explained in a previous section, electrodes have been implanted in the brain for days or weeks, permitting repeated studies in a relaxed atmosphere, with the patient in bed or sitting comfortably in a chair. From Penfield's publications and from implanted-electrode studies, a considerable amount of information has demonstrated that brain stimulation may induce anxiety, fear, hostility, pleasure, feelings of loneliness, distortion of sensory perception, recollection of the past, hallucinations, and other psychic manifestations. From all this material, I shall select several representative examples dealing mainly with ideation, which is perhaps the most interesting and least understood of the mental processes.

### Speech Increase

Patient A. F. was an 11-year old boy committed to an institution because of his uncontrollable epileptic seizures and destructive behavior (see Higgins *et al.*, 1956). Since his response to drugs and treatment was unsatisfactory, brain surgery was decided upon. To direct the operation, four electrode assemblies were implanted in the temporal lobes for six days. During this time, intracerebral activity was recorded, and several spontaneous seizures were registered. Exploration of the patient included several tape-recorded interviews of from one and a half to two hours, behavioral observations, and 69 intracerebral stimulations. Study of the collected data indicated the existence of a focus of abnormality in the left temporal tip, and this area was successfully removed. Recovery from surgery was uneventful, and in a few weeks the boy was able to enjoy a normal life and return to school. Five years later he was still seizure-free.

In our investigations, the conversations between patient and therapist were tape-recorded while the spontaneous electrical activity of the brain was also being registered, and programmed stimulations were applied to different cerebral points. The general procedure was explained to the patient, but, to avoid possible psychological influences, he was not informed of the exact moment of the stimulations. To establish behavioral and electrical correlations, the recorded interviews were transcribed, divided into periods of two minutes, and analyzed by two independent investigators who counted the number of words and identified and quantified the verbal expressions according to 39 different categories. Table 1 shows the stimulation effects on verbal production. During this interview, the patient was quiet and spoke only four to 17 words every two minutes. Whenever point RP 1–2 was stimulated, the patient's attitude changed; he became more animated, and his verbal output increased sharply to a mean of 88 words per two-minute period.

TABLE 1

(From Higgins, Mahl, Delgado, and Hamlin, 1956)

| Stimulations<br>Time interval | RP 1-2 (N-7)<br>2′Postim. | <br>2′Prestim. | t-Test<br>P-Value | All Others Stimulations (N-7)<br>2′Postim. | <br>2′Prestim. | t-Test<br>P-Value |
|---|---|---|---|---|---|---|
| Mean % friendly remarks | 6 | 53 | 0.02 | 17 | 10 | —[a] |
| Mean $N$ words by patient | 17 | 88 | $<0.01$ | 4 | 9 | 0.15 |
| Mean $N$ words by Int. | 43 | 46 | —[a] | 16 | 30 | $>0.30$ |

[a]Insignificant by inspection.

These effects were repeated seven times, and in each stimulation the patient appeared to be especially optimistic, emphasizing the pleasant side of sensory perceptions and the happy aspects of his memories and ideas, with many of his comments affectionately directed and personally related to the therapist. Verbal expression was spontaneous in character, his usual personal style and phraseology were preserved, and conversational topics were related to the experimental situation without a preferred theme. Table 1 shows that the evoked increase of words and of friendly remarks were highly significant, as evaluated by the $t$-test, and also that the effect was specific because it was not produced by stimulation of other cerebral points.

## Sexual Ideation

In three different patients, thoughts and expressions with sexual content were induced by electrical stimulation of the temporal lobe. The first case, S. S., was an intelligent and attractive woman, 32 years old, who had suffered from uncontrollable epileptic attacks for several years. During the interviews she was usually reserved, but the first time that point A in the second temporal convulsion was excited with 6 volts, she became visibily affected, holding the hands of the therapist to express her fondness for him and to thank him for all his efforts. Several minutes later, after another stimulation of the same point, she started to say how much she would like to be cured so that she might marry, and other stimulations of point A were also followed by flirtatious conversation. The provocative play and ideas expressed under stimulation of point A did not appear following stimulation of other cerebral points and contrasted with this woman's usually reserved spontaneous behavior.

The second patient, V. P., was a woman 36 years old who had suffered from epilepsy since childhood. Point C in the temporal lobe was excited five times at intervals of from five to 10 minutes, and after each stimulation the patient's mood became friendlier; she smiled, questioned the therapist directly about his nationality, background, and friends, and declared that he "was nice," that his country (Spain) "must be very beautiful," that "Spaniards are very attractive," and she ended with the statement "I would like to marry a Spaniard." This particular train of thought and manner of speaking seemed completely spontaneous, but it appeared only after stimulation of point C in the temporal lobe, and no such shift to a flirtatious mood was noted in her spontaneous conversations following stimulations of other cerebral points.

The third case of evoked change in sexual ideology was a young epileptic boy, A. F., who, following stimulation of point LP 5–6 in the left temporal cortex, suddenly began to discuss his desire to get married. After subsequent stimulations of the point, he elaborated on this subject, revealed doubts about his sexual identity, and voiced a thinly veiled wish to marry the male interviewer.

### Experiential Hallucinations

Hallucinations evoked by electrical stimulation of the brain have been lucidly described by Roberts (1961), who wrote: "It is as though a wire recorder, or a strip of cinematographic film with sound track, had been set in motion within the brain. A previous experience—its sights and sounds and the thoughts—seems to pass through the mind of the patient on the operating table. . . . At the same time he is conscious of the present. . . . The recollection of the experiential sequence stops suddenly when the electric current ceases. But it can again be activated with reapplication of the electric current." The hallucination may develop during the stimulation, with a normal-like progression of movements and sounds, which appear more real and vivid than when the events actually happened. It is as if the patient had a double life, one in the past recalled by the electrical stimulation, and another in the present, perceiving all the sensory stimulation of the surroundings, but both with a similar quality of reality, as if the person had a "double consciousness" of subjective sensations. In some cases, components of the hallucination are completely new and do not belong to the subject's past experience, but usually, as Penfield (1952, 1958, 1960) emphasized, the responses are a detailed reenactment of previous experiences, an exact "flash-back" activation of memories.

In one of our patients with intracerebral electrodes, detailed study of the tape-recorded interviews demonstrated that the perceptual content of some experiential responses was related to the patient's thoughts at the moment of stimulation. For example, when the patient was talking about her daughter's desire for a baby sister, a stimulation was applied to the temporal lobe and the patient heard a female voice saying "I got a baby—sister." Baldwin (1960) has reported a similar observation in which the content of visual hallucinatory responses evoked in a 28-year old man varied with the sex and identity of the observer seated before him in the operating room. In a previous article (Mahl *et al.*, 1964) we have suggested that "The patient's 'mental content' at the time of stimulation is a determinant of the content of the resulting hallucinatory experiences," and we offered the so-called "altered-state hypothesis" in which the essential effect of stimulation is to alter the state of consciousness of the patient in such a way that primary process thinking replaces secondary process thinking. (See Freud, 1900.) According to this hypothesis, the electrical stimulation of the temporal lobe would not activate memory traces in the ganglionic record, as postulated by Penfield, but would induce a state of consciousness which would increase the functional probability of primary processes.

### Pleasure

The possibility that "pleasure centers" might exist in the brain was supported by the extensive work of Olds and his collaborators (1954, 1956, 1961), who demonstrated that rats prefer to stimulate some points of their brains by pressing a treadle, than to satisfy drives of hunger, thirst, and sex. Positive behavioral qualities of cerebral stimulation have been confirmed in other species including the cat (Sidman *et al.*, 1955) and the monkey (Bursten and Delgado, 1958). However, "pleasure" has an experiential factor which animals cannot report because they lack verbal communication. Only studies in humans could reveal whether electrical stimulation of the brain is able to induce pleasurable sensations. The study of patients with implanted electrodes yielded affirmative evidence (Delgado, 1960; Sem-Jacobsen and Torkildsen, 1960). In one of our cases, stimulation of the temporal lobe evoked "pleasant tingling sensations of the body" which were openly declared to be very enjoyable. The patient's mood changed from its usual peaceful state to one of giggling and laughing. She teased the doctor and made fun of the experimental situation with humorous comments.

In another patient, temporal-lobe stimulation evoked "statements avowing his pleasure at being 'up here' and 'subject to us' which were classified as 'passive compliance' " (Higgins *et al.*, 1956). For example, when the patient had been silent for five minutes, a point in the temporal cortex was stimulated and he immediately exclaimed, "Hey! You can keep me longer here when you give me these; I like those." and he insisted that the "brain wave" testing made him "feel O.K." Similar statements followed stimulation of other temporal points, but were never expressed spontaneously in the absence of excitations. The statistical significance of these results was $P < 0.001$, as contrasted by $X^2$ analysis.

During increased pleasure, the subjects were oriented mainly toward themselves, and they often reported experiencing agreeable physical sensations, while during artificially increased speech and changes in sexual ideology they expressed friendliness for the nearby people. In both cases, there was a shift of emotional mood to a happy interpretation of reality, and this experience was interpreted by the patient as spontaneous and valid, usually without being directly related to the stimulation. A shift from pleasurable thinking to friendliness and to sexual ideas has been observed in some cases.

Probably the most significant conclusion derived from electrical stimulation of the awake brain is that functions traditionally related to the psyche such as friendliness, pleasure, and verbal expression can be induced, modified, and inhibited by direct stimulation of cerebral structures. This discovery may be compared with the revolutionary finding almost two centuries ago that contraction of frog muscle may be induced by electricity without need of the soul's "animal spirits," because experimental analysis of mental functions can now proceed without implicating metaphysical entities. Research concerning the electrical driving of emotions, anatomical correlates of memory, or electrical signals related to learning does not interfere with personal ideas about the natural or supernatural destiny of man and does not involve theological questions, which should be disassociated from neurophysiological inquiry. In addition to electrical stimulation, there are now techniques for exploration of brain function which include electrical recording, chemical stimulation, intracerebral chemistry, and electron microscopy. The task that we are facing is the correlation of neuro-anatomy and physiology with mental functions; the investigation of cerebral areas involved in psychic manifestations; the analysis of their electrical and chemical background; and the development of methods to induce or inhibit specific activities of the mind.

Already we know that some structures, including the hypothalamus, amygdala, central gray, and temporal lobe, are involved in emotional phenomena, while other areas, such as the parietal cortex, do not seem to participate in psychic experience. Brain research has expanded rapidly in recent years with the creation of institutes for multidisciplinary studies, but this field should attract even more of our intellectual and economic resources. Human behavior, happiness, good, and evil are, after all, products of cerebral physiology. In my opinion, it is necessary to shift the center of scientific research from the study and control of natural elements to the analysis and patterning of mental activities. There is a sense of urgency in this redirection because the most important problem of our present age is the reorganization of man's social relations. While the mind of future generations will be formed by pedagogic, cultural, political, and philosophical factors, it is also true that education is based on the transmission of behavioral, emotional, and intellectual patterns related to still unknown neurophysiological mechanisms. Investigators will not be able to prevent the clash of conflicting desires or ideologies, but they can discover the neuronal mechanisms of anger, hate, aggressiveness, or territoriality, providing clues for the direction of emotions and for the education of more sociable and less cruel human beings. The precarious race between intelligent brains and unchained atoms must be won if the human race is going to survive, and learning the biological mechanisms of social relations will favor the cerebral victory.

Electrical and chemical analyses of mental functions have introduced new facts into the much debated problem of mind-brain relations. In the interpretation of data, we should remember that spike potentials, neurohumors, and synaptic transmitters may represent happiness and sorrow, love and hate, war and peace, and in the near future we can expect to find answers to classical questions concerning psychological aspects of the physical brain. How can electrical stimulation of the temporal lobe be felt as pleasure, music, or fear? Why is a ferocious monkey tamed by applying a few volts of electricity to its caudate nucleus? As discussed in a previous article (Delgado, 1964b), psychophysical correlations may be related to the two elements which transmit information in the nervous system, namely, the *material carrier* and the *symbolic meaning*. In the reception of sensory inputs, there is an initial *electrical coding* which is the carrier necessary for neural circulation of impulses. When a monkey, a savage, or a civilized man looks at a pencil, the received visual stimulus is transformed into electrical signals and transmitted through optic pathways to the brain. At the levels of retina and optic nerve, the coding of the stimulus depends on the visual input, independent of its possible meaning. Symbolism is created by the association within the brain of two or more sensory receptions or of present and past experiences, but it does not depend on the material structure of the object or on the pattern of its electrical coding. For a naive monkey or for a savage, the pencil is a neutral object; for a writer, the pencil is full of associations, uses, and meaning. Symbolism is not intrinsic in the object, nor inborn in the brain: it must be learned. The most important symbolic tool of the mind, language, is not invented by each individual; it is a cultural gift of the species. The symbolic meaning may be considered an *immaterial element of mental functions* in the sense that it is related to a spatio-temporal association between two or more sensory receptions and not to the material structure of the inputs. The elements for symbolic recognition already exist in the electrical code of the transmitted signals; however, they are not determined by the pattern of the code but by spatio-temporal relations between present and past codes which cannot be deciphered by any instrument if the reference point of the past is not known. These temporal and spatial relations may be considered as material or immaterial, depending on the investigator's point of view. Obviously, the relations depend on the material existence of some events, but, at the same time, the relations are independent of the material organization of each event. It is a question of definition, and, if we explain the meaning of our terms, there is no conflict. I think, however, that it is more practical to consider symbolism as *non* material in order to emphasize the relativity of its existence and the fact that it does not depend on the intrinsic qualities of matter but on the previous history of the object and of the observer. In the last analysis, behavior could be reduced to movement of atoms, but if we are discussing the emotional behavior of the monkey, it would be difficult to explain it in terms of orbiting particles, and it is far more useful to employ psychological concepts. It should be clarified that, in the observer, conscious understanding of meaning is probably dependent upon progressive steps of electrical subcoding of sensory inputs with the creation of new material and symbolic elements related to the activation of a new series of chemical and electrical phenomena affecting specialized neurons. However, the distinction between material carrier and symbolic meaning simplifies the interpretation of neurophysiological data, because analysis of events in receptors and in transmitting pathways will provide information about the carrier but not about symbols. At the same time, it should be expected that electrical stimulation of neuronal groups may activate processes related to both material carriers and symbolic meaning. This working hypothesis may help in the differentiation between cerebral mechanisms responsible for transmitting inputs and for cognitive processes of received signals.

From its beginning, wiring of the human brain aroused emotional opposition even among scientists, while similar wiring of the heart or of the bladder has been received enthusiastically. The difference in attitude was no doubt related to a more or less conscious personal fear that our identity could be attacked and that our mind could be controlled. Personal traits such as friendliness, sexual inclination, or hostility have already been modified during cerebral stimulation, and we can foresee other influences on emotional tone and behavioral reactions. Electricity is only a trigger of pre-existing mechanisms which could not, for example, teach a person to speak Spanish, although it could arouse memories expressed in Spanish if they were already stored in the brain.

Entering into the field of speculation, I would like to comment on one question which has already caused widespread concern. Would it be feasible to control the behavior of a population by electrical stimulation of the brain? From the times of slavery and galleys up to the present forced-labor camps, man has certainly tried to control the behavior of other human beings. In civilized life, the intervention of governments in our private biology has become so deeply rooted that in general we are not aware of it. Many countries, including the United States, do not allow a bride and groom to marry until blood has been drawn from their veins to prove the absence of syphilis. To cross international borders, it is necessary to certify that a scarification has been made on the skin and inoculated with smallpox. In many cities, the drinking water contains fluoride to strengthen our teeth, and table salt is fortified with iodine to prevent thyroid misfunction. These intrusions into our private blood, teeth, and glands are accepted, practised, and enforced. Naturally, they have been legally introduced, are useful for the prevention of illness, and do generally benefit society and individuals, but they have established a precedent of official manipulation of our personal biology, introducing the possibility that governments could try to control general behavior or to increase the happiness of citizens by electrically influencing their brains. Fortunately, this prospect is remote, if not impossible, not only for obvious ethical reasons, but also because of its impracticability.

Theoretically it would be possible to regulate aggressiveness, productivity, or sleep by means of electrodes implanted in the brain, but this technique requires specialized knowledge, refined skills, and a detailed and complex exploration in each individual, because of the existence of anatomical and physiological variability. The feasibility of mass control of behavior by brain stimulation is very unlikely, and the application of intracerebral electrodes in man will probably remain highly individualized and restricted to medical practice. Clinical usefulness of electrode implantation in epilepsy and involuntary movements has already been proved, and its therapeutical extension to behavioral disorders, anxiety, depression, and other illness is at present being explored. The increasing capacity to understand and manipulate mental functions of patients will certainly increase man's ability to influence the behavior of man.

If we discover the cerebral basis of anxiety, pleasure, aggression, and other mental functions, we shall be in a much better position to influence their development and manifestations through electrical stimulation, drugs, surgery, and especially by means of more scientifically programmed education.

These possibilities pose tremendous problems. As Skinner asked recently (1961), "Is the deliberate manipulation of a culture a threat to the very essence of man or, at the other extreme, an unfathomed source of strength for the culture which encourages it?" Scientific discoveries and technology cannot be shelved because of real or imaginary dangers, and it may certainly be predicted that the evolution of physical control of the brain and the acquisition of knowledge derived from it will continue at an accelerated pace, pointing hopefully toward the development of a more intelligent and peaceful mind of the species without loss of individual identity, and toward the exploitation of the most suitable kind of feedback mechanism: the human brain studying the human brain.

## ACKNOWLEDGMENTS

Part of the research mentioned in this paper was supported by grants from the United States Public Health Service and the Office of Naval Research. Some of the studies were conducted during a John Simon Guggenheim fellowship. The experimental and editorial collaboration of Caroline Delgado is warmly acknowledged.

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