Exploring the Mind-Brain Relationship

Robert G. Heath, M.D., D.M.Sci.

Exploring the Mind-Brain Relationship

Robert G. Heath, M.D., D.M.Sci.

Moran Printing, Inc.
Baton Rouge, Louisiana
Printed 1996

CONTENTS

PREFACE

This monograph comprises much of the data collected during laboratory investigations by personnel in the Tulane University Department of Psychiatry and Neurology to establish some correlations between mind and brain. When, in 1949, I was appointed the founding Chairman of the combined department, a major objective was to develop a multiphasic research program in which scientists from many disciplines would work together toward the common goal of elucidating the physical basis of mental activity to provide more effective treatment for psychiatric and neurologic disorders. The names of the many dedicated participants in the studies are reflected in the references at the end of this monograph.

Tulane provided an ideal environment for this endeavor. The President of the University, Rufus C. Harris, J.D., and the Dean of the Medical School, Maxwell E. Lapham, M.D., assigned research a high priority. Charity Hospital, the principal teaching hospital, had a wealth of patients with widely diverse illnesses, many of which were unresponsive to the treatments available at the time. Our therapeutic efforts with those patients and others are described in this two-part monograph. It was heartening to ease the torment and anguish of those patients even for short periods.

In Part I, I review the theoretical basis for the techniques we developed to gather our data. The formulations we evolved derived from clinical psychiatric and psychologic data, particularly psychody-

namics. Part II is a compilation of the significant data we collected within the context of the overall theme of this monograph. Informed consent was obtained from every participant in our studies, as well as his or her responsible relative or legally authorized representative, since some patients were mentally incompetent. In the early days, all procedures were approved by the Medical School administration. When an institutional human use committee was established, procedures were submitted to the committee for approval.

Over the years, the various University and Medical School administrations encouraged our efforts and steadfastly supported us during periods of controversy in this field. In addition to Dr. Harris and Dr. Lapham, I am most grateful to John J. Walsh, M.D., formerly Chancellor of Tulane Medical Center, Herbert E. Longenecker, Ph.D., formerly President of Tulane University, and Charles C. Sprague, M.D., formerly Dean of the Medical School, to name a few, without whose support these studies would not have been possible. I also appreciate the cooperation of Jesse Bankston, who was Director of the Louisiana State Department of Hospitals during many of the years this work was in progress. Most recently, I am beholden to Daniel K. Winstead, M.D., the current Chairman of the Tulane Department of Psychiatry and Neurology, who has provided me with encouragement and support to complete this monograph. And I would be remiss not to acknowledge the important funding by The Commonwealth Fund during the early years of this research.

I am especially indebted to Irene Dempesy for her dedication and assistance in developing this monograph. As Administrative Assistant for the program beginning in 1954, she participated in much of this research, has helped to compile the data, and has typed and assisted in the editing of this manuscript. Without her contributions, it is unlikely that this monograph would have been completed.

The editorial skills and the constructive and friendly suggestions of Lois DeBakey, Ph.D. have been invaluable.

Finally, I have been fortunate in working with a talented technical staff, who remained with the program for many years. I am particularly indebted to Katherine L. McCarron, Herbert J. Daigle, and Charles J. Fontana.

This monograph presents the highlights of an exciting and gratifying experience extending over 40 years that was further enhanced by rewarding interactions with colleagues, residents, and medical students. When we initiated the program, we were young and vigorous and expected to have many answers within a short

time. But the answers proved frustratingly elusive, and we sometimes felt like throwing in the towel. There were always a few members of the team, however, who would dig in their heels and insist we try again — and we did. If our findings inspire other investigations or contribute to advances in years to come, they will have served their purpose.

Robert G. Heath, M.D.
New Orleans, Louisiana
1995

PART I

INTRODUCTION

Since the mid-1940s, our multidisciplinary research program at Tulane sought information concerning the physical basis of the mind as a prerequisite for the development of specific biologic treatments for behavioral disorders. Numerous interdependent studies in patients and animals provided direction for this program.

A psychiatrist, in evaluating a patient, conventionally focuses on environmental factors — past experiences and recent stresses — that might have contributed to the illness. Changes in brain function that might account for the patient's inappropriate emotionality or the more severe symptoms of psychosis, such as delusions, hallucinations, or violent behavior are not usually considered. However, our data suggest that symptoms correlate with alterations in brain function that produce the disorder. We hope that our findings will provide impetus for development of more effective biologic approaches to behavioral problems.

To design experiments that would yield information on the physical basis of mental activity, we had to begin with behavioral observations. These findings, together with the limited information about brain function and behavior available forty years ago, furnished direction for developing neurophysiologic studies to elucidate further the brain's relationship to behavior.

From a review of the dynamic observations that proved most useful in establishing the basis for our neurophysiologic studies, it is

evident that emotion, which can be viewed both physiologically and psychologically, is an important bridge between mind and brain. As our investigations focused on emotion, it also became increasingly apparent that sensory perception and memory, conventionally considered to be separate entities, are in integral relationship with emotion. In Part I, I review the psychodynamic theory and behavioral observations that provided evidence for the relationship and served as the rationale for the techniques we developed in order to collect physiologic and biochemical data for correlation of brain function with some mental functions. The information that was gathered suggests that sensory perception and memory are subserved by the same neural network as that for emotion. As long as a hundred years ago, William James (1890, 1950) speculated on the relationship of these three phenomena. Our findings provide support for his theorization.

PSYCHODYNAMIC OBSERVATIONS LEADING TO BIOLOGIC INVESTIGATIONS OF THE BRAIN AND BEHAVIOR

Establishing a Theoretical Framework for Relating Mind and Brain

Behavior is action or doing, and human behavior is the consequence of activity of the mind. Sherrington (1937) defined the mind as "the manager of muscle." Since doing is related basically to satisfaction of metabolic needs, it is essential to survival. In man, doing or activity of the mind is integrated by thought, emotion, and feeling. Freud also related mentation to activity, when he defined thought as trial behavior (Rado, 1946-65). Symbols are manipulated in the mind, thereby eliminating the need for repetitive trial and error. Although it is axiomatic that activity of the mind is in a one-to-one relationship with activity of the central nervous system, a one-to-one correlation may never be demonstrated. Considerable progress has been made, however, toward establishing cross-correlations between activity of the mind and activity of the brain.

Before we could develop methods for collecting data, we had to establish a useful hypothesis. Our initial approach, admittedly rudimentary, was to consider some crude correlations between behavior of evolving species and evolutionary changes in the central nervous system, thus providing a relationship between levels of behavior and central nervous system levels (Heath, 1954; Rado, 1946-65; Rado, 1956; MacLean, 1970). This approach suggested that certain aspects of behavior observed in humans, which corresponded to behavior of lower animals, might be the consequence of activity of common

neural structures, whereas behavior uniquely characteristic of man was the consequence of activity of those structures of the central nervous system that are unique to man.

The Role of Biologic Needs — Pain and Pleasure

Evolutionary changes in the central nervous system and associated behavioral changes have been described previously (Heath, 1954; Rado, 1956). Briefly summarized, they indicate that primitive, even unicellular, organisms, in which neural mechanisms consist only of contact receptors, respond behaviorally to contact stimulation and show evidence of a primitive memory process (Fox, 1983; Kandel and Schwartz, 1981). The response in primitive organisms of approach and absorption or retreat and avoidance seemingly invokes the basic pleasure-pain principle that regulates the behavior of every living organism, regardless of its level of evolution. The organism is activated by internal or external stimuli, which create a state of disequilibrium. That, in turn, results in activity (behavior) to restore a state of equilibrium. These fundamental principles, observable in the simplest organism, prevail in all living species. Biologic needs, modified by environmental factors, are the primary motivating force for activity. For successful adaptation, it is axiomatic that approach behavior, associated with the pleasure response, must be toward something of positive survival value. Contrariwise, avoidance behavior, associated with painful feelings, must be away from something of negative survival value. In the absence of such a relationship, the organism will not thrive or even survive. (The person who abuses drug is a flagrant example. He obtains immediate pleasure, but his behavior in no way relates to survival.) This basic principle of presumed reward-punishment related to survival persists through all levels of behavior, including the most complex patterns of human beings.

Environmental input (education) can result in the ability to defer immediate pleasure or endure pain temporarily, for the sake of enhanced pleasure later. Successful adaptation usually requires that which is pleasurable (eliciting "approach" behavior) to have utility value and that which is painful (eliciting "riddance" behavior) to have no utility value. As the nervous system develops and more complex behavioral patterns evolve, these basic features remain.

Correlation of Evolving Nervous System Levels with Behavioral Levels

Midbrain-Emotion. — Moving up the phylogenetic scale (fish and reptiles to lower mammals), one sees the appearance of hind

brain structures, the basal ganglia, and an enlarging midbrain (thalamus and limbic lobe) with primitive cortex. And with this evolution of the central nervous system, emotion is in intricate relationship with distance sensory receptors for sight, hearing, and smell. Specific patterns of response, consequent to detection of signals from a distance, are now possible.

The evolving species with these capabilities adapts more efficiently, being able, through distance sensory receptors, to identify objects of negative or positive survival value before contact is made and to react accordingly. Emotional behavior involves immediate arousal and response. As more complex behavioral patterns evolve, the basic behavioral regulators of pleasure and pain are retained. If the object is of positive survival value, the result should be pleasurable emotion (love, hope) leading to "approach" behavior. An object of negative adaptive value, on the other hand, should prompt painful emotion (rage, fear) and result in "riddance" behavior (rage resulting in attack-destroy and fear resulting in flight-avoidance). Memory patterns become progressively more complex. Fixed instinctual memory is characteristic of species with an evolving hind brain, related to vestibular proprioceptive function, and basal ganglia (corpus striatum). Illustrative of this development are the fixed, repetitive behavioral patterns of fish, amphibia, birds, reptiles, and lower mammals (Ariens-Kappers, 1928; Lorenz, 1937; Spalding, 1954; MacLean, 1973).

Cortex-Thought. — As the cerebral cortex increasingly developed, thought emerged, and, with thought, the increased ability to modify behavior through learning (environmental happenings) and to anticipate and plan the future (in contrast to immediate behavioral response that characterizes emotional behavior). With maximal cortical development came the use of symbols and the development of language and intellect. Increasingly complex behavioral patterns now rapidly emerged as a result of the ability to incorporate new information from environmental stimulation and to reason and, based on this information, to look ahead and plan the future. While the cortex was enlarging and becoming more complex, however, a corresponding enlargement occurred in those subcortical structures associated with emotion and memory (Armstrong, 1986). This conjoint cortical-subcortical growth provides a neural basis for the continuing interrelationship of the behavioral phenomena of abstract thought and emotion.

Anthropologic data also provide some broad information concerning the relationship between brain structure and behavior of

the hominid species, which first appeared about six million years ago. Two-million-year-old skulls of the hominid, the oldest discovered thus far, indicate that their cranial cavities were small compared to that of modern man. Artifacts indicate their behavior was hardly distinguishable from that of subhuman primates, such as the great apes. As many as five different hominid species probably existed at one time, becoming extinct as they failed to adapt to the environment. More information has accumulated on Neanderthal man, who appeared about 150,000 years ago and probably coexisted with two hominid species. Compared to modern man, his brain was at least as large, but the forebrain was less well developed. He became extinct soon after the precipitous emergence of Cro-Magnon 35,000 to 40,000 years ago. It appears that Cro-Magnon was the result of a minor genetic change, the consequence of which was a well-developed forebrain and extensive and more complex wiring of the cortex. The configuration of man's brain today is very similar. The changes in behavior that have occurred in the past 35,000 years have been the result of creativity and the ability to accumulate and pass on new information, rather than of structural changes of the brain.

It was Neanderthal man who first used fire in a controlled way and developed crude stone tools. He also began to care for the young and disabled. As a result, he managed to endure and dominate for more than 50,000 years. But he lacked innovation and creativity. His skills did not improve. He traveled very little, remaining in essentially the same geographic area. When Cro-Magnon appeared, Neanderthal man was unable to compete. Cro-Magnon's tools and weapons were increasingly efficient. He traveled ever-greater distances. He developed foresight and could plan and organize. Most importantly, he could communicate and thus disseminate information.

Twelve thousand years ago — a flash of time in evolution when one considers that reptiles prevailed for 150 million years — civilization began with the discovery that seeds could be stored for later planting and animals could be domesticated. With the ability to communicate, new knowledge accumulated at an ever-accelerating rate. The advances have been dramatic — from the spoken language to symbolic paintings of cave dwellers to the writings of the Sumerians of Mesopotamia to the invention of the printing press, and now, the computer. And the telephone, radio, and television provide almost immediate access to new information.

The vast cultural changes that have resulted from the availability of new information can be illustrated in almost all fields of en-

deavor, perhaps most strikingly in transportation. For most of modern man's existence, transportation was limited to the speed of the beast of burden. The steam engine was developed only some 200 years ago. Then came the internal combustion engine and aircraft. By World War I, man was able to travel 100 miles per hour. With the development of the jet engine near the end of World War II, flying speed increased to 600 miles per hour and eventually to 2,000 miles per hour. And now, with rockets providing speeds of 25,000 miles per hour, man is traveling to outer space. A graph of speed against time would show virtually a flat line and then an almost perpendicular takeoff, representing the developments of the past few years. From the early use of wind and fire for energy, we have unlocked the secrets of the atom and now have the prospect of unlimited energy in the form of nuclear fusion.

Changes in medicine have occurred at a parallel pace. A student of Hippocrates could have practiced adequately until the 1920s. Now, new medical knowledge becomes available almost daily through the scientific journals and other media. A parallel can be demonstrated in nearly every scientific field. And in every instance, the evolution is the result of new information becoming available and man's ability to innovate, rather than a further change in brain structure — cultural evolution rather than biologic evolution. It is hypothetically probable that an infant born 30,000 years ago at the dawn of civilization, were he projected into today's culture, could grasp current events and adapt to modern technology as well as a child born today, since his brain would have the same capacity. Today, New Guinea natives, who were born into the Stone Age culture of their parents, are self-governing, drive automobiles, fly airplanes, and use computers.

As a result of forebrain development, man dominates life on earth, and his control over physical matter increases steadily. This evolution has not been without ominous and potentially catastrophic complications, however. Man's demands, particularly in the field of transportation, have caused ever-faster consumption of fossil fuels and consequent increased release of carbon dioxide and methane. The postulated greenhouse effect is becoming a reality. Meanwhile, the development of nuclear fusion, a clean energy source, is slowed by economic considerations. Heralded medical advances and atavistic religious concepts contribute to the severe population problem. Food supplies are dwindling, and starvation is increasing.

But the greatest threat is the fact that man, in common with

early Homo sapiens and animals, continues to display behavior rooted in the emotional brain — greed, unreasonable fears, violence, aggression. Unfortunately, modern man's unique forebrain provides the intellect and creativity to act out these primitive emotions in more and more destructive ways. The caveman's club has progressed to the bow and arrow to guns to aerial bombardment to nuclear submarines and to the hydrogen bomb delivered by rocket. In spite of his abstract knowledge, modern man has perpetrated the Crusades, the Inquisition, and the Holocaust. The ancient animosities of the Middle East have persisted, often escalated by competitive religious philosophies that, paradoxically, were designed to provide moral rules for enhancing man's behavior.

What does man's much-heralded intellect, the consequence of a minor structural change in the brain, represent? Is it indeed the laudable development it is usually considered to be? Or, because of the technologic changes it has brought about, is it, figuratively speaking, a malignant development destined to destroy life on our planet? Can we count on a brighter future of expanded frontiers for all people? Or will man's destructiveness lead to a long winter and the end of life on earth? Are we on a genetically developed course parallel to the maladaptive developments that led to the extinction of the australopithecines and Neanderthal man? The first step in confronting these questions is to elucidate brain mechanisms underlying behavioral patterns. Possibly, some of the techniques used in our studies may begin to shed light on the interactions of the new brain with the older brain subserving emotion.

Behavior-Central Nervous System Levels in Man: A Dynamic Process

Since I will be referring to both neurologic levels and levels of thought, their usage should be clarified. In terms of neurologic levels, subcortical levels of the brain are below that of the cerebral cortex, which is the brain's highest level. In terms of levels of thought, emotional thinking is considered lower-level (shared with animals), originating in subcortical levels of the brain, whereas abstract, precise, unemotional, creative thought is considered the highest level of thought, having evolved in association with the brain's cortical levels.

Obviously, man's behavior is not governed solely, or even predominantly, by abstract, logical intellect based on accumulated factual information. It is apparent from behavioral observation, combined with introspection, that there is a continuously fluctuating relationship between the human behavioral characteristics of emotion

that are shared with lower species and high-level abstract thought. Introspective data reveal a range of thought levels from abstract, relatively unemotional exact thinking (mathematical and scientific thought, where symbol and referent approach a one-to-one relationship) to intensely emotional thinking (characterized by wishfulness, lack of precision, and need for immediate action). In this scheme of behavioral levels, consciousness resides at the highest level and the unconscious at lower levels. Rather than a sharp dividing line between the two, there are gradations.

Dreams are the lowest level of thought accessible to introspection. They reflect the prevailing emotional state and are understood only if the dreamer's emotional preoccupation is known. The thinking of the psychotic demonstrates low-level thought. His delusions, representing his psychologic reality projected into actual reality, reveal thoughts that remain at the unconscious level of the nonpsychotic person, whose integrated mental apparatus automatically excludes them from conscious awareness.

There is a continuous and dynamic relationship between levels of thought. The highest level that can be achieved varies strikingly from one person to the next. Whereas some persons are capable of very high-level, unemotional abstract scientific thought, others cannot move much beyond a level of thought pervaded with and influenced by wishful emotion. Levels fluctuate widely. When one is preoccupied with emotional thinking (anger, fear, pleasurable fantasies, hunger, sex), lower-level thought dominates and higher-level thought is diminished or extinguished. The most accomplished scientist cannot ponder the intricacies of a scientific equation when he is in a highly charged sexual state or in a state of rageful dyscontrol or panic. In other words, he, too, is sometimes influenced by primitive, self-centered, often unreasoning, emotional thought that cannot always be sublimated by plunging into a dedicated effort.

In the proposed theoretical framework relating behavioral levels to central nervous system levels, fluctuations occur in the relationship between activity at the higher levels for thought (cortex) and the lower neural levels for emotion (subcortex). Cortical activity is dominant when one's concept of self in relation to the world is realistic, whereas subcortical activity is dominant during emotional periods of wishful thinking (particularly during dreaming associated with intense pleasure) or overwhelming rage or fear. The maximal distortion of reality — depersonalization and profound disruption of emotionality, as in the psychotic state — suggests that activity in the

brain's circuitry for emotionality and alerting is severely impaired. These were important considerations in devising physiologic techniques for testing the hypothesis of a relationship between behavioral levels and levels of the central nervous system.

Behavior-Central Nervous System Levels and Concept of Self

Factors influencing the evolution of self-image. — The self, as consciously perceived, is an important aspect of mental activity. It was therefore a relevant component of the behavioral framework we used in formulating our physiologic experiments. Throughout life, the self is in integral relationship with sensory perception, emotion, and memory. Emotion and sensory perception are significant in establishing self-image, which continuously fluctuates in association with the psychological levels of behavior. Complementing the concept of behavioral levels, the phenomenon of self-image provides additional leads for relating brain function and behavior, and has resulted in the formulation of expanded hypotheses that are testable by physiologic methods.

Self-image, unique for each individual, changes as thought level changes, with corresponding changes in activity occurring at levels of the central nervous system. When one is indulging in a wishful fantasy (emotional thought), self-image is quite different from that when one is contemplating the problems and realities of everyday life (high-level, abstract thought). A person's self-image can abruptly inflate or deflate — from a Walter Mitty, who overcomes all obstacles, to a self-deprecating failure. Self-image determines one's concept of the universe, which can be conceived only in terms of self. It has been said poetically that a universe disappears when a person dies.

Self-image is profoundly altered in various clinical disorders. The manic patient with grandiose delusions and an excessively inflated self-image becomes the center of a contracted universe. The depressed patient, on the other hand, denigrates himself, and his shrunken image causes him to retreat into isolation. The expressional, hysteric patient, also with a deflated self-image, invokes a different pattern. Needing reassurance of being loved, the hysteric assumes the center of attention and demands an admiring audience. Depersonalization, an extreme condition, is a common symptom of psychosis in which there is a discontinuity of self, the person being unaware of who he is. Psychotomimetics can induce a similar discontinuity of self and can produce disturbances in sensory perception. Self-image changes instantaneously with ingestion of mood-al-

tering drugs, such as alcohol, the pain-suppressing and pleasure-inducing opiates, cocaine, and marijuana.

Although conceptualizations concerning development of self are vague, there are some features with which one can grapple to develop testable hypotheses. Two distinct kinds of input are seemingly operational in the development of self. The first, sensory stimulation, must be adequate to activate the neuronal mechanism so as to make it receptive to the second, the changing interaction of the child with his environment during the earliest period of development. Numerous observations suggest that development of a healthy concept of self requires specific and adequate sensory input. When (and if) a functioning neural mechanism is established (requiring genetic predisposition and sufficient early sensory stimulation), the relation of the developing individual to his environment plays a significant role in his evolving self-image.

The role of perception and emotion in activation of the neural mechanisms correlated with self-image. — The manner in which a concept of self develops has been the subject of considerable conjecture and study. Largely on the basis of personal introspection, William James (1950, 1890, Volume I, Chapter 10) speculated on a chronologic relationship between "feeling" and self. He related the active, conscious factor in self to emotion, and referred to a sense of self-development by way of mouth activity (sucking, swallowing). Observations on infants corroborate his speculation. Factors in the infant's development of an identity separate from the mother are the coming and going at the breast, sucking and swallowing, and the associated warmth and tenderness. The pleasure of feeding (mouth pleasure), proprioception (movement), and somatosensation (touching, warmth) are influential interrelated events in the initial stage for the establishment of a sense of self. The consistency and persistence of this relationship are apparent from introspective data that show the linkage between mouth pleasure and tenderness, love, and self-image, as well as between proprioceptive-somatosensory input and an integrated self. The linkage is similarly evident in daily happenings throughout life. Alimentary deprivation and satiation dramatically influence one's relationship to the external world: whereas self-image shrinks when one is hungry, it expands after a satisfying meal.

Self is notably affected by proprioceptive-somatosensory input. The feelings of pleasure and security that derive from being held and caressed by a loved one enhance self-image. Pleasure is evident in the delighted response to being tossed into the air or to riding on

a merry-go-round or roller coaster with a trusted person. Stature is likewise influenced by stimulation of other sensory modalities. The feeling of gaiety induced by a Strauss waltz or that of patriotism by a John Philip Sousa march expands self-image, whereas the sadness induced by Wagner's funeral march shrinks it.

The earliest memories of the mnemonist "S," reported by Luria (Luria, 1968, pp 77-78), highlight the importance of the interaction of feelings, self-identity, and memory:

> This is the sense I had of my mother: up to the time I began to recognize her, it was simply a feeling — "This is good." No form, no face, just something bending over me from which good would come . . . Pleasant . . . Seeing my mother was like looking at something through the lens of a camera. At first you can't make anything out, just a round, cloudy spot . . . then a face appears, then its features become sharper.

Our collection of neurophysiologic data that elucidate the neural basis for these interrelationships evolved from initial serendipitous observations made by the Harlows (Harlow and Harlow, 1962) in monkeys raised in isolation for the first three months of life. Their sensory-deprived monkeys characteristically had profound impairment of emotional expression, which progressed to permanent pathologic behavioral patterns. The monkeys assumed unusual postures and meaningless rocking movements. They often showed inappropriate violent-aggressive behavior. They could not relate to others of their species and usually could not mate. Features of their behavior so closely resembled the objective behavior of psychotic patients that some psychoanalysts considered the findings to be supportive of the then-popular concept that the etiology of schizophrenia in their patients was a schizophrenogenic mother, that is, the mother's pathologic relationship to the patient when he was a child was the crucial factor in the patient's development of schizophrenia. In later experiments in monkeys, however, Mason and associates (1968) showed that the absence of somatosensory stimulation, particularly vestibular proprioception (muscle-joint-tendon stimulation) and touch, was the most important factor, a finding congruous with William James's speculations about the importance of movement (vestibular proprioception) and touch in the development of a concept of self.

In studies in patients in which clinical symptoms have been correlated with neuropathology, neurologists have localized neural mechanisms for integrating sensory data into a concept of body

schema that is in dynamic relationship with the environment (Adams and Victor, 1977 — Chapter 12). Motion in space provides awareness of one's body schema. The neural structures involved are those for sensory input into the cerebellum and interconnected nuclei within the brain stem. The importance of the relationship of sensory perception, integrated emotionality, and the concept of self is further substantiated by sensory isolation experiments in human subjects. When a person is deprived of sensory input — particularly vestibular proprioception and touch — he rapidly, within hours to days, develops profound disturbances in emotionality and sensory perception and a disorganized concept of self that resembles psychosis (sensory isolation psychosis).

It was these observations in animals (chiefly the findings of Mason) and human subjects that first motivated us to explore the role of the cerebellum and the somatosensory thalamus, in particular, as participants in the neural circuitry for emotion. Later, subcortical relay nuclei for other sensory modalities were also shown to be integral functional participants in this neural system for emotion (Heath, 1973; Harper and Heath, 1973, 1974; Heath and Harper, 1974). Important anatomic and functional relationships among other brain sites where activity has been correlated with emotion were also observed in physiologic experiments we conducted in some of Harlow's isolation-raised and control monkeys (Heath, 1972b).

Whereas these observations point to the importance of sensory input in the development of a healthy neural circuitry for emotion and self-awareness, there is also an abundance of data concerning the importance of the infant's relation to his environment (in those with adequate established structure-function through sufficient stimulation) in the evolution of self-image. Since the manner in which a person relates to the environment is dependent on his developing physical maturation, many aspects of this evolution are consistent from one person to another.

Interaction of biologic factors with environmental influences in developing stages of self. — Biologic factors, which gradually change during maturation of the person whose neural mechanism is intact and who has had sufficient sensory stimulation, influence the manner in which that person interacts with the environment to develop a self-image. The imprinting during the biologically influenced, changing relationship with environment not only affects the person, but has been a major factor in shaping man's culture — specifically, his institutions. The evolution of self has a complex history because of man's biologic characteristics. These characteristics are responsible for the consistencies in self-concept from one person to the next, at a given period of time, as well as from one generation to the next. Many basic features of man's developmental history are remarkably permanent and significantly influence his later behavior.

In contrast to other species, man is essentially helpless for a prolonged period after birth. Since his early survival is almost wholly contingent on the action of others, earliest self-image is in the context of complete dependence. The newborn infant develops tensions as his biologic needs intensify (to be fed, to be made warm). He cries out his discomfort, his need is magically fulfilled, and he experiences pleasure. Initially, unaware of the intervention of others, he knows only that he expresses a wish and it is granted. The adaptive pattern that evolves from this developmental stage, often referred to as omnipotence or omnipotence of desires (Ferenczi, 1913) has such strong impact that a residual core of one's initial self-concept and associated mode of adaptation endures — and has to be contended with — throughout life.

As the infant develops and begins to realize that other persons (usually the parent) are involved in the fulfillment of his desires, the stage of absolute omnipotence modifies gradually to one of delegated omnipotence. There is a beginning awareness that fulfillment of his desires depends on outside agents. "Mother (or Dad), do this . . .; give me that." During this period, he also starts experiencing the reality that the parent (or parental surrogate), whom he considers an extension of himself, sets limits and makes demands, in addition to performing as he wishes. Thus, the initial stage, when the self is not conscious of others, evolves into an awareness that the power of self is exercised through agents. And, little by little, there is movement to an orientation based in reality-testing — away from the initial position of being the center of the universe and towards an objective appraisal of one's true place in the universe. There is broad variation from one person to another, however, in the level of maturation eventually achieved. Whereas some attain a high level of reality orientation, others remain psychologically immature. Despite the degree of maturation reached, however, individual behavior fluctuates in association with level of psychological awareness because of the memory core of the earlier adaptive patterns, and during the diurnal cycle of every individual, there is some regression to wishful, emotional thinking. For example, even a person who usually functions at a mature level will, if severely stressed and feeling helpless and unable to cope, regress to a replication of the infantile relationship to authority and pray for the

protection of the deity. Initial requests to mother and father become the root of prayers. A reflection of this tendency are the statistics showing a rise in church attendance during periods of war or natural disaster and a decline when peace and affluence prevail.

With severe psychopathology (as in the psychotic state), reality is so distorted that low-level, unconscious thought, in the form of delusions, becomes reality. Primordial omnipotence manifests itself. The patient declares he is Napoleon or Caesar or Jesus Christ or God. The normally integrated person with intact defenses, on the other hand, healthily expresses his omnipotent drive for control in a socially beneficial way — the artist paints, the scientist experiments, the poet writes.

In summary, self-image evolves from an infantile stage, when one's perception of self is of being at the center of and completely controlling the environment (primordial omnipotence) through a stage of increasing awareness of others who act as agents (delegated omnipotence), toward a gradually increasing awareness of self in relation to reality. The agents of delegated omnipotence (parents or parental surrogates) begin to make demands, in addition to fulfilling wishes. Thus, the educational process begins, whereby a value system or an automatic self-operating scheme, or conscience, becomes established. It is the conscience that determines the manner in which a person fulfills his biologic needs and meets cultural demands — his pattern of adaptation. Regardless of the level of psychological maturation that a person achieves, however, the core of the imprinted patterns of the early stages remains and emerges to affect behavior manifestly.

Knowledge, the acquisition of factual information, usually results in the reduction of stature or size of self. Reality testing, with which one can accurately appraise one's role in the scheme of things (the universe), can be humbling and painful, in contrast to the wishful, omnipotent-like self-image characteristic of low-level thought. The self can be identified with all levels of consciousness, and the image of self varies greatly concurrent with the level of awareness. An observation interpreted realistically at the highest level of thought can be characteristically distorted and self-centered at a lower thought level. (A bird perches on the limb of a tree. The wind blows and shakes the tree. The bird remarks, "Look what I have done.") Even use of information or knowledge can be at a reduced level of awareness. For example, scientists working to evolve complex formulas can compete for approval at a childish (emotional) level. In the psychotic, who

has no modifying defenses, the primordial concept of self is on the surface, and is apparent in his disordered thought. Like depersonalization and dreaming, the psychotic's hallucinations represent distortions in boundaries of self. He perceives the content of his own mental activity in the form of a voice or vision coming from outside of self.

It is healthy for the self-image to expand with successful, worthwhile accomplishment, and it is appropriate for it to shrink with poor performance. But the self-image can readily be inflated artificially, most commonly by the use of intoxicants. Along with the feeling of pleasure, this is the principal appeal of such euphoriant drugs as alcohol, cocaine, and heroin. During endogenously-occurring states of elation (for example, the manic state), the self is also profoundly inflated. When the self-image is expanded, the universe shrinks proportionately. Conversely, in some clinical conditions (for example, depression), the self-image is profoundly shrunken, and the person's universe, as a result, expands proportionately. Thus the relationship of the self-image to the surrounding world fluctuates significantly in association with his prevailing emotional state.

Relating the Psychology of Self and Brain Activity

Certain psychodynamic and behavioral elements in the development of self prompted significant physiologic experiments in bridging mental activity and brain activity. The observation that the concept of self consistently relates to levels of psychological awareness provided background for development of physiologic methods that disclosed significant correlations between psychological phenomena and brain activity. In animals, electrical stimulation of the septal region had induced alerting and heightened awareness and, seemingly, a pleasurable feeling, whereas ablation had resulted in marked reduction in level of awareness (Heath, 1954a, Heath and Hodes, 1954). In our earliest studies in patients, distinct recording abnormalities, in the form of spike and slow-wave, occurred in the septal region in association with reduced level of psychological awareness during psychotic behavior (Heath and the Tulane University Department of Psychiatry and Neurology, 1954; Heath, 1966, 1975).

The behavioral observations in psychotic patients of a relationship between an impaired concept of self and of emotionality and disturbances in sensory perception, coupled with behavioral observations in sensory-deprived monkeys, led to anatomic and physiologic studies in animals in which subcortical sensory relay nuclei were shown to be directly connected to brain sites implicated in emotion and level of awareness (Harper and Heath, 1973, 1974; Heath and

Harper, 1974, 1976). Studies were later conducted in patients, in whom physiologic changes in the sensory system or in sites for emotion, or both, could be correlated with the introspective data they reported (Heath, 1975, 1986a, 1986b; Heath and Walker, 1985).

CONSCIENCE — MAN'S AUTOMATIC SELF-OPERATING BEHAVIOR

Parental Influences

Elaboration of psychodynamic observations to document the mechanisms by which individual patterns of behavior evolve further emphasizes the important interrelationship of emotion, sensory perception, and memory in the development of behavioral patterns, and points up their importance in providing a bridge for correlating behavior and brain activity.

Conscience, as used here, is broadly defined as the principal mechanism that determines a person's established pattern of behavior. It develops as a result of the person's interaction with his environment, his earliest experiences being the most influential, that is, his interactions with his parents or parental surrogates, relationships that change with maturation. The emotion associated with the interactions with his parents is the important factor in conscience formation. During the period immediately after birth, the child's survival is totally dependent on the parent. From the child's perspective, the parent exists only to serve him. Gradually, however, the parent becomes the delegated agent, acting as a disciplinarian in addition to serving. It is in this relationship, between the ages of two and six, during the stage of "delegated omnipotence," that the conscience begins to develop. There are two crucial components: (1) to stop the child from doing what he wants to do that is not acceptable, and (2) to move the child into doing what he does not want to do but is salutary. The child's behavioral response is established through punishment (pain) and through reward (pleasure). The critical ingredient in each proposition is love. Withdrawal of love, the fundamental feature of every punishment, is a threat to the infant's security. The parent's nonverbal message communicated to the child is, "I will no longer function as the executor of your desires." This is interpreted by the child as "I will oppose you," and, in his view, this danger generates the emergency emotion of fear or rage, or an admixture of both. In contrast, reward

(pleasure) is associated with the receiving of love. Reinforcement of this value system, which will ultimately comprise conscience, continues in this context of the child-parent relationship.

In the child's mind, parental omnipotence is enhanced by virtue of the parent's ability to detect transgression through circumstantial evidence (even though the parent is absent during the transgression). From this early relationship, the child's concept of an all-seeing, all-knowing authority is established. It is requisite for the development of internalized signals of what is right and what is wrong. With continuing maturation and further reality contact, the child begins to recognize that the parent is not omnipotent. But the earlier relationship of helpless child to executive parent predisposes transfer of the earlier concept to a deity, whose omnipotence is absolute and who is therefore capable of providing the ultimate in both reward and punishment. Thus, the earliest stages of biologic helplessness and consequent relation to authority imprint the need for a continuing relation to an all-seeing, all-knowing authority — a god.

The child's initial experiences of being rewarded and punished by the parent become automatic and internalized. The physical presence of the parent is no longer necessary, being replaced by other authorities and reinforced by religion. This is the foundation for emergency control that makes it possible to anticipate events instantly and to adapt to them. Self-warning, self-criticism, and self-restraint all derive from being warned, criticized, and controlled by parental authority, now extended to the deity. In the same manner, reward mechanisms become internalized, self-reward deriving from having been rewarded by authority evolving into a god.

Emergency emotions of fear arise to inhibit transgression. The feeling of pleasure associated with anticipation or performance of a worthwhile deed expands self-image (stemming originally from compliments by the parent, now extended into a self-operating "pat on the back"). It is through these learned patterns of behavior that one's morality is formed and subsequently functions. Since ultimate punishment and reward are administered by the supreme authority, the deity, we refrain from cheating and stealing and perform altruistic acts. The influence of the deity outweighs society's punishment or reward. Most people, figuratively speaking, do not steal because they do not want to go to Hell. Good deeds are performed fundamentally because they provide an entrance into heaven. These automatic patterns of response are regulated by painful or pleasurable emotions.

Transgression: Cause and Consequence

Despite self-restraining mechanisms, transgression does occur, evoking different, but qualitatively consistent, emotional responses. Although poorly defined genetic or constitutional factors have a role, transgression principally occurs because one's conscience formation is flawed, usually as a result of learning experiences. If early interactions with the parent resulted in loopholes in self-operating mechanisms, then self-punishment and self-reward will not be commensurate with behavior that is in the best interest of the individual or of society, or both. Similarly, if parental authority was not adequately reinforced with the concept of an all-powerful deity, conscience is flawed and transgression occurs more readily (the person steals unless a policeman is continuously present).

There is a dynamic interrelationship between intensity of motivation and restraints of conscience. When basic biologic needs are minimal, conscience usually prevails. But as needs intensify, the likelihood of transgression increases. Even a person whose conscience formation is relatively sound may become enmeshed in a situation in which transgressive behavior seems to be the only course of action. Figuratively, the balance can be tipped with the force of need overwhelming the restraining pressure of conscience. For example, a man, who is ordinarily law-abiding, is very likely to steal for the sake of survival if he and his family are starving. During wars, sexual infidelity increases among usually faithful married persons who have been sexually deprived for long periods. When need is overpowering, "thou shalt not steal" and "thou shalt not commit adultery" fall by the wayside.

This dynamic interrelationship between need and the restraint of conscience is apparent in the behavioral pattern after transgression. The transgressive act, if culminating in satiation, allays the need, and the force of conscience becomes proportionately stronger, with ensuing guilt and associated diminution of self-esteem and dread of the consequences. Although fear of specific punishment ranges widely from social ostracism to trial and imprisonment to damnation and hell, the basic common denominator, rooted in early training, is loss of love (rejection). Mechanisms originally used in childhood emerge to regain love. There is the magical wish that the event had not occurred. There is remorse and the urge to confess, to atone, to expiate, to undertake punishment for absolute forgiveness. Since loss of love is the basic consequence of transgression, the safety of being loved can be restored only by being forgiven.

Guilty fear is a specific emotion. It differs from real fear, specifically in the behavioral response that is induced. With real fear, the result of genuine danger, the person responds by escaping, thereby removing himself from the danger. With guilty fear, running is not adaptive. Conscience is internalized, the result of interaction with authority. One cannot be restored to safety (being loved) by escaping; the only effective mechanism for regaining love and security, as learned in childhood, is to gain forgiveness.

Self and Social Groups

Just as emotion is fundamental in establishing one's value system through the learning experience with the parent, it is also the basic factor in establishing the patterns by which a person adapts to social groups. Here, too, it is necessary to consider the stages in development of self in order to understand how one relates to others and to social systems.

The family is the model for social organization, providing a strong formative influence on the manner in which we react to social groups. In the family, the pattern of dominance and submission is fixed biologically with mother and father in supremacy, a prototype of an aristocratic society. This pattern of dominance and submission is a consistent feature of all social groups. As previously discussed, the parent functions in the early stage of development as the omnipotent extension of self. The child's situation becomes complicated by the birth of a sibling, who puts an end to his privileged position. No longer is the parent "my almighty extension" exclusively. The new sibling's demands of the parent create envy and jealousy in the older child.

A consistent chronology of emotional interactions evolves as a result of the new sibling's arrival. The older child has a strong desire to eliminate the newcomer. This intense response, generating murderous impulses, has been characterized clinically as "breast envy." The previously privileged older child, forced by reality to relinquish his illusory lust for omnipotence, makes a bitter compromise. Since he can no longer be the exclusive, omnipotent one, he begins to struggle to be the favorite. At this stage, the educational goal of the parent should be to make each child feel equally loved. But this is unachievable, since parents inevitably have a favorite child.

The loss of privilege by the child who is not the favorite is very painful. His desire for privilege must be compromised to a drive for equality, stemming from the fear of being underprivileged or dis-

criminated against. These events in the evolution of self concept, basically occurring in the nursery, are imprinted, and subsequently influence the way one relates to society. The person who has achieved privilege wants to keep things as they are, and he tends to be conservative. In contrast, the person who has been discriminated against identifies with the underdog, and he is apt to be a liberal reformer. His striving for equality, however, is not a primary urge, but a temporary compromise. Once equality is achieved, he will often bid for supremacy — to be the favorite. In so doing, he may permit infantile strivings for omnipotence to surface. The intensity of his drive to reverse the process that occurred initially in the nursery setting is proportionate to the degree to which he feels he has been unjustly treated. These behavioral trends are evident in all social groups (student organizations, scientific societies, labor unions, political organizations). (Adolf Hitler was an extreme example of overt strivings with manifest delusions of omnipotence.)

The essential ingredient for which the individual strives is love (affection, recognition, respect). A child can receive material things in equal proportion to siblings and still feel unloved. The person who strives for affection may try to substitute worldly goods and acquire wealth, or achieve fame through scholarly pursuits. But these alternative gratifications fail to fulfill his need for love. They are mere compromises, which do not alleviate the continual, often painful, feelings of rejection. These early intrafamilial relationships with parents and siblings strongly influence a person's ultimate automatized patterns of adaptation to social groups. They predetermine attitudes toward authorities, peers, and subordinates — whether one is competitive or cooperative, and with whom, and whether one feels compassion or guilt, and when. By way of illustration, the daughter who is threatened by the birth of a younger sister is prone to be inordinately competitive with women in her adult life. The learning process ideally evolves from the relationship with authority into automatic reward and punishment of self — reward for acts beneficial to self and society and punishment for acts detrimental to self and society. The potential weaknesses in this development are apparent, however, when examined in the light of the mechanisms involved in evolution of conscience.

The conscience begins to develop early, the most formative period being between two and six years of age, when the focus of interest is principally on such trivia as sphincter training, scheduling of food intake, orderliness, and curbing of self-stimulation for sexual pleasure. Under ideal circumstances, a timely change in focus occurs

with maturation, with a gradual shift in emphasis to traits of more social significance, such as honesty, consideration of others, and sharing. This process requires a modified relationship with authority. Through identification with idealized persons (schoolteacher, scoutmaster, coach, family physician, minister), their values become important, and they are emulated, with incorporation of their values into the self. If the values are constructive, the person matures and becomes a more effective and productive member of society. On the other hand, a neighborhood gang leader, a rich drug dealer or gangster in a ghetto, or a politician who achieves notoriety and wealth through graft can, unfortunately, also serve as an idealized authority.

For a large number of people today, the desirable growth process fails to occur or is only partly effective. As a result, the self-operating value system is arrested at the infantile stage. The focus of the obsessive-compulsive neurotic, for example, continues to be on orderliness and cleanliness. These issues can be so overpowering that, in extreme examples, the timing of bowel functions is more important than a nuclear crisis.

Loopholes in the Function of Conscience

The potential exists for development of loopholes in the conscience scheme.

Crime into virtue. — The transformation of crime into virtue is probably the most universal and devastating loophole in the conscience scheme. Throughout recorded history, and probably long before, man has been preoccupied with the questions, "What is the nature of the world about me?" and "How shall I behave?" Answers are in the context of the parent and the parental extension (deity, prophet, idol) and are modified by the situation and the culture. The core predilection is to behave according to the dictates of the deity, who controls the universe. Children, primitives, and even mature adults retain this concept, a derivative of imprinting during the infant's initial relation to the all-powerful parental figure.

It is the authority, parent extended into deity or deity-surrogate, who defines what is crime and what is virtue. Our entire value system is based on reward and punishment, first defined by the authority and then incorporated into the self. It is continually reinforced by the mechanism of *ultimate* reward or punishment (heaven or hell).

The laws provided by religion to govern behavior, extended into civil law, have made it possible for man to coexist with his fellowman, thereby contributing to his ability to survive and develop.

But human authorities have often redefined crime and virtue. Some of mankind's greatest tragedies have occurred when crime has been reinterpreted as virtue. Organized religion, because it speaks for the ultimate authority, has been the most effective instrument for manipulating values, and has been responsible for some of the most destructive events in history. For example, we are taught to live by God's command, "Thou shalt not kill," yet massive killings have been carried out in God's name when a charismatic authority has chosen to alter the command and redirect the populace. During the Crusades, the command was "Thou shalt kill those who are infidels." The Teutonic knights, in the service of Christianity, invaded Central Europe and killed the barbarians. The Spanish conquistadors slaughtered the heathen Indians. Those who were not "true believers" (of another faith) were tortured during the Inquisition. During the holocaust of World War II, large numbers of people were eliminated because of their religion. Today, terrorists are assured by their authorities that suicidal missions guarantee their admission into heaven. Such reinterpretations by authority restructure the restraining forces (emotion) of conscience.

God has to be on "our side" during wars, if we are to overcome the restraints of conscience and kill. The German aggression against the Jews was possible not only because of Hitler's authoritative role, but also because he skillfully exacerbated a theme initiated by Martin Luther in the 1500s. Luther, the German founder of Protestantism, was "both a passionate anti-Semite and a ferocious believer in absolute obedience to political authority" (Shirer, 1960, p. 236). Not only should the Jews be driven out of Germany, but they should be stripped of all material things and their synagogues and houses burned. Four centuries later, the Nazis followed Luther's advice. Hitler fused the authority of the church with his own authority.

Religious exploitation of conscience occurs in many forms. A recent trend is the way in which certain unscrupulous television evangelists, capitalizing on fear of death and the hereafter, extract money from viewers and followers by promising, through their prayers, to assure them forgiveness and eventual salvation.

Paradoxical responses to pain. — A small percentage of people develop a paradoxical reaction to painful feelings. Rather than pain (fear) serving as a deterrent, it becomes a signal for pleasure as a result of complications in the learning process. When one commits an act that is forbidden and finds pleasure in it, the pleasure is enhanced by virtue of the pain that preceded the action. This is most

dramatically, and sometimes tragically, illustrated in the sexual sphere. For the masochist, absorption of physical pain becomes an essential antecedent to a pleasurable response. This reaction to painful emotion is also illustrated by the kleptomaniac who, rather than being deterred by fear of being caught, steals for the paradoxical pleasurable excitement that is elicited by the possibility of being caught.

Shifting of fear into rage. — For some, fear of being caught in a transgressive act can shift readily to anger. Fear is painful, reducing one's self-image or stature and thus serving as an effective deterrent. When fear shifts to rage, however, self-image is enhanced, thereby eliminating the emotional deterrent and making it much easier to transgress. The rage is often associated with righteous indignation, a rationalization to justify the rage. A simple example is the person who ragefully drives through a stoplight, proclaiming that the light should not have been placed there.

Impairment of conscience by alteration of the neural basis for emotion with lesions or chemicals. — Since conscience (the automatic self-operating behavioral patterns derived from interaction of biologic functions and learning experiences) operates by emotion (reward and punishment), any process that interferes structurally or functionally with the neural mechanism for emotion impairs the conscience mechanism.

Brain damage resulting from a variety of pathologic conditions (head injury, brain tumor, encephalitis) can significantly disrupt the conscience mechanism. After the epidemic of von Economo's disease, there were many reports of a syndrome of psychopathic, amoral behavior (Wilson, 1940). It was difficult to establish the exact neural site of the lesion responsible for the pathologic behavior because lesions were so diffuse and extensive.

Function of conscience can also be profoundly impaired by drugs that alter emotionality by acting on the neural network for emotion. Abuse of such drugs is responsible for many of today's social problems — disrupted family life, crimes of violence, increased psychiatric morbidity, and a considerable increase in mortality (drug overdoses, drug-related accidents and homicides, suicides).

The two principal actions of the commonly abused drugs are (1) to reduce such painful emergency emotions as anxiety, tension, and fear, and (2) to induce feelings of pleasure. They thus compromise the fundamental regulators of behavior. Drugs used most often to reduce anxiety and tension are alcohol and the benzodiazepines. Those used most often to induce pleasure are cocaine, the opiates,

and marijuana. Abuse of these substances, through their effect on the neural mechanism for emotion, can abolish conscience. When use of a drug induces a pleasurable feeling that rivals the pleasurable self-reward resulting from behavior beneficial to self and society, there is a temptation to take the drug rather than perform a constructive act. When a person with a healthy conscience performs an altruistic act, even though the immediate effect may be inconvenience or pain, he is motivated by the anticipated reward from authority. When ingestion of a drug abolishes the painful anxiety generated by a functioning conscience, transgression is more likely to occur, since the deterrent effect of fear of punishment is diminished. With such release, one is free to cheat, to steal, to kill, or to break other laws that provide social cohesion.

Social Issues Consequent to Conscience Alteration by Drug Abuse

The fundamental mechanism by which commonly abused drugs affect behavior — the way they impair conscience and performance by their specific effects on the brain — is not widely understood by the public. Nearly every segment of society — sports, entertainment, the military, transportation, executive offices, assembly lines — has been affected as a result of substance abuse. The drugs are attractive because they relieve tension or temporarily produce a pleasant alerting effect that may enhance performance. Their long-term effects, however, not only harm the user, but pose danger for all of society. The response to proposals for mandatory drug-testing has often been outrage — that that would be interference with personal liberty, a right guaranteed to citizens of the United States by amendments to the Constitution and acts of Congress. Instead, it is implied, we should rely on the word of the suspected person. This naive concept fails to take into account that the drug abuser's conscience mechanism is impaired, and, consequently, his word is not reliable. Further, those who oppose mandatory drug testing fail to consider the rights of the public to be protected against the dangers inflicted by those who abuse drugs.

Those who deal in illegal drugs take relatively small gambles for potentially huge profits. When a plane is carrying a cargo of drugs with a potential value of $20 million to $50 million, or more, the risk of losing it or of paying a fine of $100,000 and serving a short prison sentence, or both, are of little consequence. Only when the fundamental issues of reward and punishment are adequately understood will it be possible to pass laws to combat this overwhelming problem. Meanwhile, elected and appointed government officials in many

countries are enjoying substantial payoffs from the illicit drug trade. In our own country, organized crime and organized gangs are reaping phenomenal profits. As the social structure for law and order breaks down, the innocent victims are losing their neighborhoods, their cities, their countries, and their lives to those who trade in illegal drugs.

Two countries, China and Saudi Arabia, have substantially reduced or eradicated illegal drug trade and use by establishing severe punishment that far outweighs potential reward. Both countries invoke the death penalty for those who profit from the sale and distribution of illegal drugs. China, in addition, has modified the reward side of the equation by providing opium-producing farmers with alternative income-producing opportunities, and has also established programs of treatment and rehabilitation for drug abusers. As the epidemic of drug abuse intensifies and spreads in the United States, such extreme measures may have to be considered. Regrettably, programs of education and compulsory drug testing, as well as costly efforts to curb the inflow of drugs into this country, have had negligible impact on this problem that many consider the major crisis our nation faces.

The issue of drug abuse is discussed extensively here because it serves as a dramatic illustration of the correlation between the neural substrate and emotion, and consequently, its effect on conscience function. Furthermore, it documents forcefully the profound impact that physical manipulation of reward and punishment, through chemicals acting on the nervous system, can have on a society.

Recent progress has been made in clarifying the mode of action of drugs of abuse. They have been shown to modify cellular function by acting on specific receptors. The systems subserved by the implicated cells are also being identified. Receptors for anti-anxiety agents are principally in the system that is activated in association with states of anxiety and tension. Receptors for pleasure-inducing drugs are at sites in the neural network where activity correlates with feelings of pleasure. In experiments in animals (and, to a limited extent, in human subjects), administration of drugs has been a valuable tool in identifying the neural network for pleasurable as well as aversive feelings (Heath, 1964a, 1972d; Heath, Fitzjarrell, Fontana, and Garey, 1980; Heath and Fitzjarrell, 1984).

THE ROLE OF EMOTION AND MEMORY IN NORMAL AND PATHOLOGIC BEHAVIOR

In the adaptational psychodynamic framework, behavior is considered to be the consequence of interaction of environmental influences and biologic drives (Rado, 1946-1965). Maladaptive or neurotic behavior in persons with intact central nervous systems is the result of faulty learning. Psychotic behavior, in contrast, results, in whole or in part, from structural alteration (organic disorder) or from biochemical-metabolic alteration (so-called functional psychosis) of the nervous system. The manner in which emotion and memory have provided a bridge between mental activity and brain function in healthy, neurotic, and pathologic behavior will be elaborated.

Healthy (Adaptive) Versus Neurotic (Maladaptive) Behavior

The basic moving forces in behavior are biologic needs essential to survival, such as alimentary (food), evacuatory (elimination of bodily wastes), reproductive (sex), and respiratory (inhaling of oxygen and exhaling of carbon dioxide). Such needs, in a continuous dynamic state (intensifying, becoming satiated, intensifying again), are influenced by the cultural milieu — means of earning a living, social acceptance and prestige, special taboos.

A biologic need creates a "motivational state" that pervades behavior at all levels. As the biologic need intensifies, it generates feelings of tension and discomfort — as with hunger, the need to evacuate, the urge for sex; in extreme conditions, the feelings are painful. In contrast, action that satiates the biologic urge is pleasurable. The intensity of the pleasure is commensurate with the need: the hungrier a person is, the more he enjoys food; the longer one has been deprived sexually, the greater the pleasure with sexual fulfillment. With satiation, the force of the underlying biologic need — the motivational state — fades.

The behavioral pattern that is generated to satisfy the biologic need is shaped by learning experiences that begin at birth. The pattern that ultimately evolves is the result of the interaction between the need-force and the related learning experience. Ancillary behavior, associated with each biologic behavioral sphere, evolves as a consequence of learning experiences relating to satiation of a specific need. For example, the infant experiences movement, warmth, tenderness, and security in association with alimentary fulfillment. These feelings are therefore integrally related to satiation through caloric intake and become expanded characteristics of the alimentary sphere

of behavior. Attitudes regarding discipline (orderliness, cleanliness) derive from learning experiences associated principally with evacuative functions (and other scheduled activities). If there are severe conflicts with authority in association with initial sphincter training, extremes of defiant rage or submissive fear, or both, are likely to develop in relation to authority, often accompanied by such evacuative disturbances as constipation (defiance) and diarrhea (over-compliance).

Behavioral patterns of sexual activity and attitudes are also shaped by the child-parent interaction. The child who is threatened with physical damage when he experiments with sexual pleasure may focus excessively on intactness of his body. In the extreme, this can become the basis of hypochondriacal symptoms. If, in order to curb his sexual activity, the child is threatened with warnings that such activity is unclean or that it will result in ostracism, he will associate sexual arousal with fears of rejection and its consequences.

Rado (1946-1965) organized his adaptational framework to examine behavior in terms of the interaction between biologic need and associated learning (memory) for each biologic sphere of behavior. In this dynamic process, a state of disequilibrium characterized by increasing tension-discomfort (a motivational state) is generated as the need (a biologic process) intensifies. The manner in which the need is satiated is influenced by learning that is imprinted in an emotional context. This interaction establishes the individual's mode of psychological adaptation. If the signal (feeling-emotion) and the elicited response are in the interest of self and society, the behavior is adaptive. The behavior is maladaptive or neurotic, on the other hand, if the need elicits an emotional response that is inappropriate for the situation. For example, a person is behaving neurotically if, out of fear, he seeks escape (avoidance behavior) from pleasure that would be in his own interest or that of society, or both. Behavior is likewise maladaptive or neurotic if pleasure is elicited (approach behavior) when anxiety and apprehension (avoidance behavior) would be more to the point — the elation of a kleptomaniac when he steals. Thus, neurosis is the consequence of a flawed emotional response (usually inappropriate fear or rage, or both) and the basis for the inappropriate signal is determined by early learning experiences (imprinted memories) during interaction with parental authority.

This adaptational formulation of neurosis contrasts sharply with the concept of neurosis formulated by Freud (1920, 1933), who failed to consider the effects of the prevailing biologic motivational state on behavior. He regarded all pleasures as sexual and propounded a developmental relation among alimentary (oral), evacua-

tive (anal), and sexual (genital) functions. In adaptational psychodynamics, on the other hand, awareness of the motivational state is critical to understanding a given behavioral act. For example, the alimentary apparatus (mouth) contributes to sexual pleasure only if the motivational state is sexual; more often, it functions in the service of caloric requirements. The evacuative machinery may contribute to sexual pleasure if the motivational state is sexual, but if the biologic need is evacuative, that is the way it functions. In a sexual motive state, all sensory modalities (vision, hearing, olfaction, touch) enhance alimentary pleasure.

In some respects, the last concept of anxiety that Freud (1936 published in German in 1926) formulated is similar to the adaptational formulation. At that time, he considered the inappropriate anxiety of neurotic patients to be a reaction to early learning (conditioning) based on childhood experiences. Anxiety, he reasoned, was similar to the fear a person experiences when he is exposed to real danger. In essence, all anxiety is real fear perpetuated by memories. A critical shortcoming, however, was his failure to consider that rage is also an emergency response to danger. He focused instead on vague concepts of instincts, including the death instinct, to explain the emotion we now understand as rage.

In Rado's adaptational framework, the ideal learning experience is one in which the person modulates the pattern for fulfilling his biologic needs (as well as patterns of ancillary behavior) so that he and the society in which he lives optimally benefit. Ontogenetic development provides abundant opportunity for faulty learning. That is a risk to which man is exposed for the advantage of a prolonged learning period (in contrast to other species). The role of emotion (reward-punishment) in the learning experience was detailed previously. In the ideal learning situation, painful emotion (anxiety, rage) should evolve only in association with adversity — real danger — whereas pleasure-reward should activate and reinforce behavior that is beneficial to self and society. Anxiety can thus be positive (healthy, adaptive), as well as negative; it can be essential for survival when it is focused on real danger.

Life-threatening dangers faced by contemporary man, by comparison with primitive man, are relatively uncommon. Nevertheless, he often mobilizes himself for defense — "fight or flight" — as a result of emergency emotion generated by inappropriate learning. Such bodily preparations while adequate for meeting real danger are usually counterproductive for effective functioning in society. Furthermore, because of overactivity of the autonomic nervous system generated by the persistent emotion, they can lead to so-called psychosomatic illness (Cannon, 1932).

In neurotic disorders, symptoms represent psychological repair or defenses the person has developed to alleviate the pain of inappropriate emotion generated through interaction of a specific biologic sphere of behavior and faulty learning. To illustrate briefly, depression is a disorder that evolves from problems in the alimentary-dependency-love sphere of behavior. The characteristic symptoms of depression derive from loss of love. When loss is real — death of a loved one, rejection by a lover, or even loss of a pet or of money — the symptoms are classified as normal grief. If they are not complicated by faulty learning, they will spontaneously disappear in a reasonable time. In sharp contrast, if the characteristic symptoms are present as a reaction to imaginary loss of a love relationship, the result of aberrant learning during early development, the depression is pathologic or neurotic. Such loss (deprivation, insecurity) is rooted in relationships that were initiated during feeding and associated activities of cuddling and rocking. The person who has difficulty dealing with tenderness, warmth, and closeness is prone to develop neurotic depression, since he imagines, albeit unrealistically, that he is going to be deserted. His reaction of anger to the unrealistically perceived loss often precipitates a breach with the loved one.

Symptoms of depression are almost inevitably associated with eating disturbances; caloric intake is the basic need around which (through associated learning) the emotional-behavioral symptoms of depression develop. Other symptoms represent the associated behavioral patterns. The agitation and irritability associated with depression are manifestations of repressed anger that cannot become overt for fear of further alienation by the person who is presumably doing the rejecting. Self-condemnation — invocative and expiatory behavior — is the reparative attempt. By confessing and imploring to be forgiven, the depressed person is striving to be restored to the position of being loved and nourished.

Maladaptive behaviors (defensive patterns) due to inappropriate emergency emotion from faulty learning in the biologic sphere of evacuative behavior evolve from the struggle with parental authority about training and are manifest by obsessive-compulsive symptoms. Obsessive symptoms are thoughts derived from rage toward authority that is repressed for fear of retaliation. Compulsive symptoms are actions that are symbolic gestures of appeasement derived from fear that is similarly repressed. Both categories of symptoms are garnished by magical thinking and exaggerated concern over the omnipotent pow-

ers of the authority, a characteristic of this stage of development. Personality patterns of compelling orderliness and cleanliness, or the strong counterreaction of slovenliness, are often accompanied by irregularities in bowel function (constipation, diarrhea).

Excessive emergency fears about sex underlie symptoms of hypochondriasis (bodily damage) and account for defective sexual performance (impotence, frigidity), as well as assorted patterns of performance. These symptoms also represent defenses and reparative processes to alleviate the inappropriate emotional response in a specific biologic sphere of behavior.

In this formulation for the cause of neurosis, inappropriate emergency emotion — anxiety-fear or rage, or both — is the crucial pathognomonic factor. One might therefore ponder why the use of anti-anxiety drugs would not be ideal therapy. The benzodiazapines, for example, which alter receptors that are activated during painful emotion, are very attractive to persons with neuroses because of their prompt action in alleviating the pain of adversive emotion. But in prescribing anti-anxiety agents, one first has to explore the basis for the anxiety, since drugs cannot discriminate between anxiety that is inappropriate (maladaptive behavior) and that which is appropriate (adaptive, desirable behavior). Anxiety-fear is not only appropriate in some instances, but effective performance depends on it when one is faced with a difficult challenge (competing in the Olympics) or real danger (being robbed at gunpoint).

Even in the treatment of neurosis, the usefulness of anti-anxiety drugs is limited. While providing symptomatic relief through reduction of painful feelings, the medications, by themselves, fail to alter the psychodynamic factors responsible for the inappropriate emotion. They can even prove harmful by reducing the patient's motivation to deal with the mechanisms underlying and causing the inappropriate emotion. Persons experiencing long-term suffering of painful emotion are particularly vulnerable to becoming dependent on the relief-providing anti-anxiety drugs. In the treatment of neuroses, their use should be limited to adjunct therapy and weighed against such complicating factors as the potential for dependency. In short, the widespread use of anti-anxiety drugs in today's society may be more detrimental than beneficial.*

---

* Certain other drugs, by altering cellular function at specific sites in the circuitry for emotion-sensory perception, can have a salutary effect, with fewer undesirable side-effects, in treating some behavioral disorders. For instance, lithium carbonate has proven effective in treating mood-cyclic disorders, particularly the manic phase. Drugs capable of altering the metabolism of catecholamines have been shown to have therapeutic benefit in several disorders. Norepinephrine uptake blockers, for example, are effective in the treatment of depression, and several serotonin uptake blockers are also helpful in the treatment of depression, as well as obsessive-compulsive disorder, Tourette's syndrome, and migraine.

The Psychotherapeutic Relationship

In psychotherapy, the patient's early childhood relation with authority is replicated, with the therapist representing the parent-authority. Called "transference" in psychoanalysis, this patient-therapist relation provides a milieu for recapitulation of the patient's behavioral patterns against the background of the initial child-parent relation from which they evolved. The therapeutic rationale is that exposing the basis for the maladaptive behavior permits its correction through the insight made available, as well as through remedial alterations in the relationship made by the therapist. Whereas interpersonal therapy has proved effective as an investigative method for understanding the mind, it has been disappointing as a treatment.

Although the infantile basis for the imprinted neurotic behavior is readily exposed during psychotherapy, the patient's insight is usually insufficient to alter it. Even when a correct interpretation is repeatedly made — sometimes hundreds of times — the inferior patterns are so established that they often cannot be eradicated. That is understandable, since memory traces are most firmly imprinted at an early period in the context of emotion.

Emotional factors are of great importance in obtaining a therapeutic response. Thus, the effective therapist is the one who best alleviates the patient's inappropriate, painful anxiety by symbolically providing sheltering warmth and comfort (love) at opportune times. Further, he provides rewarding approval for the patient's constructive behavior — a symbolic "pat on the back by parent." Behaviorists focus on manipulating pain and pleasure. Some psychoanalysts propound the "corrective emotional experience." Even so, the fact that interpersonal relationship therapies have only minimal effectiveness in altering patterns imprinted during early childhood underscores the importance of emotion, perception, and memory in understanding behavior. These observations provide impetus to the search for more effective ways than interpersonal relationship therapy alone for modifying the brain mechanisms for these functions, so that behavioral disorders can be prevented and effectively treated.

Psychotic Behavior

Psychotic behavior is a consequence of altered cellular function at specific sites of the brain (Heath, 1962, 1966, 1975, 1982; Heath and the Tulane Department of Psychiatry and Neurology, 1954; Heath and Walker, 1985). As with everyone, learning influences the behavior of the psychotic person, and inappropriate emotion secondary to faulty learning can adversely affect the psychotic's behavior, just as it does the neurotic. But the development of psychotic behavior requires the added dimension of a pre-disposing organic process affecting the brain. The principal clinical feature of psychosis, not manifest in neurosis, is aberrant contact with reality. The psychotic person has gross thought disturbance in the form of delusions (a manifestation of reduction in level of thought) and, often, associated perceptual disturbances, the most extreme of which are hallucinations. He is autistic. His emotional responsiveness is defective. His affect is often flat and in some psychoses, his memory is impaired. His ability to integrate feelings of pleasure is notably reduced. Awareness of self is altered, sometimes so profoundly that he is depersonalized (does not know his own identity). Many factors can impair cellular function to induce psychotic behavior. Traditional approaches consider three broad causes of psychotic behavior:

(1) Psychoses without structural abnormalities, in which altered cellular function is due to a metabolic disturbance without demonstrable histologic cellular defect. (Schizophrenia and mood cyclic disorders are the most common of these so-called functional psychoses, which can also be produced experimentally by sensory and sleep deprivation.)

(2) Psychoses resulting from demonstrable cellular anomaly (microscopic and often gross).

(3) Toxic psychoses, from exposure to exogenous toxic substances by inhalation, ingestion, or injection.

In our studies over the years, we demonstrated changes in brain function, in the form of spiking in the septal region, sometimes reflected at other directly connected brain sites, that characteristically occurred with the three forms of psychosis and correlated with common symptoms. Each form of psychosis is also manifested by certain unique symptoms, suggesting there may also be unique differences in brain function. Clinically, the three forms of psychoses differ principally in terms of memory deficit (degree of confusion, disorientation).

Interrelationship of Sensory Perception, Memory, and Emotion

A Neural Basis for Memory

Much has been written about the important role of emotion in psychodynamic formulations, with little focus on the dynamic relationship of emotion to sensory perception and memory. Physiologic data suggest that these functions have a common neural basis, and clinical data indicate they continually influence one another.

Moving up the phylogenetic scale, we find that environment has an increasingly important role in determining behavioral patterns. Correlated with development of the cortex and enlargement of associated subcortical structures, learning and memory increasingly influence behavior. This influence is maximal in man. Critical examination of clinical data that help to relate memory to neural mechanisms is essential for an understanding of the mind-brain relationship. Memory, the store of things learned, is a determining influence in the formation of one's behavioral patterns — one's standard pattern of adapting — and critical in establishing one's personality — the manner of interacting with others and of responding to situations.

Influence of Sensory Perception on Memory and Emotion

Perception through each sensory modality can activate memories and feelings. Marcel Proust (1934) vividly illustrated memory recall with feelings of exquisite pleasure prompted by the taste of tea and cake. A profound emotional response and extensive memory recall can similarly be initiated by a visual stimulus (a painting, a street or pastoral scene, the face of a stranger) or by an auditory stimulus (music, a fog horn, a train whistle). A vivid example of how sensory input affects emotion and memory is the psychosis that can be created within 48 hours in a person who is deprived of sensory input.

A large body of information that highlights the integral relationship between memory, emotion, and sensory perception, particularly the role of sensory input in memory, has also been gathered in studies of persons with memory disturbances, as well as persons with exceptionally good memories. Perhaps the most extensive documentation of an exceptional memory was by Aleksandr Luria (1968), the Russian psychologist, who wrote about a newspaper reporter in Moscow (Restak, 1979). The young man could imprint memories based on sights and sounds and by interrelating sensations, he could

enhance his memory. Other modalities of sensory input similarly affect memories and emotion. Odors, in particular, and somatosensation (touching, stroking) can prompt recall of past experiences and associated emotional responses.

Influence of Memory on Emotion and Sensory Perception

Careful introspection reveals the many different ways that memory relates to emotion and sensory perception. Most emotional reactions are the result of memory recall. Even in those instances when profound emotion is seemingly generated by a current event, the current happening is soon associated with memories of similar or related past events, and the emotional response intensifies or attenuates accordingly.

Inappropriate anxiety is the result of faulty learning perpetuated by imprinted memories. The presenting neurotic symptoms are maladaptive attempts to neutralize that painful emotional state. Repression, that is, the blotting out of memory, occurs when it is too emotionally painful to recall an experience. Sigmund Freud's initial studies of the mind were prompted by Joseph Breuer's reports of alleviating symptoms of hysteria in patients by having them recall repressed traumatic events (memories) and associated emotional catharsis while under hypnosis (Breuer and Freud, 1895).

The traumatic neuroses also graphically illustrate the relation of memory to emotion and sensory perception. If a soldier is exposed to life-threatening danger and becomes overwhelmed with fear, he will subsequently repress memories of the incident. Under hypnosis, while recalling the sights, sounds, and associated feelings that occurred during the traumatic episode, he experiences therapeutic release of the intense emotion and often an end to the state of emotional dyscontrol.

Influence of Emotion on Memory and Sensory Perception

The manner in which emotion affects memory and sensory perception likewise becomes apparent by introspection. We learn and remember when we are emotionally motivated. Without motivation, the learning process is less efficient. We can recall memories that were established during states of emotional arousal. Most of us of a certain generation remember exactly where we were and what we were doing in 1941, when we heard the news of the attack on Pearl Harbor, and in 1963, when we heard that President John F. Kennedy had been shot. When we are exceedingly emotional, as when a traumatic event

occurs, the effects become generalized and blend with old memories of shocking events that created a similar emotional response. Inevitably, as the older frightening episodes are recalled, feelings that are reactivated are accompanied by associated sensory perceptions (visual images and sounds associated with the trauma of an automobile accident — blood, screams, screeching of tires). Paradoxically, if a memory is too painful, profound emotion can obliterate it from consciousness through repression.

Mood, memory, and sensory perception are clearly interrelated. During depression, when the prevailing emotion is one of despair, one recalls gloomy, self-condemnatory events. The depressed person loses his sense of taste and appetite and selectively perceives visual and auditory events in keeping with his depressed mood.

Emotion-Sensory Perception-Memory: Window to Understanding the Mind-Brain Relationship — Summary

Psychodynamic behavioral observations directed many of the physiologic experiments in animals and treatments in patients that have provided data for establishing correlations between activity of the mind and structure-function of the brain. The interrelated phenomena of emotion, sensory perception, and memory are the basis for understanding the mind as the integrator of behavior. These related functions, for which there is a physical basis, determine whether behavior is healthy-adaptive or unhealthy-maladaptive. Emotion, through reward and punishment, is the basis for establishing one's mode of behavior or value system, that is, one's conscience. There is a consistent, continuing relation between emotion and memory. Feelings and related sensory perception are influential in the evolution and continuity of the concept of self.

In our studies, attention was directed to both the subjective and objective components of emotion, whereas some investigators of the physiologic basis for behavior have deliberately disregarded the subjective component as too vague. A specific emotion can be identified accurately, however, only if its subjective qualities (feeling tone) are described along with its objective characteristics. For correlation of both the subjective and objective aspects of emotion with central nervous system activity, Sandor Rado's (1962) broad categorization of emotions (in accordance with their subjective components) as pleasurable (welfare) and painful (emergency) has been useful. In successful adaptation, pleasurable and painful feelings are signals related to healthy behavior and, basically, to survival. A constructive act elic-

its pleasurable emotion. When one is faced with danger, painful emotion takes over. Love and hope are welfare (pleasurable) emotions, whereas fear and rage are emergency (painful) emotions.

Alteration in level of awareness or arousal characterizes emotion, both pleasurable and painful. Emotion also has corresponding physical components. Peripheral physiologic changes correlated with emotion, manifest in both smooth and skeletal musculature and expressed through the autonomic (visceral) and somatic nervous system, have been extensively investigated in human subjects, as well as in animals. The central nervous system component of emotion has also been extensively investigated and was the focus of many of our studies. In patients, the site of brain lesions associated with impaired memory and, in animals, the effects of experimental lesions on memory tests provide leads into the neural mechanism for memory.

Sensory pathways with relay nuclei are also well established. As our investigations progressed, it was increasingly apparent that emotion altered sensory perception and memory and was, in turn, affected by them. Indeed, so interrelated were these phenomena (usually considered separate entities) as to suggest their neural substrate was one and the same, or at least closely interlinked. Thus, knowing the role of emotion-perception-memory in mental activity, along with delineation of the neural network for emotion and its functional relationship with the neural substrate for perception and for memory, can provide the basis for developments toward understanding the physical basis of mind. These relationships among emotion, perception, and thought were consistently demonstrated in physiologic-diagnostic and therapeutic procedures in our patients. This knowledge can serve as a critical step forward in the development of preventive measures and more specific treatments for behavioral disorders of all types. It can lay the foundation for understanding the effects of interpersonal relationships on behavior, as well as the effects of physiologic and pharmacologic treatments.

PART II

PRELUDE

A major purpose of this monograph is to report correlations between nervous system activity and behavior observed during investigations carried out in our laboratories since 1949. No attempt will be made to review the extensive literature on this subject comprehensively. Historical material and results from other laboratories will be cited when they are pertinent as background for our studies.

Direction for our biologic studies of brain function and behavior came principally from psychodynamic observations (presented in Part I) that highlighted the important interrelationship among the phenomena of emotion, sensory perception, and memory. Our goal was to gather data on the neural basis for these phenomena as the keystone for interrelating brain function and mind. Although establishing the neural basis for mind was obviously unachievable, we hoped, by demonstrating some correlations between brain activity and mental activity, to narrow the gap between brain function and behavior.

Most of the data presented here are from therapeutic deep-brain electrode studies on a series of intractably ill patients. With our methods, we were able to demonstrate correlations between brain activity and subjective and objective behavior. In the schizophrenic patients in the series, we also investigated the biochemical and immunologic changes underlying the altered brain function that correlated with their behavioral disorders. Anatomic, physiologic, and

chemical data from animal studies preceded and complemented the data obtained from the special patients.

Reports directed toward establishing the neural substrate of behavior have usually been based on animal research, on studies in human subjects in which correlations have been demonstrated between behavioral phenomena and peripheral autonomic nervous system function, or on postmortem studies of the human brain. The major shortcomings of these approaches have been two-fold: (1) the absence of introspective data (subjective component) in the animal studies that are essential to understanding emotion, and (2) the absence of methods for synchronizing and thus correlating brain activity with ongoing behavior. The advent of psychosurgery partly fulfilled one of these prerequisites. The ablative psychosurgical procedures were not only more precise than spontaneously occurring lesions, but were also performed on patients capable of reporting their thoughts and feelings (introspective data) before and after the surgical procedure. The behavioral result of loss of brain tissue at specific sites consequent to the psychosurgical procedure could be ascertained, but it was not possible to monitor activity of the remaining brain that was occurring in association with behavioral events. By and large, the procedures were limited to undercutting or removing cortical tissue. Although they helped to elucidate the role of the cortex in emotional behavior, these procedures provided no information on the function of the extensive subcortical neural network. Some data concerning function of the amygdala in emotion resulted from coordination of the subjective reports of psychiatric patients with their recordings from that site before it was ablated (Mark and Ervin, 1970).

Evolution of the Tulane Program

Implantation of Brain Electrodes and Cannulas in Patients

In 1950, on the basis of extensive animal studies that provided some indication of the deep brain sites involved in emotion, we developed stereotaxic techniques for accurate implantation of electrodes into specific, predetermined subcortical brain sites of intractably ill patients (Hodes, Heath, Founds, et al, 1954; Becker, Founds, Peacock, et al, 1957). Most patients participating in the studies had schizophrenia, but some suffered from a variety of other disorders recalcitrant to all available treatments: intractable depression, Parkinson's disease, and epilepsy, as well as intractable pain from carcinoma or advanced rheumatoid arthritis.

With the techniques used in the earliest patients, the electrodes for recording and stimulation were implanted into only a few sites and did not remain in place longer than four days. Hence, the opportunity for repeating the therapeutic electrical stimulation was severely limited, and, as a result, beneficial effects were often brief. In the first group of 24 patients (22 with schizophrenia and two with carcinoma) who participated in our studies in 1950-52, electrodes were implanted into the septal region (with one exception, the first patient), caudate nucleus, and anterior thalamus. In most, the response to stimulation of the septal region was encouraging (Heath and the Tulane University Department of Psychiatry and Neurology, 1954). Notable improvement occurred for a short time in the schizophrenic patients, who had failed to benefit from electroshock or insulin therapy. Their psychotic symptoms subsided for a short time, and they became alert and communicative. Whereas the beneficial effects from stimulation of the septal region lasted only a day or two in some, they endured longer in others. A particularly striking result was obtained in Patient 2 (A.D.), a catatonic schizophrenic who, in 1950, was the second patient accepted for the procedure after courses of insulin and electroconvulsive therapy had failed to alleviate her symptoms. Experiencing almost complete remission of symptoms, she attended four years of high school and graduated before disabling psychotic symptoms recurred.

By the end of 1952, we had developed our stereotaxic techniques to the point that deep and surface electrodes could be implanted into many more brain sites and maintained in accurate position for a year or more. In addition to placements in the septal region, caudate nucleus, and anterior thalamus, electrodes were also implanted into other thalamic nuclei, the globus pallidus, deep cerebellar nuclei, hippocampus, hypothalamus, cingulate gyrus, mesencephalic tegmentum, and medial and lateral geniculates. With the ability to stimulate specific sites repeatedly for many months and thereby modify aberrant physiologic activity and behavior, we obtained more gratifying therapeutic results.

The improved techniques also permitted prolonged monitoring of physiologic activity at precise brain sites and simultaneous collection of introspective data during fluctuations in the patient's clinical state (changes in emotional state, as well as relapses and remissions). Further, the intracranial stimulation that was possible with the implanted electrodes permitted documentation of both subjective and objective responses of the patient to activation of various specific brain sites.

Use of deep electrode techniques for diagnosis and treatment of behavioral disorders was curtailed by the rapid evolution of pharmacologic treatments. At most neurologic centers today, deep electrodes are used for short periods only for recording or stimulation, or both, in diagnostic and therapeutic studies of epilepsy and intractable pain. Moreover, in contrast to our studies of the 1950s and 1960s, the number of brain sites into which electrodes are implanted for today's studies is very limited. Thus, our data demonstrating correlations between various types of behavior, including subjective reports of feelings, and brain activity at deep brain sites are unique.

The therapeutic effects we obtained with stimulation were generally longer-lasting in patients with illnesses other than schizophrenia, such as epilepsy and intractable pain. Also, the immediate effects of stimulation to pleasure-inducing sites in the septal region were more dramatic in the *non*schizophrenic patients. The attenuated pleasure response to septal region stimulation of the schizophrenics, their recording abnormality focal in the septal region in association with psychotic behavior, and their clinical symptom of anhedonia led us to assume that receptors, particularly in the septal region, were somehow impaired, since there was no consistent evidence of structural alteration of the brain. On the hypothesis that the impairment might result from a metabolic change that affected transmitter function, our next approach to the problem of schizophrenia was to devise methods for chemical stimulation of focal brain sites, a technique we also used later in patients with other intractable illnesses.

After extensive experimentation in animals, a cannula was developed in 1959 that permitted intracerebral chemical stimulation of the brain (Heath and Founds, 1960). With stereotaxic methods, the cannula was accurately implanted into preselected sites in the parenchyma or ventricles and, like the electrodes, was maintained in position for as long as a year. This fulfilled the essential criteria of placement accuracy, minimal destruction of brain tissue, asepsis, flushing, and volumetric accuracy. It provided an added therapeutic dimension to the method of electrical stimulation of the brain by allowing appraisal of the effects on mental activity of introduction of various neurotransmitter chemicals into precise sites.

By 1950, when we first used deep brain electrodes in patients who were considered hopelessly ill, a number of animal studies had suggested that subcortical brain sites played a role in emotional expression. Whereas some objective manifestations of emotion, sensory perception, and memory could be assessed in animals, critical and

subjective manifestations could not be monitored. By using our deep electrode techniques, which generated physiologic data, in fully conscious patients capable of reporting their thoughts and feelings, we added the essential subjective dimension. The human data, in turn, provided direction for more meaningful animal investigations.

Our decision at the end of the 1940s to develop techniques for implantation of electrodes into specific subcortical sites of patients evolved from my experience as a participant in the Columbia Greystone Project (studies involving ablation of selective areas of the cortex in psychotic patients), as well as from data accumulated from a number of animal studies (Mettler and Mettler, 1942; Heath, Freedman, and Mettler, 1947; Mettler, 1949). Cortical ablation of parts of the frontal lobes (lobotomy and topectomy) had produced only minor changes in emotion, perception, and memory of psychotic schizophrenic patients. They continued to have profound emotional impairment, disordered thinking (delusions), and sensory disturbances (hallucinations). The results suggested that the frontal cortex influenced the neural mechanism for emotion, but was not integral to it. On the other hand, ablation or stimulation of certain subcortical sites of animals so profoundly altered emotional behavior as to suggest that the neural network for emotion was largely subcortical.

The investigative and therapeutic techniques introduced at Tulane were used only in patients in whom all conventional treatments had failed and in whom informed consent had been obtained. In the 1950s and 1960s, most patients accepted for our procedures suffered intractable mental illness. Most were schizophrenic, since animal studies had indicated that therapy with use of deep electrodes and cannulas might be more effective than treatments available for schizophrenia at the time. Later, when neuroleptic medications became available and were proving effective in alleviating symptoms in many psychotic patients, our techniques were used in only a few schizophrenic patients who failed to benefit from exhaustive trials with all categories of drugs.

When we initiated these procedures, we were also motivated by the fact that they were less damaging than the conventional treatments being used. Electroshock was in wide use, and lobotomies were being performed on many chronically ill patients. Patients who were accepted for our procedures had failed to respond to electroshock therapy and, during the pre-neuroleptic drug era, the psychiatrists who rigidly screened our patients considered lobotomy or ablative surgery as probably not beneficial. Our decision to stimulate subcortical brain structures of intractably ill schizophrenic patients

was made after observations that undercutting (lobotomy) or removal of the frontal cortex (topectomy) failed to alter effectively the profound disturbances of emotionality characteristic of the schizophrenic. Although preliminary results of stimulation provided a rationale for its use in the treatment of epilepsy, Parkinsonism, intractable pain, and advanced rheumatoid arthritis, patients with those illnesses were accepted for our procedures only if they continued to be incapacitated after all other available treatments had been given reasonable trials. Since these patients were not mentally ill, they also served as controls for the findings obtained in the psychotic patients.

Reception of our Therapeutic Studies

Even though the techniques we introduced were less damaging and potentially more effective therapeutically than many that were in popular use at the time, our reports of initial results obtained in patients had a mixed reception, at best, from the scientific community. The negative reactions were often intense. Most were nonspecific and imprecise, rooted in emotion, with accusations of "mind control" and "mind manipulation." The reality was lost that we were treating patients with sick minds who could be helped only by redirecting their minds towards health. In sharp contrast to the mind control" that can result from interpersonal therapy, use of addictive drugs, and membership in certain cults, it was never possible to control the mind with our techniques, nor was that our intent.

Developments in psychiatry and neurology in the United States, involving relations between the two specialties, influenced the reception of our reports. Before and during the early 1940s, psychiatric patients were often treated by neurologists, who were called neuropsychiatrists. In psychiatry, psychoanalytic thinking was increasingly dominant. Infantile experiences and other environmental interpersonal factors were considered the principal (or sole) factors responsible for behavioral disorders, including that of schizophrenia. The schizophrenogenic mother was deemed the predominant etiologic factor in schizophrenia. Manic-depressive illness was attributed to faulty maternal influences. The concept of a biologic basis for neurosis and the functional psychoses — that behavioral disturbances might result from changes in the neural substrate — was foreign to most psychiatrists.

In the late 1940s, seemingly in reaction to the dominance of psychiatry by psychoanalysis, neurology became increasingly dissociated from psychiatry. As the neurologist's interest in electrodiagnostic techniques (electroencephalography and electromyography

and later, evoked potentials) increased, it became unnecessary for him to treat psychiatric patients in order to earn a living. In division of the territory, the so-called functional psychoses, schizophrenia and manic-depressive disease, became psychiatric, whereas epilepsy, often associated with behavioral disturbances, became neurologic.

In light of more recent developments, the separation was fallacious. We and others have demonstrated that the severe behavioral problems that sometimes develop interictally in epileptics derive from changes in activity at the same deep brain sites that are affected in so-called functional psychosis (Koella and Trimble, 1982; Heath, 1962, 1982). Further, the aberrant behavior characteristic of schizophrenia has been shown to be associated with abnormal electroencephalographic activity at deep brain sites, and recent findings indicate that an autoantibody is probably responsible. If that prevails, the neuropathology of schizophrenia would be as clear as it is for myasthenia gravis, systemic lupus erythematosus, and multiple sclerosis, all conventionally considered to be neurologic disorders. The organic brain syndromes initially stayed with psychiatry, but neurologists have recently developed an increased interest in dementia and are retaining patients with that disorder.

In the past 25 years, the field of biologic psychiatry has emerged as evidence pointing to a biologic substrate for behavior has accumulated. Research development in biologic psychiatry has also generated interest in neurology, and behavioral neurology has spawned as a subspecialty. But the early efforts at Tulane to establish the neural basis of mental activity, well before the general upsurge of interest in the biologic basis of behavior, fell into a chasm between the specialties of psychiatry and neurology.

In this section, I will review both published and unpublished data from the Tulane research program since 1950 in order to provide a perspective for our current concept of the brain's neural network for emotion, perception, and memory. When it is apropos, the rationale we evolved in devising experiments and the reasons we later qualified our theories for collecting data will be described. The point we have reached is a stepping stone. There is much work still to be done before this broad subject is completely understood.

Background: Historical Highlights

An accurate demonstration of the neural basis for emotion requires correlation of nervous system structure and function with both the subjective and objective components of emotions. Animal

research is limited by the absence of the subjective component. Their nervous system function can thus be correlated only with observable behavior and peripheral physiologic measurements. In human subjects capable of reporting feelings, the shortcoming has been the lack of techniques for adequate monitoring of associated central nervous system mechanisms, a source of frustration for many years. This brief review of early experiments, along with some pertinent recent studies, is designed to portray continuing attempts to relate brain function to mental activity.

Early in the twentieth century, attempts to relate emotion to the central nervous system resulted in considerable controversy concerning two principal theories of emotions. The original theory, popularly known as the James-Lange theory of emotions, was based principally on subjective feelings (Lange, 1887; Lange and James, 1922; Cannon, 1927; James, 1950). Since cortical function was considered basic to conscious awareness, the cortex, along with peripheral receptors, was deemed the principal central nervous system site for emotion. In 1931, Cannon (Cannon, 1931) summarized the theory as follows: "According to the James-Lange theory an object stimulates one or more receptors, afferent impulses pass to the cortex and the object is perceived; thereupon currents run down to muscles and viscera and alter them in complex ways; afferent impulses from these disturbed organs course back to the cortex and when there perceived transform the 'object-simply-apprehended' to the 'object-emotionally-felt'; 'the feeling of the bodily changes as they occur is the emotion — the common sensation, associational and motor elements explain all,' to quote James's expression."

In his own theory of emotion, Cannon included the thalamus as part of the neural mechanism (the so-called thalamic theory), with the explanation that emotion has a particular quality attributable to thalamic activity. Although his "thalamic" theory was likewise based principally on subjective evidence, it was also supported by emerging clinical neurologic evidence suggesting that changes in emotional expression (objective components of emotion) occurred with lesions at the thalamic level (Head, 1920; Herrick, 1924). Cannon's theory provided a framework for animal experiments that demonstrated some correlations between the nervous system and emotional expression. In investigating the neural basis for emotion, physiologists emphasized that the methods available permitted correlations only with objective manifestations of emotional states. They were pessimistic about the prospects of relating neural activity to the subjective components of emotion.

In animal experiments, Bard (1928) showed that removal of the cerebrum anterior to the thalamus did not eliminate emotional behavior but, in fact, often produced objective changes of a type seen with excessive rage. This response was termed "sham rage." In dealing with the subjective versus objective aspects of emotion, Bard (1939) wrote: "The word emotion implies both a mode of acting and a subjective experience. In experimental work on animals, emotions can be studied only as behavior patterns; to consider the subjective aspects of emotion in an animal is to proceed on the basis of an inference which, however plausible, has no place in objective physiological work." In an extensive review of his research relating central nervous system activity to emotional expression, Bard noted that his correlations were confined to the physical phenomena that characterized emergency emotion and commented that it was virtually impossible to detect patterns in animals that would be a manifestation of feelings of pleasure.

In elaboration, Zanchetti (1967) wrote: "There is no doubt that this [behavioristic approach] is the only means available when the location or the functioning of the neural mechanisms of emotion are [sic] to be studied with lesion or stimulation experiments, which obviously cannot be performed on man. Little progress, moreover, can be expected in this field if introspective methods are applied to the study of human emotion."

In a series of studies in cats, in which the effects of ablation were correlated with patterns of behavior, Zanchetti (1967) demonstrated that the neural mechanism for emotional expression extended far caudal to the thalamus and implicated the mesencephalic reticular activating system. He related his findings to Lindsley's (1951) activation theory of emotion. Lindsley's data indicated that sensory stimuli from peripheral sensors activated the brain stem reticular formation which, in turn, excited subcortical structures in the hypothalamus and rostral midbrain involved in somato-visceral integration. Further, they suggested that those structures discharged to the periphery, by way of the descending chain of reticular neurons, and thereby produced bodily arousal of emotional expression.

Zanchetti, in his overall concept of the role of the mesencephalic reticular activating system in emotional expression, suggested that the reticular system projected rostrally to activate the cortex and thereby produce psychological arousal. He further proposed that afferents from the cortex and limbic structure reciprocally influenced patterns of emotional expression by modifying the level of ex-

citation of the neurons in the descending reticular system. Whereas his experiments demonstrated that neurons at the brain stem level participated in emotional expression, they were not designed to demonstrate the total neural circuitry involved in emotion.

To substantiate his hypothesis concerning the interaction between the so-called limbic system and the reticular activating system, Zanchetti cited anatomic data of Nauta and Kuypers (Nauta and Kuypers, 1957; Nauta, 1958). However, the introspective-inspective studies we conducted in patients indicated that the neural structures involved in emotion are much more extensive than (and sometimes disparate from) those Zanchetti highlighted on the basis of the anatomic studies by Nauta and Kuypers.

While citing evidence to demonstrate participation of the thalamus and mesencephalic structures in behavioral patterns of emotion, Zanchetti, Lindsley, Nauta, and Kuypers theorized, on the basis of the anatomic data, the involvement of more rostral sites in the central nervous system. They presented no evidence of a functional relation between the more rostral sites and the caudal diencephalon and mesencephalon or of a correlation with emotional behavior.

Cannon and Bard, on the basis of their experience in inducing sham rage but in the absence of substantiating data, speculated that more rostral structures — probably the neocortex — asserted an inhibitory influence on emotional expression, and Zanchetti hypothesized a modulating role on reticular neurons from higher levels.

In 1937, Papez (1937) expanded on the reports of Bard (1928) and Cannon (1931) concerning involvement of the hypothalamus in emotion. He theorized that the rich reciprocal connections of the hypothalamus, hippocampus, and cingulate gyrus represented the core of a structural neural circuitry subserving emotion. He considered the anterior thalamic nucleus an important relay between the mammillary bodies of the hypothalamus and the cingulate gyrus of the cortex, from which connections radiated to other cortical areas, thereby providing emotional coloring. In Papez's system, input from the thought level of the cortex, by way of the hippocampus through the fornix to the mammillary bodies, excited emotion. To substantiate his theory, he cited reports of the clinical effects of gross lesions of sites within his system, but the lesions also implicated areas outside. Papez's system, principally involving the medial surface of the hemisphere, was largely confined to the region that Broca (1878) had labeled the limbic lobe because it was in limbus around the brain stem.

In referring to the limbic lobe, Papez did not use the term "limbic system." That implies that those interconnected structures of the brain are an independent, self-contained, functioning system for emotion. Although "limbic system" is in general use, the limbic lobe has never been shown to be more than a functional part of a more extensive neural network subserving emotion. However, when MacLean expanded Papez's concept in his animal studies, he referred to the neural structures for emotion as the limbic system.

More extensive connections within the so-called limbic system, particularly to midbrain sites, have been shown in anatomic studies (Guillery, 1956; Guillery, 1957; Cowan, Guillery, and Powell, 1964). In describing an ascending portion of the limbic system, as well as extensive descending connections into the mesencephalon, Zanchetti (1967) presented diagrams from Nauta (1958). The significance of the anatomic interconnections of sites implicated in emotion required information about which sites were activated during different emotional states, data that were not available from the anatomic studies or the ablation-stimulation experiments.

Elaborating upon Papez's theory of emotion, MacLean (1949, 1970) advanced the theory of a triune brain and further amplified it in his 1990 monograph (MacLean, 1990). On the basis of comparative behavioral studies related to brain anatomy, he considered that the highly evolved human brain comprised three parts: (1) a core reptilian brain, which accounts for stereotypical and seemingly genetic memories and behavioral patterns related to neural development of the upper brain, midbrain, and basal ganglia; (2) a paleomammalian brain with primitive cortex (largely the limbic lobe), which he considers to be the substrate for emotional behavior and associated endocrine and visceral functions, and (3) the neocortex of higher mammals, which, in man, forms the basis for such functions as reading, writing, and arithmetic.

In substantiation of his three-brain concept, MacLean cited the behavior of patients during psychomotor epileptic seizures and noted their electrical activity was sometimes confined principally to sites in the limbic lobe, with no involvement of neocortical structures. This somewhat independent activity was considered corroboration that the limbic lobe was a functioning unit of the limbic system. MacLean also cited rare instances of persons who reportedly performed tasks requiring intact intellect for which they later had no recall, as a result of seizural activity confined to the limbic lobe. In our deep-electrode studies in patients, from whom subjective data were obtained concomitant with

objective recording data (to be presented in a later section), epileptiform-like activity of both psychotic schizophrenic patients and epileptic patients, while often limited to deep structures, was more extensive than MacLean described. Amnesia occurred only in those instances in which the cortex became implicated in the abnormal activity. Within MacLean's theoretical framework, attempts were made to show anatomic relations among the "three brains," but no data were collected to demonstrate the relation between structures for sensory perception and sites involved in emotion.

Although a variety of ablation and stimulation studies in animals showed that emotional behavior was profoundly influenced by activity at sites in the limbic system, those early reports were often inconsistent. With lesions to the amygdala, for example, Bard and Mountcastle (1948) described a lowered threshold for rage behavior, whereas Kluver and Bucy (1938) reported increased passivity. Our later findings in patients, as well as in a large number of animals, in which different results were obtained when different sites in the amygdala were stimulated, provide some clarification.

In animal studies, the absence of subjective data has made it difficult to interpret the observed behavioral responses. That prompted use of the term "sham rage." Although the motor pattern of Bard's experimental animals resembled that seen with rage behavior, associated feelings were, of course, unknown. In describing the effects of hypothalamic stimulation on these animals, Masserman (1943) expressed doubt that sham rage was similar to man's spontaneous rage, maintaining that it was more likely a motor automatism unrelated to motivation or associational systems. Other investigators disagreed, contending that hypothalamic stimulation resulted in direct attack behavior that was motivational (Wasman and Flynn, 1962; Roberts and Kiess, 1964). In our program, we stimulated these deep sites in patients and obtained subjective as well as objective data.

The Role of the Cortex in Emotion and Memory

It should be pointed out that the following is by no means a well-rounded review of the role of the cortex in emotion. It is selective, limited to findings that are pertinent to data we collected in our studies of the brain's neural network for emotion.

Results obtained with frontal cortical lesions in several animal species have often been contradictory. In rats, for example, some reports indicate reduced socialization and timidity after such lesions,

whereas others described increased aggression (Kolb and Nonneman, 1974; deBruin, Van Oyen, and Van de Poll, 1983). Descriptions of the effects of frontal lobe lesions in monkeys are similarly inconsistent. In 1947, Mettler (1947) described increased socialization and extroversion of rhesus monkeys after dorsolateral frontal ablation. In more recent studies, however, monkeys with similar lesions have been described as apathetic and socially withdrawn (Fuster, 1980; Kling and Steklis, 1976).

In contrast, data gathered from human subjects after prefrontal lesions are more consistent. Frontal lobe ablation (topectomy) and undercutting (lobotomy) were used extensively in patients for almost two decades (1938-1955) to alleviate symptoms of intractable behavioral disorders or intractable pain. (Today, patients only rarely undergo lesioning of the cingulate gyrus or limited interruption of the thalamo-frontal cortex pathway as treatment for intractable behavioral disorders. In epileptic patients, however, ablation of sites on the cortex of the temporal lobe continues to be an acceptable procedure for removing epileptogenic foci.) Since the patients were able to report their thoughts and feelings, it was possible to correlate the effects of cortical impairment and mental activity. The numerous psychiatric and psychological evaluations of the patients before and after operation showed that the frontal cortex, while influencing the emotional system, did not seriously disrupt the mechanism for emotional expression (Heath, Weber, and Crandell, 1949; Landis, 1949).

Lobotomized patients showed reduced emotional response in their anticipation of future events based on imprinted memories. This was responsible, at least in part, for the improvement in some patients, particularly those with depression and obsessional-compulsive neurosis, in whom behavior was characterized by anticipation of the future in terms of fear, hopelessness, anguish, and despair. But neither lobotomy nor topectomy helped to alter the severely disrupted emotionality of the schizophrenic patients. The results of undercutting or ablation of the cingulate gyrus were similar in affecting the emotional system without significantly changing the mechanisms for emotional expression or memory (Mettler, 1949; Ballantine, Cassidy, Flanagan, and Marino, 1967). These findings in patients augment the clinical data (based on retrospective reports) available when Papez formulated his concept of the role of the cingulate gyrus in man, and they add the subjective reports not available in animal studies.

Limited unilateral ablation of the temporal lobe likewise induced little change in the mechanism for emotion of epileptic pa-

tients except when removal of a focus had altered seizural patterns that were affecting the emotional state through their influence on subcortical structures. The reports that altered emotion in epileptic patients is related to cortical lateralization have been difficult to substantiate, since epilepsy also profoundly affects activity of deep brain structures, and many of the changes that are described relate more to subcortical activity (Bear, 1979).

Some investigators have reported an affective component for language in the non-dominant hemisphere (Heilman, Scholes, and Watson, 1975; Ross, 1981). Comprehension of emotional language has been localized in the temporal lobe and that of emotional expression in the non-dominant frontal lobe at a site homologous to Broca's area on the dominant side. The concept of cortical lateralization of emotion also gains support from the treatment of intractable physical pain by unilateral lobotomy. The most consistently effective relief derived from undercutting of the frontal lobe of the non-dominant hemisphere, which interrupted connections between the prefrontal cortex and subcortical structures.

Despite the provocative conclusions stemming from these studies, that is, that there is cortical lateralization for certain functions involving emotion, they are incomplete, since subcortical structures are also implicated directly or as a consequence of influences through efferent connections from the cortex. On the other hand, cortical ablation studies have shown that although cortical input can influence emotional expression and feeling, it is not a major component of the mechanism for emotional expression or of the perception of emotional feelings.

Electrical stimulation at neocortical sites likewise induced little change in emotion, except when the stimulus was at a site that activated an epileptic focus or excited the motor strip to produce seizures. Penfield and associates (Penfield and Jasper, 1954; Penfield and Perot, 1963; Penfield, 1975) have attributed profound changes in emotion, often associated with "psychic" or "experiential" phenomena (including complex visual and auditory hallucinations, memory flashbacks, and erroneous interpretations of the here-and-now), to neocortical stimulation of the temporal lobe. This conclusion is not in keeping with our findings, and Gloor and associates (Gloor, Oliver, Quesney, et al, 1982) have also questioned it. Penfield and associates studied epileptic patients in whom electrodes were restricted principally to the temporal lobe. More recent data, including ours, indicate that the phenomena described by the Penfield group were probably due to spread of activity to underlying deep nuclei in the temporal

lobe and to distant interconnected sites (where, as we have demonstrated, activity correlates more precisely with many of the phenomena described), rather than solely to neocortical activation.

Cortical ablation also had negligible effect on memory. When temporal lobe epileptic foci were removed by unilateral ablation, the resulting minor changes in verbal and visual memory may have been due to modification of the epilepsy (Milner, 1975; Novelly, Augustine, Mattson, et al, 1984). Seemingly, ablation of dominant and of submissive hemispheric sites has different effects on memory. The minimal changes that occurred with removal of discrete temporal lobe cortical sites contrast sharply with the profound memory disturbances that occurred after bilateral temporal ablations, including ablation of the hippocampus.

With the process of encephalization, it is apparent as one moves up the phylogenetic scale that some functions become much more dependent on the cortex than others. Motor function and vision have precise cortical localization in primates. Whereas lesions of the motor cortex induce permanent paralysis in primates, their effect on motor function in lower mammals is minimal. In primates, lesions of the visual cortex produce blindness. On the other hand, lesions of the cortex do not grossly impair audition, which is less represented at the cortical level.

Briefly, then, experimental data indicate that the role of the cortex in emotion, sensory perception, and memory is to integrate the input from subcortical sites. The profound changes that result from lesions of certain subcortical sites contrast sharply with the less dramatic effects of cortical lesions.

Animal Models for Identifying the Neural Substrate for Emotion

In the Tulane program, studies were carried out not only in animal models, but also in patients who were undergoing treatment for intractable illnesses. The data were reciprocal, those from one set of studies augmenting the other. Most of the experimental data directed toward identifying the extensive subcortical neural network for emotion derived from experiments conducted in our laboratory.

Ablation Studies

Mettler and Mettler (1942) had described profound changes in levels of psychological awareness and disturbances in emotionality

in the cat after destructive lesioning of the caudate nucleus. The gross lesions were made by incisions through the cortex and removal of the caudate nucleus by suctioning, a procedure that also destroyed adjacent tissue. In experiments I later conducted at Columbia University and then at Tulane, more discrete lesions were made in cats by suctioning and with closed stereotaxic techniques. Behavioral impairment was not pronounced when the lesions were limited to the head of the caudate nucleus. When discrete lesions were similarly made to the anterior thalamus (often damaged by the open suctioning method), a key anatomic site in the hypothetical Papez circuitry for emotionality, no gross behavioral changes ensued. But the type of behavioral changes described by the Mettlers did result when the lesion involved the more medial and basal forebrain nuclei. We named this site, which included several discrete nuclei, the septal region.*

When large parts of the septal region of cats were destroyed, behavioral changes were dramatic (Heath, 1954b). The cats seemed dazed, out of contact, and had a blank stare. Emotional responsivity was profoundly impaired. Level of awareness was greatly reduced, and perception of sensory stimuli notably affected. Putting a dog in

---

* Following is a modification of the definition of the septal region of the human brain that was published in 1954 (Heath, 1954a).

> The caudal border of this region is formed by the anterior commissure; the rostral extent is the tip of the anterior horn of the lateral ventricle. It extends medially to the midline space separating the hemispheres. The dorsal extent is the septum pellucidum and the base of the lateral ventricles. It extends ventrally to the base of the brain and laterally about 5 mm from the midline.
>
> This region encompasses several different and distinct structures in the usual anatomic sense. Some of the structures included in the conventional anatomic texts are the nucleus acumbens, including the most ventral-medial aspect of the head of the caudate nucleus, the nucleus basalis of Meynert, septal nuclei proper, nucleus of the diagonal band of Broca, subcallosal gyrus, rostrum of the corpus callosum, olfactory tubercle, subcallosal fasciculus, and various olfactory pathways.
>
> When these experiments were performed (1948-52), principal known anatomic connections of the septum were as follows:
>
> (1) Afferents from the medial olfactory stria, hippocampus, amygdala, and cerebral cortex (areas 9 and 11 of Brodmann).
>
> (2) Efferents to the hypothalamus, hippocampus, amygdala, and habenula by way of the stria medullaris and pre-optic region.

the cage elicited no emergency response. Reaction to painful stimuli, such as pinching of the ear or stepping on the tail, was minimal or inappropriate. The gait was slow and stereotyped. The cats did not respond to petting. Spontaneous motor activity also declined. Most cats displayed catatonia; they could be postured, that is, their extremities could be placed in bizarre positions, where they stayed for long periods, but no motor weakness or paralysis occurred. Diminished appetite usually required tube-feeding. Almost identical behavioral changes occurred in monkeys. The behavior of the cats and monkeys that resulted from lesions of the septal region could be likened in some ways to the behavior of the psychotic schizophrenic patients. (Lesions at other subcortical sites of the cats and monkeys did not induce comparable behavior.)

Some cats with destructive lesions of the septal region also manifested severe metabolic disturbances (Heath, Weber, Hogan, et al, 1954). Whereas serum sodium levels dropped, serum potassium levels usually increased minimally. With time, blood glucose dropped, as did glycogen in muscle. Temperature control diminished, and body temperature fell over a few days to near-room temperature. Since many of the changes were similar to those reported after destruction of the adrenal cortex, we postulated that the septal region, like the adrenal cortex, played an important role in the stress mechanism, possibly through activation of the pituitary-adrenal axis (Heath and Leach, 1956). However, the finding that the adrenals of these septal-lesioned cats were intact or hypertrophied suggested there

---

> (3) Pyriform cortex projection to the pre-optic area.
>
> In summary, then, the septal region is part of the olfactory system. From its anatomic relationships, it would appear to be a correlating structure interposed between the higher neocortical level and the diencephalic and midbrain structures.
>
> Just caudal to our human septal region is the hypothalamus. Embryologically, however, the two regions are quite different. The septal region is derived from the rhinencephalon division of the forebrain, whereas the hypothalamus is an elaboration of the primitive diencephalon. Although anatomists have applied different names to several different nuclear masses within our septal region, these varied structures are developmentally part of the same system, namely, the rhinencephalon. Embryologically, the rhinencephalon includes those structures anterior to the rostral end of the third ventricle. Our principal reason for rigidly demarcating the region we have called septal is that it appears to have unique functional qualities.

might be a neural mechanism independent of the pituitary adrenal system that affected electrolytes and glucose metabolism. (This subsequently led to further experiments to determine the mechanism by which the septal region altered the stress mechanism.)

The significant metabolic changes that occasionally occurred in cats with septal lesions are puzzling. One consideration was that the function of vasopressin, which we have shown to be present in the septal region of the cat and monkey, might be impaired (Fitzjarrell and Heath, unpublished manuscript). This could cause hemodilution and consequently lower sodium levels. However, it would not explain the normal or elevated concentrations of potassium. The metabolic changes with septal lesions were similar to those seen with reduction or absence of corticosteroids. (The biochemical effects of stimulation to the septal region that complement these findings will be discussed later.)

Stimulation Studies

Several types of stimulation studies have also provided evidence of a unique role for the basal forebrain (septal region) in emotionality.

Influence of septal region stimulation on activity of the cerebral cortex. — Cortical activity was demonstrated in the cat by recording motor response of the legs to ongoing stimulation (frequency of one-per-second) of the motor cortex. During the ongoing cortical stimulation, a stimulus was applied through an electrode to a subcortical site and the result charted according to facilitation or inhibition of the cortically induced motor activity. With this method, subcortical sites that facilitated the induced cortical activity (as indicated by increased amplitude of the motor response) were the septal nuclei proper, nucleus of the diagonal band of Broca, nucleus basalis of Meynert, nucleus acumbens, medial aspect of the caudate nucleus, and parts of the gyrus rectus that, together, corresponded closely to the basal forebrain or septal region (Hodes, Peacock, and Heath, 1950; Hodes, Peacock, and Heath, 1951).

Effects of septal region stimulation on behavior. — When the septal region of the fully conscious cat with chronically implanted electrodes was stimulated, it became alert. Not only did it become more attentive and aware of its environment, but it seemed to enjoy the feelings induced by the stimulation as it purred and responded to petting.

Stimulation of sites in the septal region likewise produced

alerting and apparent pleasure in the monkey with chronically implanted electrodes. The animal showed no sign of discomfort. Later, when we modified techniques developed by Olds and Milner (1954) for self-stimulation studies in rats and applied them to the monkey, our assumption of a pleasure response was supported by the monkey's repeated self-stimulation of sites in the septal region. Although the monkey repeatedly stimulated electrodes at all sites in the broadly defined septal region, the count (number of stimuli delivered per unit of time) was highest when the monkey stimulated electrodes implanted in the more rostral part of the septal region (stereotaxic coordinates A 20 to A 23).

Effects of septal region stimulation on stress chemistry*. — Many of the changes in stress chemistry that occurred with stimulation of the septal region were similar to those seen on activation of the pituitary adrenal axis or on administration of adrenocorticotropic hormone (Heath and Leach, 1956). In patients, total white blood count increased, usually doubling and sometimes tripling. Eosinophil count dropped precipitously to less than 50% of baseline value, and lymphocytes dropped 20 to 50%. (In contrast, stimulation of the caudate nucleus and posterior hypothalamus produced minimal or no fluctuations in these measures.)

To determine whether or not the changes were through the pituitary adrenal axis, we conducted a series of experiments in female rhesus monkeys (Heath and Leach, 1956). First, electrodes were chronically implanted in the facilitatory (septal) region. After allowing sufficient time for recovery from operation, we delivered a stimulus to the septal region, after which changes in total white and red blood count, differential white count, eosinophils, and total urinary 17-ketosteroids were noted. Qualitative urinary steroids were recorded by paper chromatography. The monkeys were then adrenalectomized and maintained on constant daily low doses of cortisone. After passage of sufficient time to secure an adequate baseline, the monkeys were again stimulated in exactly the same manner and followed with the same battery of tests. This procedure was repeated on several oc-

---

* The findings reported here, suggesting a strong neural mechanism for stress chemistry, provided a therapeutic rationale for later studies in which we stimulated the septal region of patients suffering from advanced rheumatoid arthritis and cancer in whom conventional treatment with steroids was no longer effective. Since stimulation to the septal region had been shown to induce pleasure, a second motivation was to relieve their intractable pain.

casions in the adrenalectomized monkeys. To explore the possibility that biochemical changes resulted from activation of accessory adrenal tissue, the animals were administered adrenocorticotropic hormone (ACTH) and followed with the test battery. In no instance did the ACTH produce any alterations that would have been expected had accessory adrenal tissue been present. Furthermore, on postmortem examination, a careful search was conducted for the presence of accessory adrenal tissue, and none was found.

In a series of four female monkeys that were adrenalectomized, septal stimulation produced changes in total urinary 17-ketosteroid output, as well as in behavior, which paralleled, or in some instances exceeded, those that occurred after the same stimulation procedure in the same animals before adrenalectomy (Heath and Leach, 1956). Not only did the output of total urinary 17-ketosteroids increase as a result of the stimulations following adrenalectomy, but in all instances there were changes on the papergrams, indicating the presence of new steroids, not only in the 17-ketosteroid group, but also of other steroids. To rule out the possibility that these changes were related to the supplementary cortisone, we conducted parallel studies with monkeys maintained on salt alone. Although there was a high mortality rate in this small series, we were able to carry two animals through the procedure, and the changes were of the same nature. One monkey was maintained on Doca Acetate (Organon Inc.), which does not readily convert to 17-ketosteroids *in vivo*. Again, similar changes were noted throughout the procedure.

In order to explore the role of the pituitary in this phenomenon, we conducted similar studies in which we attempted to destroy the pituitary gland. Two monkeys were similarly prepared with chronically implanted electrodes, and the chemical changes after stimulation to the septal region were determined. The pituitary was then damaged by electrolysis, an electrode having been inserted into the sella. The animals were then maintained on one daily dose of ACTH, administered at the same time each day so that the daily fluctuation of eosinophils and white blood count could be determined as part of the baseline. Precisely the same stimulus as that given before hypophysectomy was repeated in the monkeys, followed by the same studies. In both monkeys, there was a similar eosinopenia and leukocytosis, with no alteration of the red blood count. Changes in total urinary 17-ketosteroids were likewise of at least the same magnitude as they were after stimulation, prior to the partial hypophysectomy.

Ultimately, one monkey was also adrenalectomized, after

which it was maintained on constant daily doses of 0.5 ml cortisone. After passage of sufficient time for recovery from the operative procedure and the establishment of an adequate baseline on our studies, the same electric stimulus through the same electrodes in the septal region was repeated. Several stimulations were carried out at intervals of ten days to two weeks. Approximately the same changes occurred in all indicators that we had noted before and after the pituitary damage. Careful postmortem examination failed to reveal adrenal tissue, although some pituitary tissue remained (Heath and Leach, 1956).

When these studies were carried out in 1954, techniques for measuring steroids were limited. The results suggested that the peripheral chemical mechanism for the psychologically induced stress response was not necessarily solely through the pituitary adrenal axis. Rather, through activation of the septal region, steroids could be released or mobilized from other sources. We did not pursue these early provocative findings. With the techniques now available for direct measurement of corticosteroids, as well as peptides, in body fluids, this area should be investigated further to determine whether our findings were valid or represented artifacts. In any case, they had a role in the hypotheses we formulated concerning the neural substrate for emotion.

Animal Data as a Rationale for Use of Deep Brain Electrodes in Patients

In order to establish the neural network for emotion, it was necessary to interrelate objective data from animals with the introspective data obtained from patients. Findings in animals had provided a therapeutic rationale for using deep electrode methods in hopelessly ill patients with intractable disease, principally schizophrenia and uncontrolled epilepsy, but with the potential also for alleviating symptoms of Parkinson's disease and intractable pain.

Profound impairment in emotionality, a fundamental characteristic of schizophrenia, provided the therapeutic rationale for exploring those brain sites of schizophrenic patients that animal experiments had suggested were implicated in emotion. Although the physiologic network for emotion was obviously extensive, our earliest studies in patients focused on the septal region, the subcortical site that animal studies had indicated had a unique modulating role in the network. I will describe how the data gathered from the treatment of the special patients contributed to an understanding of the network,

as well as the pathogenesis of various diseases, particularly schizophrenia. Furthermore, findings of these early studies were the basis for additional investigations that also involved biochemical and immunologic approaches.

In 1950, the biological treatments that were available for schizophrenia were electroshock, insulin, and frontal lobe ablation. None was very effective. Whereas dramatic improvement often initially followed electroshock, particularly in catatonic patients, it was usually temporary, and subsequent courses of electroshock treatment tended to be less beneficial. It was a "shotgun" approach, in that the rather intense electrical current spread diffusely to affect many cortical and subcortical sites. Since the current was most concentrated through the basal forebrain, it seemed likely that the transient improvement resulted from activation of the septal region. Against the background of our findings in animals, which suggested the septal region might be specifically implicated in schizophrenia, the results with electroshock were provocative. Animals with destructive lesions of the septal region displayed deficits characteristic of schizophrenia. Level of awareness was notably reduced and, seemingly, so was contact with reality, two cardinal features of the disease.

Since the schizophrenic has no consistent demonstrable structural lesion of the septal region comparable to that of the lesioned animal, we hypothesized that the septal region might be malfunctioning during psychosis. When electrical stimulation of the septal region of animals was shown to induce alerting and apparent pleasure, we considered the procedure might be therapeutic for the schizophrenic. In keeping with our scheme of relating levels of the central nervous system to levels of behavior, we reasoned that stimulation of the septal region, by facilitating cortical activity and activating stress chemistry, would alert the schizophrenic patient, hence raise his psychological awareness from delusional, primary-process thought, and thereby improve his contact with reality.

In the first few schizophrenic patients who participated in the studies, electrodes were implanted through a small incision made through the prefrontal cortex to expose the anterior horn of the lateral ventricles of the non-dominant hemisphere. The visualized foramen of Monro served as a landmark for the anterior-posterior parameter, since it is at the level of the anterior commissure rostro-caudally. The head of the caudate, bulging into the lateral aspect of the ventricle, defined the lateral borders. Bipolar septal electrodes were implanted medially, about 2 mm from the midline, and 10 to 25 mm

rostral to the foramen of Monro (anterior commissure) at the base of the ventricles. Additional bipolar electrodes were visually implanted into the head of the caudate nucleus and into the anterior thalamus, just caudal to the foramen of Monro.

The recordings of psychotic patients showed a spiking abnormality, in the form of spike and slow-wave, that was uniquely present in the septal region. When the region was electrically stimulated, the patient brightened and became attentive, and psychotic symptoms receded. Stimulation of the caudate nucleus or anterior thalamus, on the other hand, had little or no effect. These initial findings were sufficiently gratifying to justify implantation of electrodes into additional deep brain sites to provide a better therapeutic opportunity, as well as better localization of the area of aberrant function, and secondarily, to generate additional data relating brain function to behavior.

Human stereotaxic techniques developed in 1952 permitted implantation of electrodes with an accuracy of one to two millimeters without notable damage to the overlying cortex. The electrodes were inserted through trephine holes and fixed at the bone. They were then passed five to seven inches under the scalp before exiting, a procedure that reduced the chance for infection. Since the behavioral effects of electrical stimulation proved to be brief, we developed methods for repeatedly stimulating patients. With electrodes that held in accurate position for one to two years, it was also possible to collect physiologic data and associated valuable introspective data over a prolonged period (Becker, Founds, Peacock, et al, 1957; Heath, John, and Fontana, 1976).

Patient and Animal Findings as an Impetus for Additional Animal Studies

Sensory-isolated Monkeys: A Clue to Relating Emotion and Sensory Perception

The results in patients motivated us to conduct additional animal experiments in which a more extensive neural network for emotion was elaborated. A major impetus in furthering this effort was the opportunity to use our deep electrode techniques in monkeys raised in isolation in the laboratory of Dr. Harry Harlow. The Harlows (1962) had observed that the profound behavioral impairment of the monkeys isolated after birth became irreversible if significant sensory stim-

ulation was not provided within the first six months of life. The monkeys were seemingly autistic, and their emotional responses were inappropriate. Bizarre motor patterns often developed, consisting most dramatically of rocking movements and posturing. They displayed a preponderance of emergency emotional behavior of fear and rage. Some monkeys were excessively aggressive, and many injured themselves. They were unable to relate to other monkeys, and their sexual function was significantly impaired. The symptoms so closely resembled that of the psychotic schizophrenic patient that some psychiatrists contended the findings supported the concept of a schizophrenogenic mother (that a poor mother-child relationship or an absent mother was the cause of schizophrenia).

Mason and associates (Mason, Davenport, and Menzel, 1968), in their studies of the isolation-raised monkeys, commented on the importance of somatosensory stimulation, particularly proprioception or muscle-joint-tendon stimulation, for normal development. The results of later studies by the Harlows (Harlow, Harlow, and Suomi, 1971) concurred with Mason's observations that monkeys raised without a mother, but with siblings, developed normally, suggesting that the somatosensory stimulation of play activity was adequate for healthy emotional development.

In our physiologic studies of the Harlow monkeys, electrodes were stereotaxically implanted into the septal region, hippocampus, amygdala, and hypothalamus, sites in patients where abnormal electrical activity had been shown to correlate with both psychotic and violent-aggressive behavior (Heath, 1972b). Electrodes were also implanted into the caudate nucleus, which served as an indifferent site, since no correlations had been demonstrated between its activity and emotional behavior. In order to record activity in neural systems for somatosensory stimulation, including vestibular proprioception, we implanted additional electrodes into the somatosensory thalamic nuclei and deep nuclei of the cerebellum. Our interest in exploring cerebellar activity arose from the data of Mason and associates, which suggested that the absence of vestibular-proprioceptive stimulation was a most important contributing factor to the development of behavioral changes in the isolation-raised animals. Healthy monkeys that served as controls had electrodes implanted into the same deep sites.

The septal and hippocampal recordings of the isolation-raised monkeys showed spiking and slow-wave activity that was similar to that of psychotic and violent-aggressive patients (Heath, 1981) (Fig. 1). In addition to changes in recordings from the forebrain structures, however, abnormalities occurred in recordings from the thalamic nu-

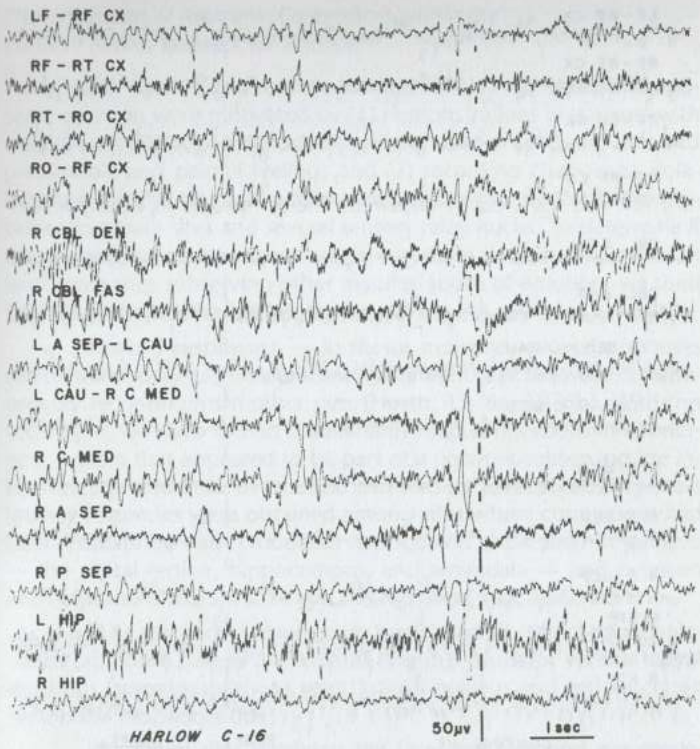

Figure 1.* *Deep and cortical recordings of a severely disturbed isolation-raised monkey, showing spiking at numerous deep sites. A–anterior. C–central. CAU–caudate nucleus. CBL–cerebellum. CX–cortex. DEN–dentate nucleus. F–frontal. FAS–fastigial nucleus. HIP–hippocampus. L–left. MED–median. O–occipital. P–posterior. R–right. SEP–septal region. T-temporal.*

**A complete listing of the abbreviations shown in the figures will be found on page 179.*

clei and deep sites of the cerebellum. In contrast, the recordings of the healthy control monkeys were essentially normal (Fig. 2). The recording changes in the isolation-raised monkeys — specifically, the sharp spiking that occurred synchronously in the forebrain, thalamic nuclei, and cerebellum — suggested an integral functional relation-

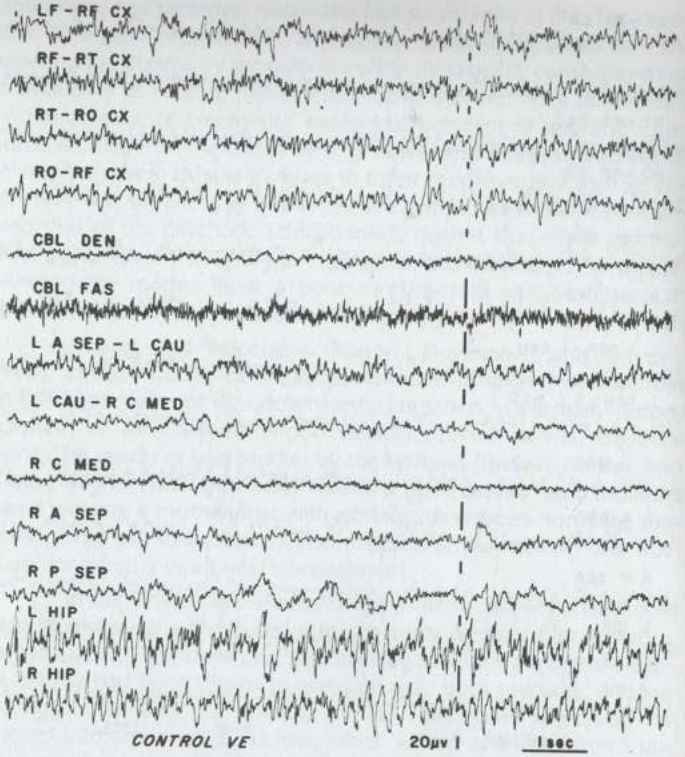

Figure 2. *Deep and cortical recordings of a feral-raised control monkey. No abnormalities noted. See legend for Figure 1 for identification of leads.*

ship and possibly direct connections among these sites. These findings prompted us to use animal models to look for anatomic connections and explore functional relations between the forebrain and sensory relay nuclei, as well as other brain sites subserving various other aspects of emotional expression, and eventually to determine if activity in this delineated neural network correlated with emotional behavior of patients.

Demonstration of Anatomic Connections within the Putative Neural Network for Emotion

Our studies of anatomic connections in the brain that subserve emotion were motivated by (1) demonstrations in patients with deep electrodes of correlations between activity at forebrain sites and pleasurable and painful feelings and (2) recording changes in isolation-raised monkeys that suggested a possible functional relation between forebrain sites and several sensory relay nuclei. To determine if there were anatomic connections among these deep nuclei, as well as with brain sites subserving other manifestations of emotion, we used the following procedures.

Evoked responses. — In rhesus monkeys, evoked responses were obtained by electrically stimulating one brain site while simultaneously recording from other sites (Heath, 1976a, 1976b). With this technique, we were able to preliminarily map connections in the nervous system that appeared to be part of a network subserving the interrelated phenomena of emotion and sensory perception. Very short latency responses were obtained among sites where correlations had been established with emotional feelings and expression in patients — the septal region, hippocampus, and amygdala — and between each of these forebrain sites and the following functional sites:

(1) subcortical sensory relay nuclei, that is, the medial geniculates (audition), lateral geniculates (vision), posterior ventral lateral thalamus (somatosensation), and fastigial nucleus and vermal cortex (vestibular proprioception).

(2) neural sites involving the face and eyes and eye movement, that is, the third nerve nuclei, superior colliculus, and inferior olive.

(3) midbrain nuclei demonstrated to be cell reservoirs for specific neurotransmitters, that is, the substantia nigra (dopamine), locus coeruleus (norepinephrine), and raphe nucleus (serotonin).

Latency responses in sensory nuclei after stimulation of forebrain sites for emotion were so short as to indicate monosynaptic connections to the other nuclear sites where activity correlated with various aspects of emotion (Heath, 1976b). The evoked potential data also indicated that the connections were reciprocal (two-way), in that stimulation of sensory relay nuclei resulted in recordings of short-latency responses at the forebrain sites where activity correlated with emotion. By this technique, other neural sites subserving various aspects of emotional expression were also shown to be connected re-

ciprocally to the forebrain nuclei for emotion and to the sensory relay nuclei.

Responses were also evoked with use of peripheral sensory stimuli. When electrical stimuli were delivered to peripheral nerves of monkeys with recording electrodes implanted at numerous brain sites, responses were recorded not only in the sensory relay nuclei for that particular modality, as would be expected, but also at the various deep nuclei where activity had been correlated with emotion. As examples of responses in known direct pathways, somatosensory stimuli elicited responses in the posterior ventral lateral thalamus after a latency time of 11 msec; auditory stimuli elicited responses in the medial geniculate after a latency time of 13 msec; and visual stimuli elicited responses in the lateral geniculate after a latency time of 12 msec. These stimuli, however, also elicited responses after relatively short latency times at other sites where activity was correlated with specific components of emotion. The latency times between termination of the stimulus and the response in the septal region, hippocampus, and amygdala were in the same range as for the sensory relay nuclei, as were the responses in sites subserving facial expression and in nuclei containing transmitter chemicals (Heath, 1976a, 1976b).

Histologic studies. — Fink-Heimer techniques were used to trace antegrade axonal degeneration after a lesion was made in a specific nucleus. Degenerated fibers traced in 15 cats that had lesions in the rostral septal region indicated septal region connections to numerous sensory relay nuclei — the medial and lateral geniculates, the ventroposterior lateral thalamus, and nuclei containing cell reservoirs for specific transmitters (substantia nigra, locus coeruleus, raphe nuclei) — as well as to the superior colliculus, inferior olive, and mesencephalic reticulum (Heath and Harper, 1976). Previously documented connections of the septal region with the hippocampus and amygdala, other forebrain sites implicated in emotion, were also demonstrated.

Ascending connections of the vermal cerebellum were also determined by Nauta-Gygax, Fink-Heimer procedure I, and cresylechtviolet methods. Degenerating fibers from the fastigial nucleus in the cat were traced into the hypothalamus, the central nuclei of the thalamus, and the cingulate gyrus, as well as into several sites of the septal region, including nucleus accumbens septi, nucleus of the diagonal band of Broca, the dorsal anterior and medial septal nuclei, and, more rostrally, into sites of the orbital gyri and into the gyrus rectus (Harper and Heath, 1973).

In both cats and monkeys, direct fastigial efferents were shown to course bilaterally into the hippocampi, dentate gyri, and subicular regions, into a focal site in the basolateral amygdalae, and into the temporal lobe neocortex (Heath and Harper, 1974). These findings provide an anatomic substrate for the influence of vestibular proprioceptive stimulation on emotion.

By axonal degeneration, a direct connection was demonstrated in the cat from the fastigial nucleus of the cerebellum to the ectosylvian gyrus (Harper and Heath, 1974). This first demonstration of a direct input from the fastigial nucleus to the sensory cortex provided a possible anatomic basis for the deficits in self-image and orientation that have been reported in patients with parietal lobe lesions. (This will be discussed further under "Function of the Parietal Cortex.")

Retrograde transport studies of horseradish peroxidase implanted into specific nuclei. — Several monosynaptic efferents to the septal region were demonstrated with the horseradish peroxidase retrograde transport technique (Clark, 1976). When horseradish peroxidase was implanted into the septal region, it was traced to numerous sites in the hypothalamus and thalamus, to the fastigial nucleus of the cerebellum, and into the substantia nigra and locus coeruleus in the brain stem.

The subcortical structural connections for emotion and interrelated functions of sensory perception, motor expression, and transmitter chemicals are summarized in figure 3. As evidenced by short-latency evoked potentials, most direct connections are reciprocal, and those to the cortex are extensive (Heath 1976b). (They will be described later during a discussion of the interaction of cortical regions with the subcortical neural network.) The data here focus principally on the subcortical neural mechanisms for emotion and sensory perception.

The manner in which activity of the neural network correlates with emotion is demonstrated by data from animals and patients. The network is much more extensive than the limbic system, which is conventionally cited as the neural mechanism for emotion. Its ramifications are probably even more far-reaching than has been shown thus far.

Demonstration of Functional Relationships within the Putative Neural Network for Emotion

Several techniques were used to demonstrate functional relations among the interconnected neural sites, principally subcortical, that were presumed to subserve various aspects of emotion and sensory perception.

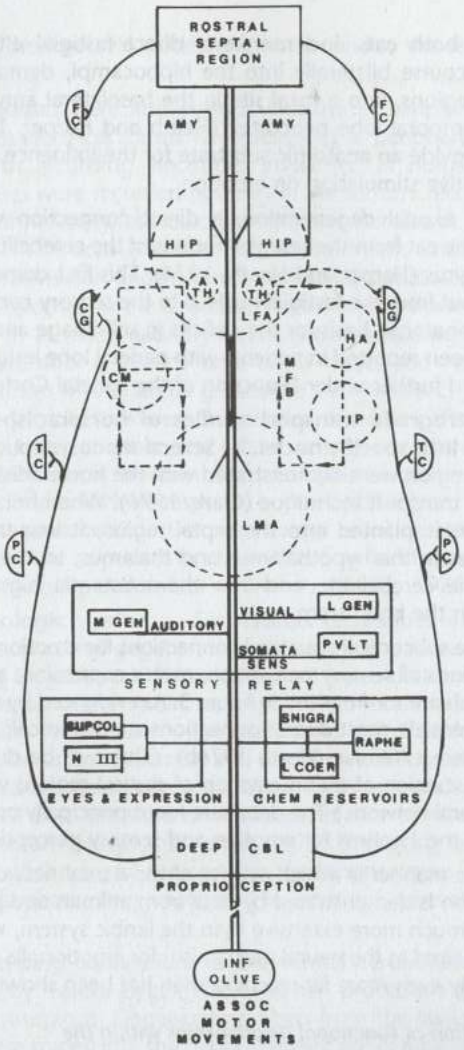

Figure 3. *Schematic diagram of brain sites and pathways demonstrated in the Tulane studies to be functionally significant in emotional expression (solid lines), superimposed on a diagram of conventional limbic forebrain (LFA) and limbic midbrain (LMA) sites and pathways (broken lines).*

Legend for Figure 3

AMY	*amygdala*	*L GEN*	*lateral geniculate*
CG	*cingulate gyrus*	*LMA*	*limbic midbrain area*
CM	*corpus mammillare*	*M GEN*	*medial geniculate*
DEEP CBL	*fastigial nucleus and dentate cerebellum*	*N III*	*oculomotor nuclei*
FC	*frontal cortex*	*PC*	*parietal cortex*
HA	*habenula*	*PVL T*	*posterior ventral lateral thalamus*
HIP	*hippocampus*	*RAPHE*	*raphe nuclei*
INF OLIVE	*inferior olive*	*SEHS*	*somatosensory nuclei*
IP	*nucleus interpeduncularis*	*S NIGRA*	*substantia nigra*
L COER	*locus ceruleus*	*SUP COL*	*superior colliculus*
LFA	*limbic forebrain area*	*TC*	*temporal cortex*

Use of irritants to create foci at specific sites. — To create a discharging focus at a specific site within the anatomically demonstrated network for emotional expression, we used cobalt or penicillin as the irritant (Guerrero-Figueroa, DeBalbian Verster, and Heath, 1962; Heath, 1976a; Heath, 1976b). A minute quantity of the irritant was introduced stereotaxically into the target subcortical nucleus of the cat or rhesus monkey. The primary focus, manifest by changes in recordings from the nucleus where the irritant was implanted, developed quickly (within one hour to one day with cobalt and within a somewhat longer interval with penicillin). Within hours to days, the primary focus activated secondary foci in recordings from distal sites, which continued to be active after ablation of the primary site. When

activity at a primary site induced activity at a distal site, it was presumed that direct anatomic and functional connections existed between the primary and secondary sites. The spread of epileptiform activity (recording activity characteristic of epilepsy) in the experimental animals was similar to the spontaneous spread of activity often observed in epileptic patients with implanted deep electrodes. (As elaborated in a later section, the patients, who were able to report their feelings and thoughts, added an important dimension, allowing correlation of the recording changes with mental activity.)

The pattern and chronology of spread fluctuated in each animal and varied from one animal to another. Figure 4 is an example of the manner in which an irritant focus in the septal region of a rhesus monkey influenced other sites in the putative network for emotional expression. Note the spread to other forebrain sites, the hippocampi or amygdalae, or both, (where activity had been correlated with specific emotional states), as well as to various sensory relay nuclei, including the cerebellum, to sites subserving expression of the face and eyes, and to nuclei containing various neurochemical transmitters. When the irritant was implanted into other specific sites within the network, it likewise influenced activity at other sites in the pathway for emotion.

Microrecordings. — Use of microrecordings made it possible to demonstrate how activity at one site affected unit activity at connected sites within the neural network subserving emotion. The principal phenomena demonstrated with use of this technique in monkeys with implanted electrodes were as follows:

(1) An inverse functional relationship was observed between sites for pleasure and sites for adversive emotion. Electrical stimulation of the septal region (an integral part of the brain's pleasure system) inhibited unit activity of the hippocampus and medial amygdala (part of the brain's adversive system) (Heath, Dempesy, Fontana, and Myers, 1978). Contrariwise, stimulation of sites in the adversive system (hippocampus, medial amygdala) inhibited activity of the pleasure system (septal region).

(2) Whereas stimulation of the paleocerebellum (fastigial nucleus and vermal cortex) facilitated unit activity in the pleasure system, it inhibited unit activity of sites in the adversive system, a finding that suggested the cerebellum functioned uniquely to modulate emotion (Heath, Dempesy, Fontana, and Fitzjarrell, 1980).

(3) Electrical stimulation of sites in the adversive system (hippocampus) activated units in the vermal cerebellum which, in turn,

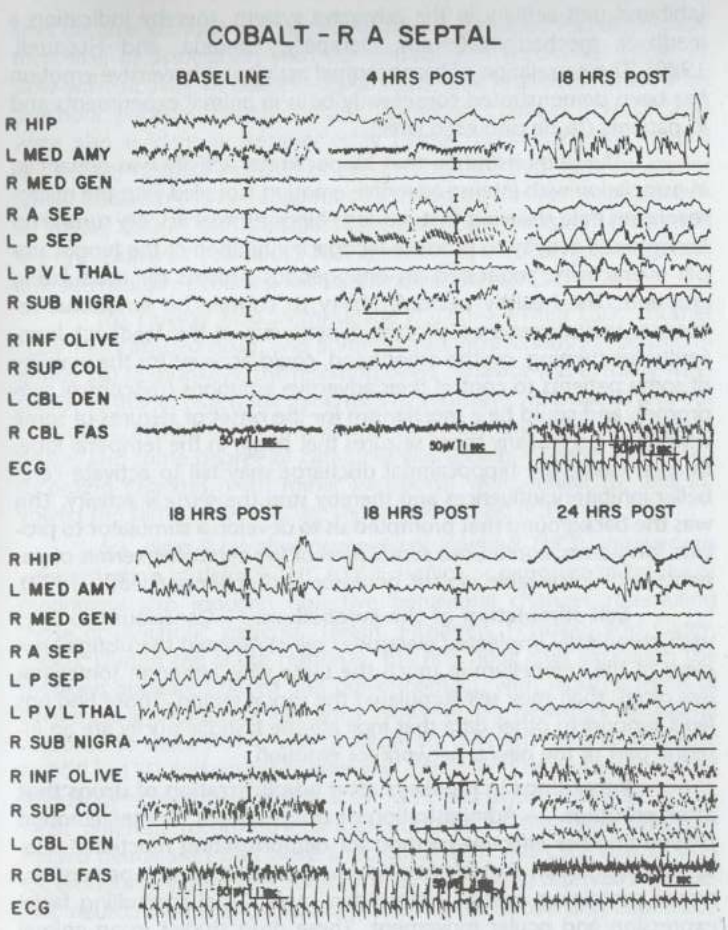

Figure 4. *Electroencephalograms from a Rhesus monkey before and after implantation of cobalt into the right anterior septal region. Note that the epileptiform activity originating in the septal region migrates to distal sites, including those affecting expression of the eyes and face (superior colliculus and inferior olive), the sensory relay nuclei (ventroposterior lateral thalamus) medial geniculate, and cerebellar nuclei), and to cell reservoirs for specific neurotransmitters (substantia nigra and locus coereleus).*

inhibited unit activity in the adversive system, thereby indicating a feedback mechanism (Heath, Dempesy, Fontana, and Fitzjarrell, 1980). The correlation of hippocampal activity with aversive emotion has been demonstrated consistently both in animal experiments and in patients (to be discussed later).

The demonstration that hippocampal activity was enhanced in association with intense adversive emotion, coupled with the microrecording data showing that induced hippocampal activity turned on Purkinje cell activity to produce feedback inhibition of the hippocampal overactivity, suggested an endogenous process for modulating emotion. The healthy person's ability to contain his emotional responses may depend on effective functioning of this feedback loop. Faulty functioning, on the other hand, could account for the inability of some patients to control their adversive emotions (dyscontrol syndrome), and could be a mechanism for the onset of seizures of some epileptics, particularly those seizures that begin in the temporal lobe. In such cases, the hippocampal discharge may fail to activate cerebellar inhibitory influences and thereby stop the seizural activity. This was the background that prompted us to develop a stimulator to provide long-term, continuous stimulation of the cerebellar vermis of patients with intractable violent behavior and epilepsy (Heath, 1977).

Self-stimulation of the cerebellum. — Conscious monkeys with chronically implanted electrodes self-stimulated the fastigial nucleus of the cerebellum in much the same way, although somewhat less often, than they self-stimulated the septal region. Those findings lend support to other data that indicate the fastigial nuclei are an integral part of the neural network for emotion.

Recordings in monkeys after administration of drugs that alter emotion. — Administration of drugs shown to alter emotion proved another effective method for demonstrating functional relations among brain sites for emotional expression, sensory perception, nuclei containing specific transmitters, and nuclei controlling facial expression and ocular movement. These drug studies in an animal model (the rhesus monkey with deep and surface electrodes) evolved from findings in deep-electrode patients of correlations between brain activity and various emotional states (see data under "Clinical Studies"). In the monkey, it was possible to implant electrodes into additional deep sites that could not be implanted safely in patients.

(a) *Phencyclidine.* — When phencyclidine (PCP), a drug commonly used by substance abusers, was administered to monkeys intramuscularly (0.25 mg/kg), profound changes occurred. The monkeys became tranquil and appeared dazed. Behavior was often catatonic-like, in association with abnormalities in recordings (spike or slow-wave activity, or both, in septal leads) that resembled those from psychotic patients (Heath, 1976a). Significant changes in recordings were also evident in sensory relay nuclei (particularly the medial geniculate, fastigial nucleus of the cerebellum, and ventroposterior lateral thalamus), in cell reservoirs for chemical transmitters (substantia nigra), and in sites that possibly influence expression reflected in the eyes (superior colliculus). Fast spindling in cortical recordings also characteristically occurred with administration of PCP.

(b) *Lysergic acid diethylamide (LSD).* — When LSD, another commonly abused drug, was administered intravenously (100 micrograms/kg) to monkeys, the resulting overt behavior was in many ways similar to that of psychotic patients. The monkeys were dazed and out of contact, staring blankly. Response to external stimuli was inappropriate, and some degree of catatonia was usually evident. Associated recording changes, with minor variations, were similar to, and involved the same brain sites as, those induced by PCP.

(c) *delta-9-tetrahydrocannabinol (delta-9-THC):* Intravenous administration of delta-9-THC (0.69 mg/kg) or exposure to smoke of marihuana also induced objective behavioral changes resembling those of psychotic patients (Heath, Fitzjarrell, Fontana, and Garey, 1980). During the acute response, the first hour after exposure, the monkeys appeared dazed and out-of-contact, with reduced levels of awareness and catatonic-like signs. However, the monkey's behavioral response to delta 9-THC was qualitatively different from its response to PCP or LSD and varied in intensity, depending on the amount and frequency of exposure to the active cannabis agent. Likewise, somewhat different recording changes occurred in the same interconnected neural sites that were affected by PCP and LSD, that is, sites for emotional expression, sensory relay nuclei, cell reservoirs for specific neurotransmitters, and brain stem nuclei subserving expression of the face and eyes.

The recordings shown in figure 5 are from a monkey that became profoundly catatonic after intravenous administration of delta-9-THC. The sharp spike and slow-wave activity in the septal region, reflected in the hippocampus, is similar to that of acutely psychotic patients. After monkeys had been regularly exposed to cannabis for three months, recording changes associated with mild apathy were continuously present in the form of ongoing spike and slow-wave activity, most pronounced in the hippocampus and amygdala. By the

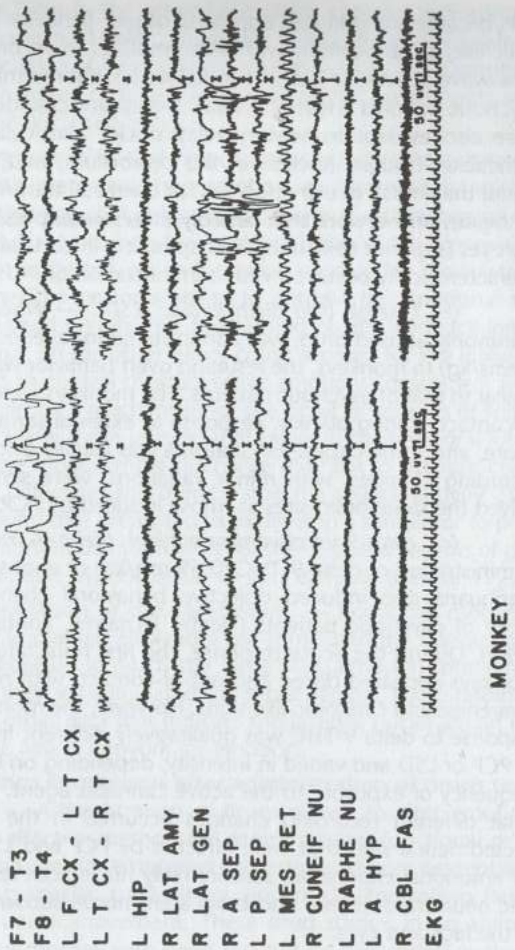

Figure 5. *Sample recordings obtained from a Rhesus monkey before (baseline) and at 14 minutes after 3.1 mg intravenous administration of delta 9-THC. Generalized slowing is evident in several leads. Associated with the monkey's catatonic behavior, theta activity occurred predominantly in the mesencephalic reticulum concomitant with spike activity in septal leads (similar to activity seen in psychotic patients).*

time exposure was discontinued at six to nine months, recording changes were permanent, persisting for an additional three months until the monkeys were killed.

As evidenced by the recording data obtained with administration of these various psychosis-inducing agents to the monkey (an extension of our work with patients), the animal models were particularly useful in demonstrating functional relations among those sites in the neural network that anatomic techniques had shown to be structurally related.

Relation of the Cortex to Subcortical Structures

As previously implied, much of the data we have gathered concerning the neural basis for emotion, sensory perception, and memory have focused on the role of subcortical structures implicated in these phenomena. That applies to animal data that have been reviewed thus far, as well as to data from patients to be presented here. Although our findings indicate that the fundamental neural mechanism for emotion is more readily demonstrated at subcortical sites, it is apparent that the cortex participates importantly by virtue of interconnections through pathways to and from subcortical sites, as well as by integrating incoming signals. The modulating role of the cortex is well documented in animal experiments and clinical observation, as reported by Mesulam (Mesulam, 1985) in his comprehensive review of the subject in 1985. Microrecordings in animals have provided valuable information, indicating that the cortex (particularly the frontal and parietal lobes) has a role (albeit less dramatic than that for subcortical sites) in processing sensory input and, more specifically, in demonstrating a relationship between sensory input and emotion (Ito, 1982; Kojima, 1980; Thorpe, Rolls, and Maddison, 1983). Because of the complexity of the cerebral cortex, however, it has been difficult to establish more precise correlations with behavior.

The techniques we used in intractably ill patients in the 1950s and 1960s, involving implantation of macroelectrodes over the brain's surface, failed to elucidate correlations between cortical activity and the behavioral phenomena of emotion, perception, and memory. Conclusions drawn about cortical function in emotional behavior that are based on results of stimulating focal cortical sites of epileptic patients undergoing various therapeutic procedures are questionable. In our studies of epileptic patients with deep and surface brain electrodes, we determined that behavioral effects of cortical stimulation were associated with spread of activity to distal subcortical sites.

Behavioral changes following lesions at specific cortical sites have been well documented. They provide some information concerning the manner in which these sites contribute to overall behavioral patterns. However, relating behavioral changes to activity at specific cortical sites on the basis of lesions is also imprecise. Changes cannot be attributed to cortical damage alone, as the lesions usually implicate subcortical sites and pathways as well. These data of behavioral changes with cortical lesions have nevertheless been useful in our attempts to establish correlations between brain function and behavior in persons in whom the brain is structurally intact.

In our studies, we have demonstrated consistent correlations between activity at precise subcortical nuclei and certain behavioral changes. Furthermore, anatomic studies in animals have shown that the nuclei affected have direct connections to some cortical sites. On the basis of our data, we have postulated that altered activity at subcortical sites affects the intact cortex to which they are connected and can result in behavioral changes similar to those seen with a lesion at the site.

The Frontal Cortex

Behavioral changes occurring with large lesions of the frontal lobe can be broadly classified as "a carefree lack of concern." Persons who have undergone such procedures (lobotomy, topectomy) are usually described as irresponsible, grandiose, childish, profane, slovenly, and facetious. Further, they lack judgement, initiative, drive, curiosity, and creativity. When lesions have been circumscribed and confined principally to the cortex, as with prefrontal ablations, the detectable deficits are less apparent (Mettler, 1949). It is generally agreed that prefrontal cortical lesions do not grossly affect memory or sensory motor functions. Lesions of the orbital-frontal and anterior-medial regions of the frontal lobe have reportedly resulted in more disturbances in affective responsiveness, whereas lesions of the dorsolateral prefrontal regions, particularly the more caudal sites (area VIII), result in more profound reasoning impairment.

In their reports, associates of the Columbia-Greystone project noted that foresight was reduced and painful affect associated with memories (depression, proneness to react with rage and fear) was strikingly diminished after prefrontal ablation (Heath, Weber, and Crandell, 1949). That would account for some of the overall favorable clinical responses to the surgical procedure, particularly those obtained in patients with depression, who anticipated the future in terms of despair and anger. Landis (1949) attributed the behavioral changes to diminished inhibitory input from the frontal lobes, which led to increased dominance by the parietal lobes and greater dependency on the immediate social environment consequent to sensory input. The behavioral effects of frontal lobe cortical lesions are more subtle, however, than the profound changes in emotionality after lesioning or stimulation of the subcortical sites in the neural network for emotion.

The Parietal Cortex

Impairment of many somatosensory functions, including the ability to accurately localize pain, temperature, touch (two-point discrimination) and position-vibration, and to identify objects by shape and size (astereognosis), occurs with lesions of the anterior aspect of the parietal cortex. Lesions of the larger, more posterior aspects of the parietal lobes, however, profoundly affect behavior through altering functions that we have theorized to be bridges between mind and brain, namely, emotion, sensory perception, and memory. The basic disturbance in patients with parietal lobe damage is an inability to summate a series of "spatial impressions" (Denny-Brown, Meyer, and Horenstein, 1952; Adams and Victor, 1985). They are unable to integrate somatosensory and other sensory input (visual and auditory), requisites for creating a self-image that is separate and distinct in relation to the outside. Patients with lesions of the parietal cortex show this impairment in such clinical disorders as Gerstmann's syndrome, amorphosynthesis, and ideomotor apraxia (Denny-Brown, Meyer, and Horenstein, 1952). From these findings with lesions, Adams and Victor (Chapter 21) have speculated that psychiatric disorders characterized by impaired sense of self may be manifestations of disturbances of the body environmental schema — functions localized in the parietal lobe. In the absence of structural abnormalities in psychiatric disorders, it is assumed that these symptoms result from altered function of the parietal lobe.

The significant role of self in understanding mind-brain relationships, and the importance of proprioceptive-vestibular-kinesthetic input (a function of the paleocerebellum) to its development were discussed in a previous section. Our demonstration in the cat of a direct pathway from the paleocerebellum to the sensory cortex provides an anatomic basis for the two structures functioning as a unit in establishing the physical basis for self (Harper and Heath, 1974). Changes in emotion consistently correlate with changes in activity of the paleocerebellum. Thus, input from the vestibular system through

the paleocerebellum to the sensory-integrating parietal cortex can be considered a functioning unit subserving a conscious awareness of self. Altered activity in the form of spike and slow-waves in the paleocerebellum, when correlated with psychosis characterized by profound distortions of self-image, illustrates the role of this functioning unit as a determinant of mental activity.

The Temporal Cortex

From the study of the effects of lesions, the temporal cortex is recognized as the area that receives and integrates auditory signals. In contrast to circumscribed unilateral lesions, bilateral lesions of the temporal cortex, particularly when parts of the hippocampus are involved, result in profound disturbances in emotion, learning, and memory, namely, the Kluver-Bucy syndrome.

In patients with deep electrodes, we have demonstrated significant correlations between changes in activity in deep temporal lobe nuclei, particularly the hippocampus and amygdala, occasionally reflected in surface cortical recordings, and altered emotion. When patients with discharging epileptic foci of the temporal cortex display severely disrupted emotion — even psychotic behavior — it is the result of spread of the aberrant activity to subcortical sites, rather than from the activity at the cortical level (to be discussed in a later section). We have assumed that auditory hallucinations are probably the result of perturbation of the receptive area for auditory signals in the temporal cortex, since we have correlated auditory hallucinations with recording changes in subcortical auditory pathways at the medial geniculate that project to the auditory cortex.

The Occipital Cortex

Nonspecific changes have been recorded from macroelectrodes over the occipital cortex during periods of profound emotion. The occipital cortex contains the primary receptive area for visual impulses that are meaningfully integrated in the association areas of the occipital lobe. We speculate that visual hallucinations result from perturbation of the occipital cortex by altered activity from subcortical nuclei in the visual pathways. This speculation is based on recording data from patients in whom changes in activity in the lateral geniculate, which projects to the visual cortex, are correlated with the presence of visual hallucinations.

Correlation of Deep and Surface Recordings with Emotional Behavior

The Patient Population

Since 1950, when we first used deep electrode techniques in the treatment of intractably ill patients, our clinical studies have paralleled animal studies. The findings in patients have suggested experiments in animals, and the results in animals have inspired new techniques for use in patients. Unlike animals, patients were capable of reporting their thoughts and feelings and were fully conscious during the deep-electrode therapeutic studies. The subjective data gathered from them, in correlation with their objective data, significantly augmented the objective data that could be obtained from animals. As techniques were improved, electrodes could be left in precise position in the brain for several months up to two years, thus permitting collection of data during various clinical cycles of a patient.

Over the years, the primary aim of our studies in specially selected, intractably ill patients has been alleviation of disabling signs and symptoms of disorders that failed to respond to all conventional treatment. The results obtained with therapeutic use of deep brain electrodes and surface cerebellar stimulations have been described previously (Heath, 1954, 1964a, 1964b, 1975, 1976a, 1977). Data presented here, gathered during therapeutic procedures, are those that contribute to the main theme of establishing relations between the brain and behavior. Toward that end, the focus will be on the establishment of brain correlates for emotion, perception, and memory, phenomena considered to be significant in the understanding of the mind, and on ways that have helped to elucidate schizophrenia and epilepsy and point the direction for additional investigations of those specific illnesses.

Our data were gathered from two series of patients. The first comprised 66 patients implanted with deep-brain electrodes, some of whom also had cannulas implanted into precise deep-brain regions for introduction of chemicals. Because animal studies indicated that stimulation and ablation of sites in the neural circuitry for emotion profoundly influenced stress chemistry, we included in that series a few patients with diagnoses of rheumatoid arthritis and cancer. Another motivation for including them, based on our findings that electrical stimulation to the septal region induced pleasure and that pleasure and pain were in inverse relation, was the hope that we could relieve their intractable pain. Two patients with Parkinson's disease

were also included in the first series after studies showed that brains of patients with Parkinson's disease had a depletion of dopamine and norepinephrine. The second series comprised 44 patients, who had electrode arrays placed over the vermis cerebellum for continuous stimulation.

Brain Mechanisms in Pleasure

When patients with deep electrodes had pleasurable feelings, whether spontaneous or induced, they were invariably associated with changes in activity of the septal region and, at times, of the dorsal lateral amygdala. If the pleasure intensified, changes also occurred in recordings of one or more of the sensory relay nuclei. Those implanted in patients were the deep cerebellar nuclei, medial and lateral geniculates, and the somato-sensory thalamus. The recording changes that occurred in the sensory relay nuclei during emotional arousal were essentially the same, whether the emotional state of the patient was pleasurable or adversive. On rare occasions, the altered activity of deep structures was reflected in recordings at the temporal cortex and at frontal and occipital sites. Scalp recordings did not reflect the change.

Spontaneous pleasure elicited during interview. — Recording changes that occurred in the septal region, lateral amygdala, and deep cerebellum while patients were being interviewed and recalling happy events seemed to correlate roughly with the magnitude of pleasure engendered by the recollection. The more intense the pleasure elicited, the more dramatic the recording changes. Even minimal changes, however, were consistent and replicable, and in one study they were substantiated by computer analysis (Heath, Cox, and Lustick, 1974).

Pleasure induced by immediate events. — Recording changes associated with current happenings were likewise commensurate with the degree of pleasure elicited. They were dramatic in a patient who became sexually aroused as he looked at an explicitly sexual movie film (Fig. 6). The changes were similar, but of shorter duration than those recorded when the same patient achieved orgasm during heterosexual intercourse (Heath, 1972a).

That study, part of an extensive therapeutic program requested by the patient to try to alter certain sexual patterns he had developed, was conducted in such a way that his privacy and that of his partner was fully protected (Heath, 1972a). They were alone in a soundproof room; the recording equipment was in an adjacent room.

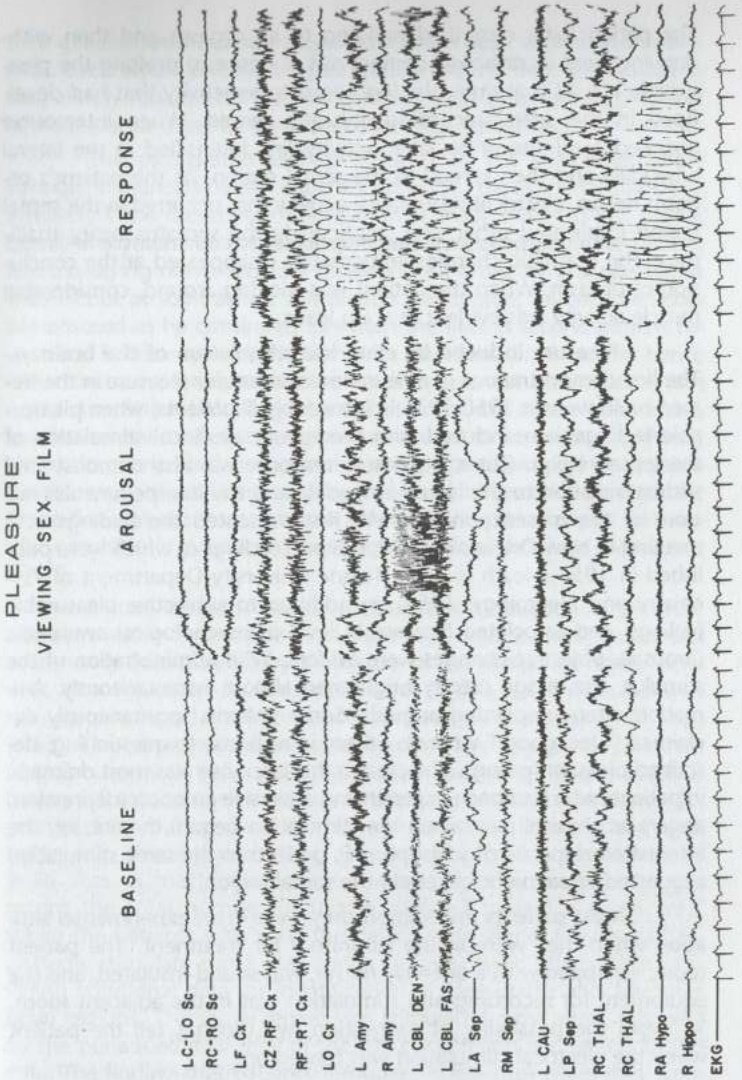

Figure 6. *Deep, cortical, and scalp electroencephalograms obtained from a patient before (baseline) and while he watched a sexual movie film.*

The patient later described building to an orgasm and then withdrawing from intravaginal contact out of desire to prolong the pleasurable act. At that time, the high-amplitude activity that had developed in the septal recording abruptly ceased. When intercourse resumed a minute or so later, activity first intensified in the lateral amygdala and then spread to the septal region. As the patient's orgasm began, electrical seizural-like activity that occurred in the septal region implicated other sites, particularly the somatosensory thalamus. The dramatic changes immediately disappeared at the conclusion of orgasm. When the patient was moving around, considerable muscle activity was evident in scalp leads.

Pleasure induced by electrical stimulation of the brain. — The first demonstrations of a neural mechanism for pleasure in the human brain were in 1950-1951 in intractably ill patients, when pleasurable feelings were induced with therapeutic electrical stimulation of the septal region. (Later, a pleasure response was also demonstrated with stimulation to the lateral amygdala and the interpeduncular nucleus of the mesencephalon.) We first presented the findings at a meeting in New Orleans in 1952, the proceedings of which were published in 1954 (Heath and the Tulane University Department of Psychiatry and Neurology, 1954). In addition to subjective pleasurable feelings, and associated increase in level of psychological awareness (arousal), objective changes were evident. With administration of the stimulus, the visage usually brightened almost instantaneously. Animation often supplanted anguish. Some patients spontaneously exclaimed "I feel good," whereas others, in response to questioning, described pleasant feelings. The pleasurable response was most dramatic in patients who had been experiencing adversive emotion (depression, anger) or physical pain when the stimulation began. In contrast, the attenuated response of schizophrenic patients to the same stimulation suggested impairment of cells in the septal region.

Most patients understood they were in an experimental situation when they were in the laboratory for treatment. The patient room, equipped with a one-way mirror, was sound-insulated, and the equipment for recording and stimulation was in the adjacent room. To avoid the possibility of suggestion, we did not tell the patient when the electrical stimulation was turned on.

Although descriptions by the patients of their response to the stimulation was usually limited to "I feel good . . . it must have been something you did," a striking change occurred in attitude. The subjects were much more positive toward the people around them and

their general surroundings. Any conversation dealt with pleasant subjects. Even when pressed to give details of how they felt, however, they simply repeated "I just feel good." (Most of us would probably be hard put to describe pleasurable feelings otherwise.)

The pleasurable feelings induced by the stimulation were strongly influenced by the patient's prevailing motivational state. For instance, if the therapeutic stimulation was administered just before lunch, enjoyment of the meal was notably enhanced. One patient was displaying only moderate interest in an erotic film he was being shown, but as soon as the stimulation was begun, he became sexually aroused as he continued to watch the film. A second patient responded in the same way to the same situation. On the other hand, when the same two patients were not in a sexual motive state, the septal stimulation induced pleasure but not sexual arousal. Therefore, unless a sexual motive state existed as a result of an external (viewing an erotic movie film) or internal stimulus (psychological or physical need), sexual arousal was not physically evident (erection or orgasm). These findings are in contrast to published reports of septal stimulation consistently producing erection in squirrel monkeys (MacLean, 1962).

In our demonstrations in patients of induction of pleasure and alertness with stimulation of the septal region, the stimulus was customarily administered by a member of the treatment team. However, after the report by Olds and Milner (1954) of self-stimulation in rats, we developed a self-stimulator for use by a few patients (Heath, 1963). The transistorized, self-contained unit generated a preset train of bidirectional stimulus pulses (0.2 msec duration, 100 per second) lasting 0.5 second each time one of the three control buttons was depressed. Each button directed the pulse train to a different deep electrode pair, thereby permitting the patient-operator a selection of brain sites. A mechanical counter was coupled to each button to record the total number of stimuli directed toward a given area. When the patients who used the device were alone, they would repeatedly stimulate some sites and steadfastly avoid others, thus providing additional data for identification of pleasurable and adversive brain regions. The septal region was stimulated most often, followed by the periaqueductal gray of the mesencephalon and lateral amygdala. The finding that patients stimulated these sites when they were alone (as indicated by the mechanical counter), as well as when they were with others, suggested that the stimulation in itself produced pleasure and that their positive reaction to their environment was probably the result of their altered feelings.

In one patient with deep electrodes, a severely impaired chronic schizophrenic, we approximated the animal self-stimulation techniques (Bishop, Elder, and Heath, 1963). He had had no observable response to stimulation of the septal region when the stimulus was administered by a member of the treatment team. It was therefore noteworthy that, when he was equipped with a self-stimulator, this intractably ill patient self-stimulated pleasure sites well beyond the controlled rate of stimulation. Even then, however, he failed to show a change in affect (somewhat typical of schizophrenic patients). He sometimes persistently pushed the button after the current was discontinued, an action that contrasted sharply with stimulation of an adversive site, when patients were immediately aware of the start and end of the stimulation. In less impaired schizophrenics and in the nonschizophrenic patients, objective changes in appearance and subjective reports of good feelings usually occurred within a few seconds to a minute after onset of stimulation and then persisted for hours to days. Compulsive self-stimulation characteristic of the pattern of stimulation in animals, sometimes supplanting such pleasures as intake of food, was not observed in the patients.

When pleasure sites of the brain were stimulated, whether the stimulation was passive (administered by a member of the treatment team) or self-administered (with use of the self-stimulator), changes in the patient's feelings were reflected in shifts in thought content and, consequently, in the associations he reported. Even though repetitious stimulations of the same pleasure site induced similar "good feelings," the content often varied. It was influenced by current happenings, as well as by thoughts the patient had when the stimulus was administered. When a patient recalled pleasurable events during his associations, they were not so-called "experiential events," that is, a record of stream-of-consciousness being replayed, as speculated by Penfield (Penfield, 1975). Instead, they were past events that had occurred in a pleasurable context — a selective memory recall.

Pleasure induced by drugs. — Deep and surface recordings were obtained from a number of patients when they were under the influence of pleasure-inducing drugs. Patients who participated in these studies, all of them previous drug users, gave informed consent. The findings were helpful in further establishing correlations between pleasurable feelings and changes in recordings that occurred principally in the septal region.

(a) *Marihuana.* — The acute response that patients had when smoking marihuana differed notably from the response of monkeys exposed to marihuana smoke (Heath, 1972a; Heath, Fitzjarrell, Fontana, and Garey, 1980). The patients displayed both subjective and objective evidence of euphoria. Their giggling, joking, and descriptions of "rushes" of pleasurable feelings correlated with recording changes in the form of bursts of high-amplitude, slow activity or fast, high-amplitude spindling, or both, occurring principally in the septal region (Fig. 7). In contrast, the monkeys, as previously described, were profoundly reduced in level of awareness, with observable behavioral signs resembling those seen in psychotic patients (catatonic stupor), and with deep brain recordings similar to those obtained from deep sites of psychotic patients.

(b) *Cocaine hydrochloride.* — Two patients, B-11 and B-12, had cocaine hydrochloride administered intramuscularly (1.5 mg) or in a ten percent solution of intranasal spray (one to two ml) (Heath, 1964a). In both subjects, a feeling of well-being was associated with changes in recordings in the form of increased spindling, principally in the lateral amygdala.

(c) *Demerol.* — When 100 mg of demerol was administered intramuscularly to each of two patients, B-10 and B-12, they said they felt better, and both showed evidence of a mild feeling of well-being (Heath, 1964a). The recordings of one subject were similar to those obtained from him during spontaneous relaxation. The recordings of the other subject showed a significant increase of focal slowing from the septal region.

(d) *Morphine sulfate.* — Intramuscular administration of morphine sulfate, in doses ranging from 10 to 20 mg, produced minimal clinical and recording changes in patients (Heath, 1964a). The subjects relaxed, but they were certainly not euphoric. Recordings were typical of a relaxed state.

Pleasure induced by direct chemical stimulation of the brain. — A number of patients with deep brain electrodes also had cannulas implanted stereotaxically into specific sites for introduction of putative chemical transmitters directly into the brain (Heath and Founds, 1960; Heath and deBalbian Verster, 1961). The cannula, developed in our laboratory, could be accurately implanted and fixed to remain in position for long-term use. It met the essential criteria of localization, minimal damage to brain tissue, asepsis, flushing (to prevent cross-contamination of one compound with another), and volumetric accuracy. (This is the same cannula that was used in the animal studies previously described.) Our rationale was that the effects of

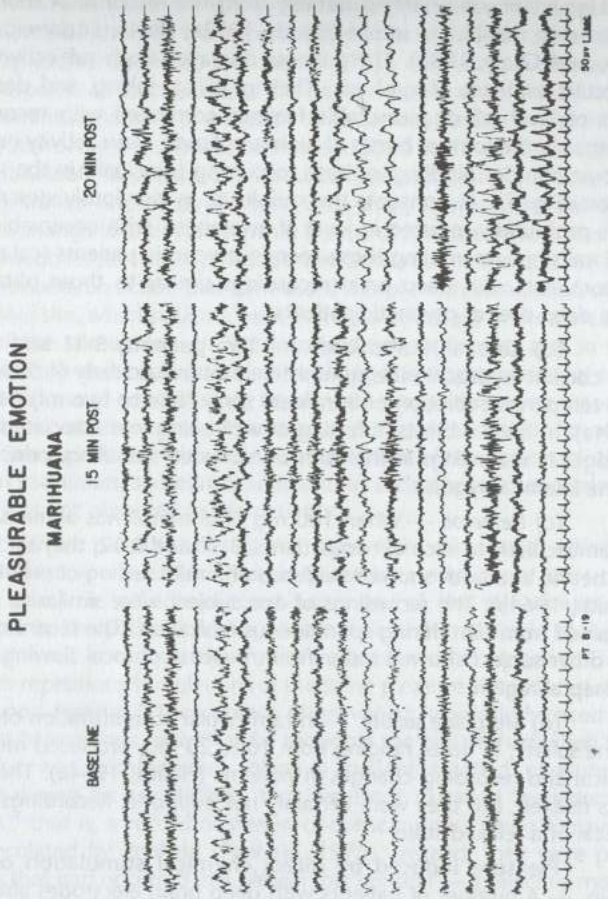

Figure 7. *Deep and surface recordings obtained from Patient B-19 just before he smoked marihuana (baseline) and at 15 minutes and 20 minutes after smoking it. Septal recordings show high-amplitude, slow-wave activity and intermittent fast spindling in association with spindling in the cerebellum.*

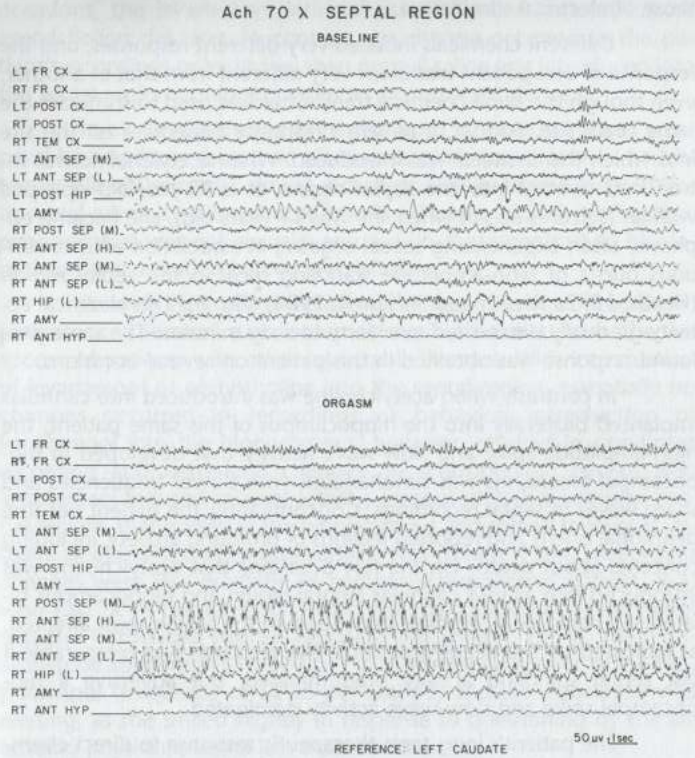

Figure 8. *Recordings obtained from Patient B-5 during an interictal symptom-free period (baseline) and during maximal effects of the introduction of acetylcholine into the septal region bilaterally. In the baseline recording, the spike and slow-wave activity in the hippocampal and amygdala leads (not reflected in surface leads) is characteristic of interictal recordings of epileptic patients. When the patient is orgasmic following administration of the acetylcholine, high-amplitude discharges are focal in the septal region. Concurrently, there is an increase in frequency and reduction of amplitude in recordings from the cortex, and a decrease in spiking and slow-wave activity in the hippocampus and amygdala.*

chemical stimulation might be more beneficial and long-lasting than those of electrical stimulation.

Different chemicals induced very different responses, and the response of one patient was often very different from that of another, even though the same chemical transmitter was used to stimulate the same brain site. Further, a patient's response depended on the site into which the chemical was introduced. When acetylcholine was introduced directly into the septal region of a 33-year-old epileptic woman (seizures began when she was 11 years old), she became euphoric, often experiencing sexual orgasm, in association with continuous bursts of high-amplitude spindling focal in the septal region (Heath, 1972a; Heath and Fitzjarrell, 1984) (Fig. 8). This electrical activity gradually diminished over forty to sixty minutes. The same profound response was obtained in this patient on several occasions.

In contrast, when acetylcholine was introduced into cannulas implanted bilaterally into the hippocampus of this same patient, the high-amplitude spike and slow-wave activity that developed in hippocampal recordings was simultaneous with slower frequencies and sharp waves in septal recordings. Concomitantly, the patient became delusional briefly and reported feelings of profound anxiety, including concerns about death. On the few occasions that acetylcholine was introduced into all four cannulas (septal region and hippocampus bilaterally), her clinical response depended on the region most affected, as indicated by the deep recordings. Her response was pleasurable if fast septal spindling activity predominated, but adversive if hippocampal spike and slow-wave activity dominated.

The patient's long-term therapeutic response to direct chemical stimulation of the brain was gratifying. During the year preceding electrode and cannula implantation, various combinations of anticonvulsant drugs (Phenobarbital, Dilantin, Equanil, Mesantoin, Mebaral, Mysoline) had failed to control her seizures, which averaged eight per week. After acetylcholine treatment to the septal region, seizures stopped. All anticonvulsant medications were discontinued and, for ten weeks, acetylcholine was introduced weekly into the septal region. For six months thereafter, she remained seizure-free. She then developed several seizures, and phenytoin sodium (100 mg t.i.d.) was prescribed. During the next ten years (after electrodes and cannulas were removed), the patient averaged only one to two seizures a year.

Before acetylcholine treatment was begun in this patient,

levarterenol was introduced into the septal region. On one of three occasions, the levarterenol induced essentially the same effects as acetylcholine did later. In contrast, no change occurred in the patient's recordings or behavior when normal saline was introduced into the septal region or hippocampus as a control substance.

In a man diagnosed as having both schizophrenia and temporal lobe epilepsy (based on electroencephalograms only — no history of clinical seizures), similar recording activity developed with intraseptal administration of acetylcholine (Heath, 1964a). He became euphoric, but was not sexually aroused, in sharp contrast to his depression and agitation before acetylcholine.

As with electrical stimulation, the response of schizophrenic patients to chemical stimulation differed somewhat from the response of patients with other intractable illnesses. With introduction of levarterenol or acetylcholine into the septal region, essentially no changes occurred in recordings or behavior. Introduction of levarterenol into the hippocampus, however, resulted in significant recording and behavioral changes. In schizophrenic patient B-9, levarterenol induced seizural activity, associated with a complex partial seizure, that started in the hippocampus and spread to involve virtually all implanted deep and surface sites (Heath, 1964). Recording changes were less dramatic in another schizophrenic patient, B-3, who had been catatonic for many years and in whom levarterenol was also introduced into the hippocampus (Heath, 1964). The high-amplitude spindling (150-200 uv) that developed focally in the hippocampus (frequency of 12-15 per second) and the associated mild alerting, as she smiled slightly in response to questioning by the attending physician, lasted less than 30 minutes.

On two occasions, introduction of acetylcholine into the lateral amygdala of a schizoaffective patient, B-22 (J.C.), resulted in focal spindling at that site and associated feelings of pleasure, the changes lasting about an hour. A third treatment a few days later, however, resulted in seizural activity that began in the lateral amygdala at the onset of a clinical grand mal convulsion, spread to the cingulate gyrus, and then involved the entire brain. We had no explanation for the variation in response.

In contrast to the pleasurable response elicited when acetylcholine was introduced into the basal forebrain, and the adversive response induced with introduction of catecholamines directly into the hippocampus, introduction of catecholamines into the putamen or caudate nucleus of Parkinsonism patients produced no behavioral

changes. This finding, coupled with the observation that electrical stimulation of the striatum produced no notable behavioral changes, suggests that the striatum is not part of the circuitry for emotion. The Parkinsonism patients thus served as control for the behavioral effects of chemical stimulation.

Inverse relationship of pain and pleasure: physiologic-clinical correlations. — The reciprocal relationship of pain and pleasure is a consistent clinical observation. If a person is experiencing adversive feelings — profound rage or fear, physical pain — pleasurable feelings are extinguished. In turn, when pleasurable feelings dominate, adversive feelings diminish. When pleasure takes over, pain disappears. When pain takes over, pleasure disappears.

Physiologic findings in our laboratory substantiate the clinical observation. When the brain's pleasure system was activated by electrical or chemical stimulation, adversive feelings were abolished. Contrariwise, when the neural system for adversive emotion was activated, pleasurable feelings were abolished. This reciprocal relationship was also evident in the deep brain recordings. Spontaneous or induced activation of the pleasure system was associated with suppressed activity of the adversive system. Contrariwise, spontaneous or induced activation of the system for adversive emotion resulted in inhibition of activity of the brain's pleasure system. This inverse relationship, demonstrable in a variety of clinical states, corresponds with animal data cited previously. In cats and monkeys, unit recordings showed the same inverse relationship between pleasure and pain sites in the central nervous system (Heath, Dempesy, Fontana, and Fitzjarrell, 1980).

Emotional pain: The results of electrical or chemical activation of the brain's pleasure system were previously illustrated. Symptoms such as depression, anxiety-fear, and intense rage were invariably eliminated when pleasure sites were stimulated.

Intractable physical pain: Physical pain of various origins was alleviated promptly and dramatically by electrical stimulation of sites in the brain's pleasure system. The pain of metastatic carcinoma, uncontrolled by high doses of morphine, for example, was relieved for as long as a week after stimulation of the septal region for 15 minutes (100 Hz, 3-5 milliamperes) (Heath, Peacock, Monroe, and Miller, 1954). For seven months before she died, Patient A-6 (L.W.), who had carcinoma of the uterus, received electrical stimulation of the septal region at intervals of one day to one week (depending on control of the pain). During that period, she was essentially free of pain and required no further analgesic medication.

Physical pain was also alleviated in patients with intractable rheumatoid arthritis. On the basis of data from animal experiments, which suggested a direct neural mechanism that influenced the biochemical system for stress and, specifically, that activated corticosteroid release, we speculated that stimulation of the septal region could be therapeutic in patients with rheumatoid arthritis whose symptoms persisted after treatment with cortisone and gold, as well as the other standard treatments. Accordingly, we used repeated stimulation to the septal region to treat two patients who were suffering from intractable pain and inflamed joints, and notable improvement occurred. In both, pain was relieved and inflammation of the joints significantly reduced.

Brain Mechanisms in Adversive Emotion

Many of the same techniques used to demonstrate the brain's pleasure system were used to demonstrate the adversive system. Emergency emotion was correlated with activity in the hippocampus, cortical medial amygdala, cingulate gyrus, deep nuclei of the cerebellum (particularly, midline paleocerebellum), and sites in the mesencephalic tegmentum. Simultaneous changes often occurred in sensory relay nuclei, where they were at the same sites and of the same nature as those recorded during pleasurable emotion.

Spontaneous adversive emotion elicited during interview. — The directed interview was an effective method for demonstrating the interrelation of brain activity and adversive emotion. The correlation was most dramatic when a patient recalled a painful experience. On such occasions, associated recording changes often materialized before the patient's adversive emotional state was clinically obvious to the interviewer. A high-amplitude spindle (150-200 microvolts) characteristically appeared in the hippocampus (11 to 14 per second), lasted one-half second to three seconds, and reappeared at intervals of three to 20 seconds. Such bursts were consistently associated with an adversive emotional state.

Examples of this phenomenon repeatedly occurred in Patient A-10 (J.M.), who participated in our studies in 1951 (Heath, Peacock, Monroe, and Miller, 1954). When interviews of him were directed by a change of subject, the spindles in his recordings could literally be turned on and off. If he was influenced to recall past incidents that had made him rageful, the spindles in the hippocampus appeared, whereas they promptly disappeared if he was asked to solve a math-

changes. This finding, coupled with the observation that electrical stimulation of the striatum produced no notable behavioral changes, suggests that the striatum is not part of the circuitry for emotion. The Parkinsonism patients thus served as control for the behavioral effects of chemical stimulation.

Inverse relationship of pain and pleasure: physiologic-clinical correlations. — The reciprocal relationship of pain and pleasure is a consistent clinical observation. If a person is experiencing adversive feelings — profound rage or fear, physical pain — pleasurable feelings are extinguished. In turn, when pleasurable feelings dominate, adversive feelings diminish. When pleasure takes over, pain disappears. When pain takes over, pleasure disappears.

Physiologic findings in our laboratory substantiate the clinical observation. When the brain's pleasure system was activated by electrical or chemical stimulation, adversive feelings were abolished. Contrariwise, when the neural system for adversive emotion was activated, pleasurable feelings were abolished. This reciprocal relationship was also evident in the deep brain recordings. Spontaneous or induced activation of the pleasure system was associated with suppressed activity of the adversive system. Contrariwise, spontaneous or induced activation of the system for adversive emotion resulted in inhibition of activity of the brain's pleasure system. This inverse relationship, demonstrable in a variety of clinical states, corresponds with animal data cited previously. In cats and monkeys, unit recordings showed the same inverse relationship between pleasure and pain sites in the central nervous system (Heath, Dempesy, Fontana, and Fitzjarrell, 1980).

Emotional pain: The results of electrical or chemical activation of the brain's pleasure system were previously illustrated. Symptoms such as depression, anxiety-fear, and intense rage were invariably eliminated when pleasure sites were stimulated.

Intractable physical pain: Physical pain of various origins was alleviated promptly and dramatically by electrical stimulation of sites in the brain's pleasure system. The pain of metastatic carcinoma, uncontrolled by high doses of morphine, for example, was relieved for as long as a week after stimulation of the septal region for 15 minutes (100 Hz, 3-5 milliamperes) (Heath, Peacock, Monroe, and Miller, 1954). For seven months before she died, Patient A-6 (L.W.), who had carcinoma of the uterus, received electrical stimulation of the septal region at intervals of one day to one week (depending on control of the pain). During that period, she was essentially free of pain and required no further analgesic medication.

Physical pain was also alleviated in patients with intractable rheumatoid arthritis. On the basis of data from animal experiments, which suggested a direct neural mechanism that influenced the biochemical system for stress and, specifically, that activated corticosteroid release, we speculated that stimulation of the septal region could be therapeutic in patients with rheumatoid arthritis whose symptoms persisted after treatment with cortisone and gold, as well as the other standard treatments. Accordingly, we used repeated stimulation to the septal region to treat two patients who were suffering from intractable pain and inflamed joints, and notable improvement occurred. In both, pain was relieved and inflammation of the joints significantly reduced.

Brain Mechanisms in Adversive Emotion

Many of the same techniques used to demonstrate the brain's pleasure system were used to demonstrate the adversive system. Emergency emotion was correlated with activity in the hippocampus, cortical medial amygdala, cingulate gyrus, deep nuclei of the cerebellum (particularly, midline paleocerebellum), and sites in the mesencephalic tegmentum. Simultaneous changes often occurred in sensory relay nuclei, where they were at the same sites and of the same nature as those recorded during pleasurable emotion.

Spontaneous adversive emotion elicited during interview. — The directed interview was an effective method for demonstrating the interrelation of brain activity and adversive emotion. The correlation was most dramatic when a patient recalled a painful experience. On such occasions, associated recording changes often materialized before the patient's adversive emotional state was clinically obvious to the interviewer. A high-amplitude spindle (150-200 microvolts) characteristically appeared in the hippocampus (11 to 14 per second), lasted one-half second to three seconds, and reappeared at intervals of three to 20 seconds. Such bursts were consistently associated with an adversive emotional state.

Examples of this phenomenon repeatedly occurred in Patient A-10 (J.M.), who participated in our studies in 1951 (Heath, Peacock, Monroe, and Miller, 1954). When interviews of him were directed by a change of subject, the spindles in his recordings could literally be turned on and off. If he was influenced to recall past incidents that had made him rageful, the spindles in the hippocampus appeared, whereas they promptly disappeared if he was asked to solve a math-

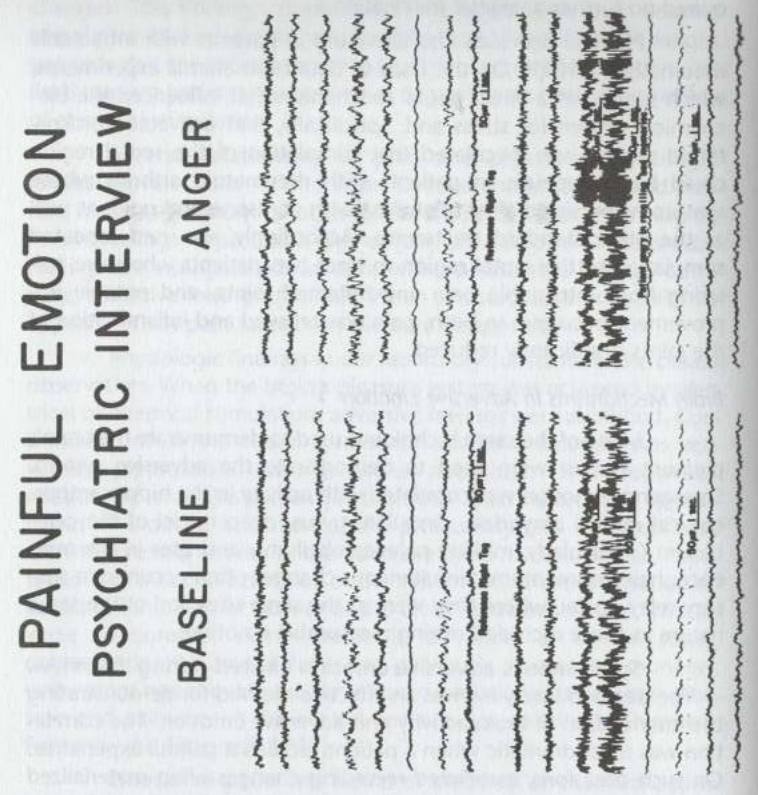

Figure 9. *Deep and surface recordings obtained during an interview with Patient A-25 (J.H.) when he was having "bad memories" that evoked anger.*

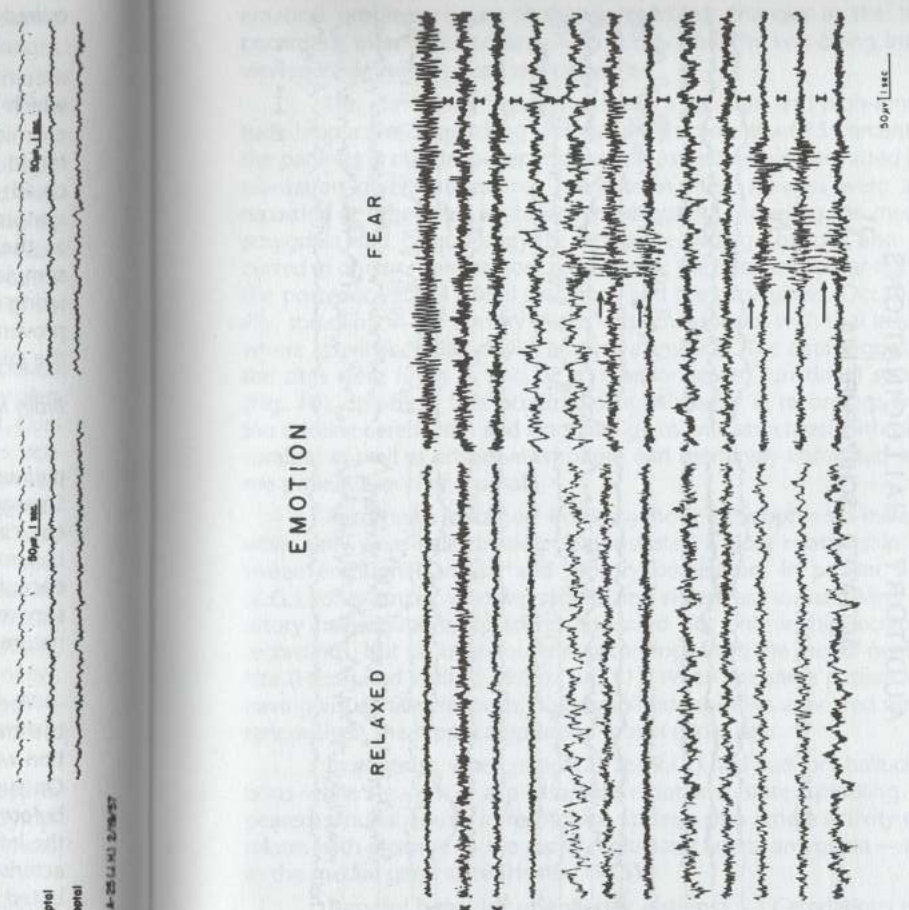

Figure 10. *Deep and surface recordings obtained from Patient B-22 during a relatively relaxed period and during an interview characterized by emergency emotion.*

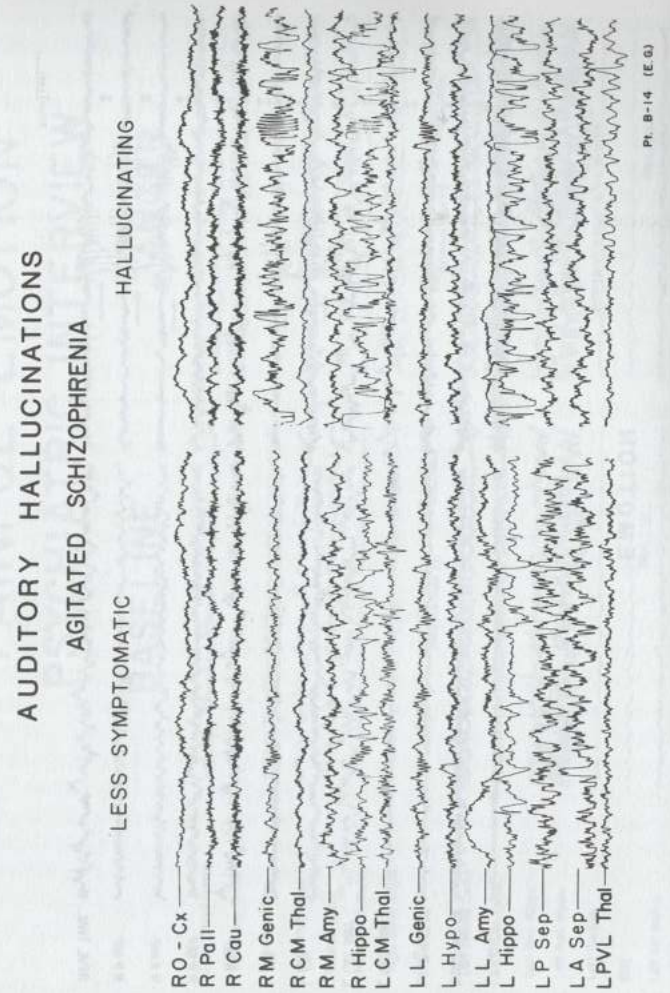

Figure 11. *Deep and surface recordings from schizophrenic Patient B-14 when he was relatively calm, contrasted with recordings when he was agitated and hallucinating.*

ematical problem. Figure 9 shows recording changes in the hippocampus of another patient, A-25 (J.H.), when he was being interviewed while having "bad memories."

The correlation between adverse emotion and high-amplitude hippocampal spindling was evident in more than 75 percent of the patients in our deep-electrode series. As techniques permitted implantation of electrodes into more brain sites, spindles were also recorded at other sites in the adverse system, including the medial amygdala and cingulate gyrus. Similar recording changes also occurred in one or more sensory relay nuclei: the deep cerebellar nuclei, the posterior ventral lateral thalamus, and the geniculates. Occasionally, spindling in the sensory nuclei was synchronous with that in sites where activity correlated with adverse emotion. The data suggested the sites were firing as part of an interconnected functional system (Fig. 10). Spindling that occurred simultaneously in recordings from the midline cerebellum and cingulate gyrus was associated with pleasurable, as well as adverse emotion, and seemingly correlated with the patient's level of arousal.

Recordings obtained from psychotic schizophrenic patients while they were hallucinating demonstrated a close relationship between emotional arousal and sensory perception. In patient B-14 (E.G.), for example, who was rageful and violent as he was having auditory hallucinations, spindling appeared not only in hippocampal recordings, but simultaneously in recordings from the *medial* geniculate (Heath and Walker, 1985) (Fig. 11). When the same patient was having visual hallucinations, high-amplitude spindles appeared simultaneously in the hippocampus and *lateral* geniculate.

In contrast, when patient B-16 (R.D.) had auditory hallucinations while he was in a pleasurable emotional state, spindling appeared simultaneously in recordings at deep sites where activity correlates with pleasure — the septal region and lateral amygdala — and in the medial geniculate (Heath, 1975).

Rageful behavior of epileptic patients. — Correlations with recording changes occurred at these same sites of epileptic patients when violent-aggressive behavior developed as a consequence of the brain abnormalities (structural or metabolic?) that caused their seizures (Heath, 1962, 1981, 1982; Mickle and Heath, 1957). During these periods, high-amplitude spindling, along with spike and slow-wave activity, was predominant in the hippocampus and medial amygdala, sites where changes occurred in nonepileptic patients in association with adverse behavior. When profound adverse emotion developed in the form of fear or rage in another epileptic patient,

spiking activity in the amygdala and hippocampus intensified without corresponding changes in surface recordings.

Adversive emotion induced by electrical stimulation. — Responses of fear and rage (and sometimes violence), varying in intensity, were evoked with electrical stimulation of sites in the mesencephalic tegmentum, hypothalamus, medial amygdala, and hippocampus. The findings, corroborating correlations established between brain function and behavior during spontaneous or interview-induced adversive emotion, further demarcated the brain's adversive emotional system. Although the response of different patients to the same stimulation often varied somewhat, it was always basically adversive. Also, the adversive response of a patient to stimulation at a specific site sometimes varied from one day to another, depending on his baseline mood (depression, anger).

The most profound response was elicited with stimulation of the mesencephalic tegmentum of patient A-10 (J.M.). He was murderously rageful as he threatened to kill the physician standing next to him. When the stimulus was turned off, the patient was perplexed by his reaction — "I have nothing against him — he was just the closest to me." He then remembered similar rageful feelings he had had in the past, calling them "gorilla-osis." "I felt like a gorilla and wanted to kill." As an example, he vividly described the exact scene and his wrath when, as a youth, his mother failed to iron a shirt to his satisfaction. The patient's response to the stimulation and associated recall of an incident in his early life substantiated the consistent observation that profound emotion and memory are interrelated and, in fact, part of the same response.

From a film made of patient A-10 during this study, it is apparent that stimulation of the mesencephalic tegmentum affected his extraocular muscles, as a result of placement of the electrodes. Third nerve nuclei or the ventrally descending fibers from those nuclei were evidently activated by the electrical current. After termination of the stimulus, the patient described his eye movements as bothersome, but not notably uncomfortable and, he said, they had nothing to do with his rage.

Adversive and pleasurable sites are in propinquity in the mesencephalic tegmentum. In another patient, B-10, mesencephalic tegmental electrodes were also close to the nuclei affecting the eye muscles, but at a pleasure site in the interpeduncular nuclei. He also commented on the involuntary movement of his eyes. But his overall response to the stimulation was so pleasurable that he asked for it to

be repeated. Later, when he was given a self-stimulator, he often repeatedly stimulated the site.

Another patient, A-8 (W.M.P.), had a pair of electrodes implanted into the lateral amygdala (a pleasurable site) close to nuclei of the medial amygdala (adversive site). She was a rather passive woman, who was always reluctant to express her feelings. A low-intensity stimulus to the lateral amygdala elicited a pleasurable response. In sharp contrast, an adversive response, characterized by rage and lashing out, was observed if the current was increased sufficiently to spread and activate the medial nucleus. As soon as the stimulating current was reduced, however, and the medial nucleus was no longer activated, the patient responded with obvious pleasure, often laughing and then, wondering aloud, "Why did I do that?" This phenomenon was repeatedly demonstrated in this patient.

In 29 patients, the consistent emotional response to stimulation of the rostral hypothalamus was fear, the thought-content varying. Visceral symptoms and changes in autonomic nervous system function usually occurred (Peacock, 1954). Pulse rate increased and blood pressure rose significantly. In all but four of the 29 patients, electrodes were implanted in the medial aspect of the rostral hypothalamus. In contrast to reports of pleasure induced in rats with stimulation of the medial forebrain bundle (Olds, 1962; Olds and Olds, 1964), hypothalamic stimulation never elicited a pleasurable response in our patients. Our results do not, however, rule out the possibility of a pleasurable response resulting from stimulation of some sites in the hypothalamus and possibly of the medial forebrain bundle. The stimulus we used probably caused a spread to the adversive sites that involve most of the hypothalamus. An adversive response was also invariably evoked with stimulation of the hippocampus.

When electrical stimulation induced anger, the patient usually lashed out and threatened the person nearest to him. When the response was fear, feelings of discomfort and anxiety unrelated to the immediate environment were usually described. The patient was aware of profound emotion that mobilized him for swift action to combat (or defend against) the person or object nearest to him should it be necessary. His behavior was fully conscious and well coordinated, not an automatism or "sham."

As soon as the stimulation terminated, the emotional state that had been induced vanished. The reactions of the patients varied. Whether they were amused or puzzled, however, they were aware of

the feelings that had developed and described them clearly, and many recalled events in their lives when they had experienced similar emotional states. Some patients thought their painful expressions of anger (resembling past anger) might be therapeutic. These data from patients capable of reporting their thoughts and feelings elucidated results obtained in animals when midbrain structures were stimulated (Brady, 1960; Zanchetti, 1967). Bard (1928) and Cannon (1931) chose the term "sham rage" to describe the behavior (observable visceral and motor symptoms) of animals after removal of the cerebrum anterior to the thalamus, since it appeared to duplicate the rage behavior of intact animals. Masserman (1943), on the other hand, concluded that the behavior was merely a motor automatism unrelated to motivational or associational factors, since it was not directed and could not be classically conditioned. Others, including Hess and Brugger (1943) and Wassman and Flynn (1962), reported that stimulation of the hypothalamus of intact cats resulted in a directed attack, whereas Roberts and Kiess (1964) presented data indicating that induction of attack behavior by hypothalamic stimulation was motivational.

Results of electrical stimulation of the amygdala of patients helped somewhat to clarify reports about that site's function that were based on the effects of lesions in animals. Whereas Bard and Mountcastle (1948) described a lower threshold for rage after amygdalectomy, Kluver and Bucy (1939) reported placidity. Our findings in patients suggested that either response can occur, depending on the part of the amygdala that is involved. The lateral amygdala is implicated in the brain's pleasure system, whereas the medial amygdala is part of the adversive system. In studies in cats, Egger and Flynn (1963) also reported disparate responses when different sites in the amygdala were stimulated.

Just as with stimulation of pleasurable sites, "experiential events" did not occur when adversive sites were stimulated, except in those rare instances when seizures were induced. Rather, the memory recall was of past events in keeping with the emotional state induced by the stimulation. Our patients, in recalling and reporting events, always described them as memories, in contrast to descriptions by Penfield and Perot (1963) of patients who relived past events as if they were current happenings.

Our findings likewise contrasted sharply with those reported by Penfield and Jasper (1954) that neither localized epileptic discharge nor electrical stimulation can elicit feelings of anger. In 1982,

Gloor and associates (Gloor, Olivier, Quesney, et al, 1982) observed no patients in whom stimulation elicited rage, in contradistinction to our published reports to the contrary (Heath, Leach, Monroe, et al, 1954; Heath, Monroe, and Mickle, 1955). MacLean (1975), on the other hand, cited two reports in which anger was part of the aura in as many as 17% of epileptic patients.

Adversive emotion induced by direct chemical stimulation of the brain. — When atropine was introduced into the septal region of two schizophrenic patients, the spike and slow-wave activity induced in the septal region (lasting about 20 minutes) was associated with exacerbation of psychotic symptoms (Heath, 1964).

In another study of six patients, catecholamines were introduced directly into the hippocampus. Whereas dopamine produced no significant change, norepinephrine induced focal recording changes characterized by increased slowing and spiking in the hippocampus 70% of the time. In association with the recording changes, patients reported feelings of despair and depression. One schizophrenic patient expressed intense anxiety during an aura preceding onset of a psychomotor seizure. The only behavioral change in another schizophrenic patient, who was catatonic and nonverbal, was arousal. Norepinephrine induced no change 30% of the times we administered it.

Brain Mechanisms in Psychotic Behavior

Recording correlates of psychotic behavior. — Findings in experimental animals had suggested that altered function of certain brain sites might correlate with symptoms characteristic of the psychotic— specifically, symptoms of defective emotional responsivity, disturbed sensory perception, and reduced level of psychological awareness. (As described earlier, these behavioral parameters were altered in animals by stimulation or ablation of the septal region.) Our techniques for implantation of small electrodes into specific brain sites of intractably ill patients provided the method for establishing the correlation.

Forty-seven of the patients in our deep-electrode series of 66 were psychotic, and in 39 the cause was schizophrenia. In 1952, we presented our first report of a recording abnormality in the septal region, in the form of spike and slow-wave activity, concomitant with psychotic behavior (Heath and the Tulane University Department of Psychiatry and Neurology, 1954). In those earliest patients, the recording abnormality was not present in the caudate nucleus or an-

terior thalamus, deep structures also implanted with electrodes, thereby ruling out the possibility that it was an artifact consequent to electrode implantation. Moreover, it was not present in recordings of nonpsychotic patients in the series. As techniques were improved and electrodes were implanted into additional deep-brain sites (shown in animal experiments to be directly connnected with and functionally related to the septal region), we noted that the septal recording abnormality, uniquely associated with psychosis, was occasionally present at other deep sites, usually the hippocampus, amygdala, deep midline cerebellum, and parts of the thalamus. (As previously described, recording changes occurred at these same sites in monkeys in association with behavioral changes induced by administration of psychotomimetic chemicals and taraxein.) Later, when methods were refined enough to permit the electrodes to remain in the brains of intractably ill patients for months (in some, for a year or more), the serial recordings that were obtained showed little or no septal aberration when psychotic symptoms remitted. With relapse, however, the recording abnormality reappeared (Fig. 12).

Abnormalities occurred at other deep brain sites of many nonschizophrenic patients, particularly epileptics, in whom spike and slow-wave activity occurred interictally in the hippocampus or amygdala, and infrequently at other deep sites and over the cortex. A few of the epileptic patients were episodically psychotic. During those periods, their recordings showed the characteristic spike and slow-wave abnormality in the septal region (Fig. 13).

Briefly summarized, our therapeutic studies with deep-brain electrodes indicated that psychotic behavior was invariably associated with a unique recording abnormality in the septal region. It prevailed regardless of the etiologic process that affected the brain to create the psychotic behavior. It was present in the recordings of schizophrenics during psychotic episodes, in recordings of patients who were psychotic as a result of an organic brain disorder (trauma, vascular disease), in recordings of epileptics during episodic psychosis, and in recordings of patients with toxic psychosis after ingestion of chemical psychotomimetics. The correlation was further established when we found that the septal recording aberration and associated psychotic behavior could be induced if we drove septal region activity by electrical stimulation of the hippocampus at frequencies of 4-per-second (Heath, 1964; Heath and Guerrero-Figueroa, 1965).

Physiologic correlates of impaired sensory perception in psychotic behavior. — As previously described, an anatomic sub-

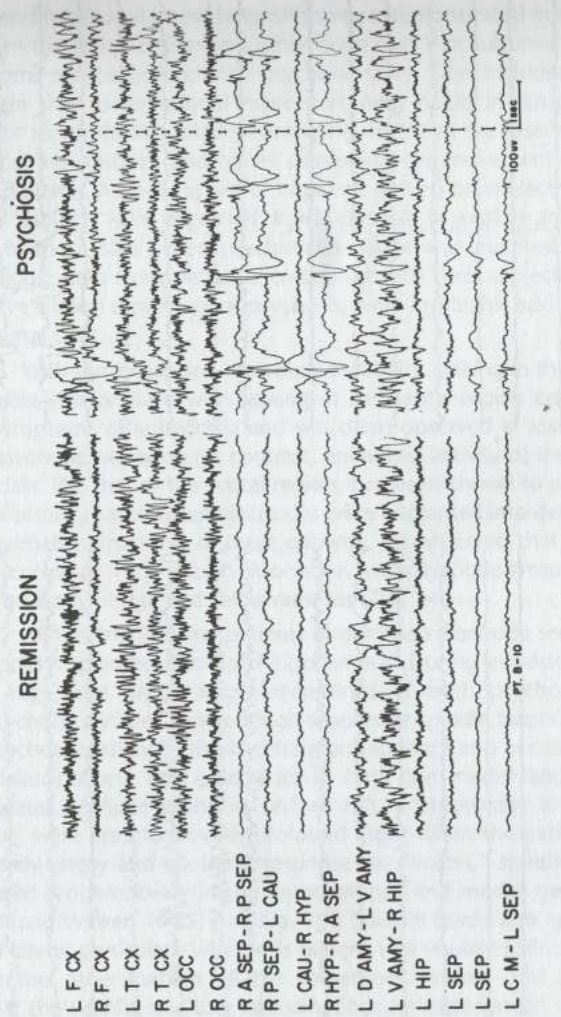

Figure 12. *Electroencephalographic recordings of Patient B-10 obtained at different times to illustrate differences in recordings when psychotic symptoms were in remission and when they were manifest.*

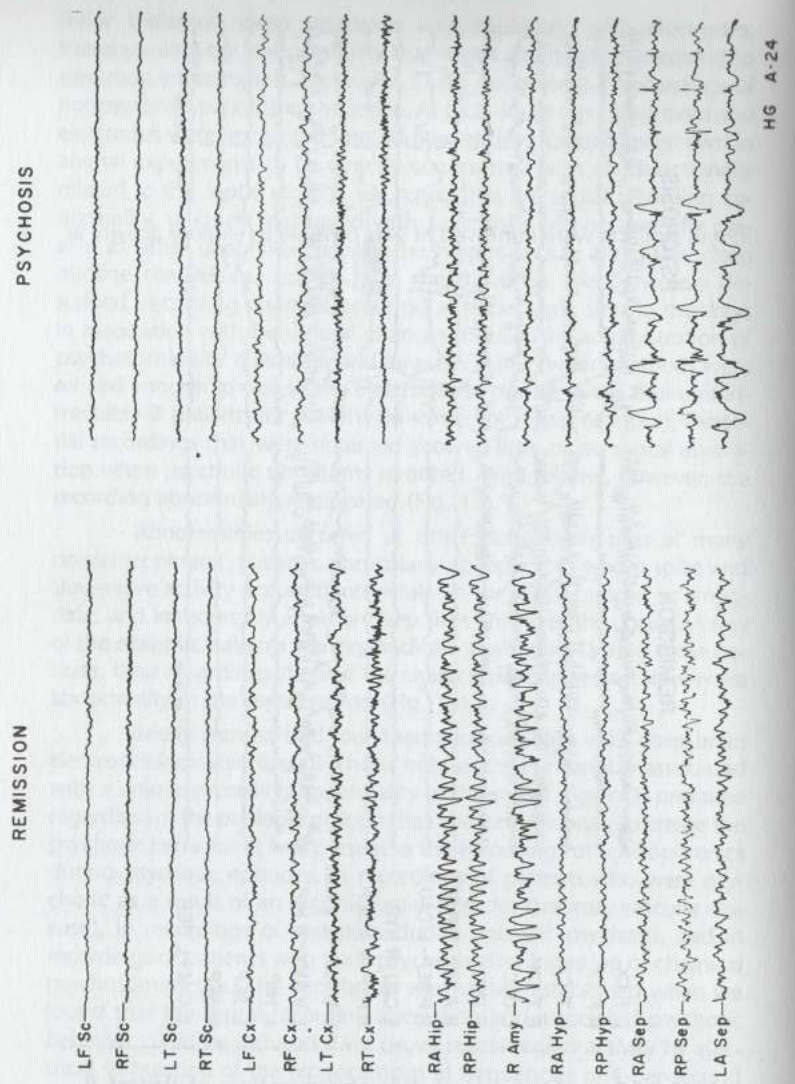

Figure 13. *Deep and surface recordings from epileptic patient A-24 when he was asymptomatic and when he was psychotic.*

strate and functional interrelationships were demonstrated in animals between the septal region and other brain sites that subserve certain symptoms associated with the psychotic state. Sites included other forebrain sites for emotional expression, relay nuclei in sensory systems for all modalities, nuclei containing cells that are reservoirs for chemical transmitters, and nuclei subserving eye movement and facial expression. As techniques for implanting deep brain electrodes in human subjects were improved, it was possible to explore activity at some of those sites when psychotic behavior was manifest. Those physiologic data from patients, correlated with their subjective and objective clinical symptoms of psychosis, were invaluable additions to the animal data.

With our expanded recording capability, spiking in the lateral amygdala concomitant with spiking in the septal region correlated with symptoms of anhedonia and was often observed in association with psychotic behavior. (In contrast, enhanced activity of the lateral amygdala, like that of the septal region, has been shown to correlate with pleasure.) Later, when electrodes were implanted into deep midline cerebellar structures of three patients, we observed that spiking also occurred at those sites in association with psychotic symptoms of impaired body image and self awareness (Fig. 14.)

All but the first few patients in our deep electrode series had electrodes implanted into the hippocampus. During episodes of intense rage, the hippocampal recordings of both psychotic and nonpsychotic patients showed high-amplitude spindle bursts. Two of the psychotic patients, who had frequent auditory and occasional visual hallucinations, had electrodes in both the medial and lateral geniculates. Hallucinations in one (B-14), a chronically ill schizophrenic, were associated with profound rage. When the patient was extremely angry and shouting responses to "voices," spindle bursts appeared synchronously in the hippocampus and medial geniculate (Heath and Walker, 1985) (see Fig. 11). Spindle bursts also appeared in the lateral geniculate when this patient was visually hallucinating. When the other patient (B-16) sometimes relaxed and became drowsy, the wishful auditory hallucinations he experienced were associated with high-amplitude spindling that occurred simultaneously in the septal region and medial geniculate. In both patients, septal spiking also occurred between the spindle bursts.

Several patients had electrodes implanted in the somatosensory thalamus. When spiking occurred in the septal region and lateral

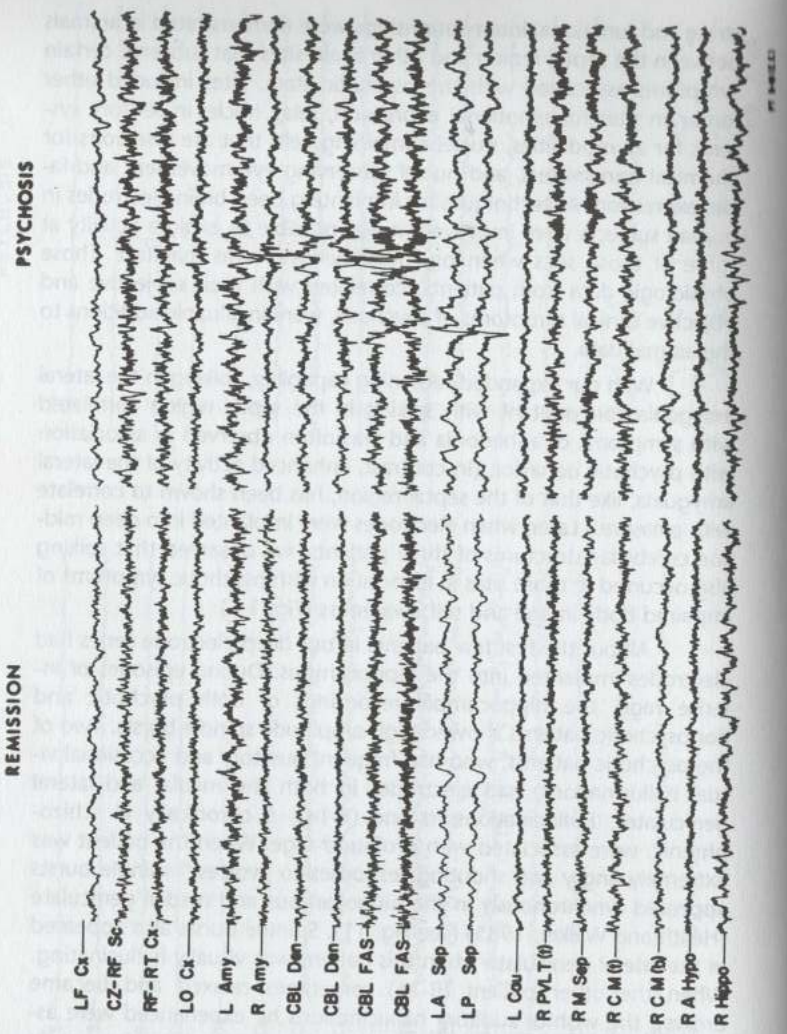

Figure 14. *Electroencephalographic recordings obtained from Patient B-19 during remission and psychosis. Note the spiking at deep cerebellar sites, as well as the septal region, when he was psychotic.*

amygdala of those patients, it was also evident in the thalamus. Thus, abnormal activity in sensory nuclei of psychotic patients correlated with their disturbances in sensory perception. (The findings paralleled those in monkeys, in which spiking occurred in recordings from the lateral amygdala, cerebellum, and other sensory relay nuclei, as well as the septal region, as a result of administration of taraxein and various psychosis-inducing chemicals.)

Relationship of Subcortical Recording Changes to Cortical Function

All distinct changes in brain activity correlating with psychotic behavior have been at specific *subcortical* sites that have direct anatomic connections to specific *cortical* sites which, based on studies of the effects of lesions, subserve specific functions. From our data, we have postulated that altered behavioral function, with associated changes in recordings at subcortical sites, is the result of altered input from the implicated subcortical site to the cortical site to which it relates. For example, recording changes in the paleocerebellum (vestibular proprioceptive system) consistently correlate with psychotic behavior. We assume that the physiologic basis for the correlation is the interaction of the cerebellum with the parietal cortex, shown to be directly connected, even though our techniques failed to pick up correlative changes in cortical recordings.

Inasmuch as lesions at both these sites produce disturbances in self-image, we postulate that their disruptive function accounts for the pathologic concept of self seen in psychotic behavior. Similarly, the observed changes in behavior that correlate with recording changes at other sensory nuclei are presumed to result from the way in which these subcortical sites influence the cortical receptive areas to which they project. Moreover, the changes in affect occurring with psychotic behavior and correlating with altered activity in the forebrain (septal region, hippocampus, amygdala) are presumed to result from the way in which these subcortical structures influence activity at specific cortical sites (the frontal and temporal lobes).

Investigating Schizophrenia in the Mind-Brain Context

Etiology and Pathogenesis

The etiology and pathogenesis of schizophrenia are not yet established. It affects one to three percent of the world's population,

the incidence varying little among cultures. Over the years, so many different theories have been advanced about its nature, none completely substantiated, that schizophrenia research has been referred to as a graveyard of investigators. The enigma remains today. Our own theoretical framework for schizophrenia has intermittently undergone change as new data have accumulated over forty years of investigation. Whereas we have not reached an end point, our findings suggest that this is a distinct neurologic disease process.

Diagnosis and Classification

Even though a consistent biological marker (structural, physiologic, chemical) has not been demonstrated, the diagnosis of schizophrenia is generally accepted and widely used. Diagnosis is predicated on clinical signs and symptoms. This poses problems since the symptoms of schizophrenia overlap with those of other diagnostic classifications. The principal presenting symptoms of schizophrenia are those of psychosis. There are numerous etiologic bases for the clinical picture of psychosis, however. Psychoses must be considered as a group of symptoms or a syndrome, and schizophrenia as one disease that can produce it. As our recording data have demonstrated, psychotic behavior, regardless of its underlying cause, consistently correlates with changes in brain function, in the form of spiking and slow-wave activity in the septal region.

In 1974, the American Psychiatric Association appointed a task force to develop a new classification and glossary of mental disorders to reflect current knowledge, leading to the publication of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III), first printed in 1980. In DSM-IIIR, the most recent effort, the descriptive criteria based on clinical manifestations are clearly presented, but boundaries between schizophrenia and psychoses of other origins are often indistinct, and the presenting picture of schizophrenia varies considerably. As a result, the term "schizophrenic spectrum" has been coined to encompass categories such as schizoaffective disorder, atypical psychosis, schizophreniform disorder, and schizotypal personality disorder. In the absence of an unequivocal biologic marker, these somewhat ambiguous descriptions of clinical signs and symptoms continue to be the only basis for arriving at the diagnosis of schizophrenia. And they must therefore be the starting point for all studies, including attempts to establish cause and pathogenesis.

A commendable effort to sharpen clinical diagnostic acumen for schizophrenia continues. Debate has been renewed as to whether

schizophrenia, a blanket label, represents a unitary disease or a heterogeneous group of disorders, and whether it has one or multiple causes. Variability in clinical course and the presence and intensity of various symptoms have formed the basis for subdivision of the schizophrenias. Since Kraepelin (1919) differentiated a pathologic entity among mental patients, which he called "dementia praecox," investigators have pondered whether the illness represents one or more entities. DSM-III, reflecting a majority opinion, favors the concept of a group of disorders of different origins.

Although it is accepted practice to apply the labels "catatonic," "disorganized," "paranoid," or "undifferentiated' in accordance with the presenting symptoms, a broad categorization suggesting two specific subtypes of schizophrenia has also been used extensively. Bleuler (1950), in his classical monograph entitled *Dementia Praecox, or the Group of Schizophrenias*, emphasized two major groups of symptoms, which he named fundamental and accessory. Fundamental symptoms, present and permanent in every schizophrenic patient, were autism and disturbances in association and affectivity. Bleuler emphasized that the intensity of the fundamental symptoms varied from one patient to another, being scarcely manifest in some and clearly obvious in others. Many patients also developed accessory symptoms, which tended to come and go. They were the more florid symptoms of psychosis, the most striking being delusions, hallucinations, and catatonia. Psychobiology, a term introduced by Meyer (1957) in 1909, stressed the importance of documenting the premorbid personality of the psychotic patient in establishing diagnosis and prognosis. Meyer believed that a clinical picture of well-defined fundamental symptoms augured for a poor prognosis and suggested a diagnosis of schizophrenia, rather than of affective disorder or other psychosis. The concept of two broad subcategories of schizophrenia is also evident in Snezhnevsky's (1971) scheme of flexible and inflexible symptoms and in the distinction made by Wing (1978) between the clinical poverty syndrome and florid psychotic symptoms.

The designations most commonly used today by those who propound two categories of schizophrenia are positive-negative schizophrenia or Type I and Type II schizophrenia or deficit and nondeficit forms of schizophrenia (Crow, 1985; Carpenter, Heinrichs, and Wagman, 1988). Differentiating the two is based on such factors as the patient's symptom picture, clinical course, and incidence of associated neuropathology. Whereas some authors infer that the two categories represent very different subtypes, others describe them as be-

ing in a sliding scale relationship. Andreasen and Olsen (1982) considered a continuum, and added a *mixed* subtype to the positive-negative distinction for those patients displaying both groups of symptoms.

Whereas the proponents of these newer diagnostic subcategories emphasize distinct features of each, they concede some common features, as well as similarities with earlier classifications. They also acknowledge that the same symptoms can be present in patients falling into different subcategories. For example, patients diagnosed as having negative schizophrenia can have a flare-up of positive symptoms, and those with positive schizophrenia might ultimately display negative symptoms. It has been reported that some patients with negative or Type II schizophrenia have enlarged cerebral ventricles, that is, an increase in ventricle-brain ratio (VBR), as well as a high incidence of demonstrable cellular abnormalities of the brain (Shelton and Weinberger, 1986; Weinberger, 1987). It has also been reported that D_2 receptors are present in type I schizophrenics, but not in Type II (Crow, 1980, 1985).

In summary, differences in signs and symptoms of the various subcategories are not precise, and physical changes in the brain (neuropathologies) do not correlate distinctly with specific subcategories. Some investigations have failed to demonstrate a significant relation between enlarged ventricles and negative schizophrenia (Owens, Johnstone, Crow, et al, 1985). The limited data that relate increase in D_2 receptors to Type I schizophrenia (florid psychotic symptoms with much in common with positive schizophrenia) are insufficient to answer such questions as "What happens when negative or Type II schizophrenics develop positive sympoms?" or "Do D_2 receptors, reputedly absent in negative schizophrenia, appear if a patient develops positive or Type I symptoms?"

Whereas some authors suggest different origins of the subcategories (Bleuler, 1950; Goldberg, 1985), others postulate a single or common cause (Crow, 1985; Rado, 1962). Those who consider schizophrenia a group of disorders with differing origins cite variations in the presenting clinical picture and the course of the illness as the principal features that influenced their thinking. But the validity of that reasoning is questionable.

Numerous illnesses of known origin are manifested by symptoms of psychotic behavior that resemble, or are sometimes identical with, those of schizophrenia, making differential diagnosis, on the basis of clinical signs and symptoms alone, difficult or impossible. The

single cause established for general paresis, for example, is the presence of the spirochete in the brain. Nevertheless, symptoms and clinical course among patients with general paresis are often as similar and as variable as in patients diagnosed as schizophrenic. Alzheimer's disease and brain tumors (at some sites), other examples of specific brain disorders that can affect behavior, also manifest inconsistent behavioral symptoms. Such variability also occurs in patients suffering from toxic psychosis, in which the common source is ingestion of a psychotomimetic agent (d-LSD, phencyclidine). Moreover, in some illnesses that do not principally or exclusively affect the brain — for example, autoimmune disorders, including lupus erythematosus — the symptoms and clinical course vary widely among patients despite a common putative origin.

These examples suggest that the concept of multiple causes for schizophrenia, based on variations in symptoms and clinical course, should be accepted with caution. On the other hand, for those who propound a common cause or unitary disease, as I do, the burden of proof is a clear demonstration of specific origin.

Rado (1962), based on his extensive experience as a psychoanalyst, formulated a dynamic concept of schizophrenia in which he postulated a progressive clinical sequence rather than simply listing and describing symptoms. His formulation was useful in our efforts to relate clinical phenomena to brain function. Many aspects of our findings in therapeutic studies of schizophrenic patients with deep electrodes were consistent with his concept of the disease.

Rado considered schizophrenia to be a genetically determined illness, the genetic predisposition resulting in damage to the integrative apparatus of the mind manifest in (1) a deficiency in ability to experience pleasure, that is, anhedonia, and (2) an impairment in concept of self, including a disturbance in understanding of body image, the extreme manifestation being depersonalization that he called "proprioceptive (kinesthetic) diathesis" (Who am I? How do I relate to my environment?). Rado considered many symptoms now listed under the categories of negative, Type II, or deficit schizophrenia, to be consequences of these two primary clinical features. In his formulation, the symptoms that resulted were anhedonia, disturbances of affect, reduction in social contacts, poverty of speech, restricted interests, and diminished sense of purpose. He considered the polyneurotic symptoms (pseudoneurotic schizophrenia) described by Hoch and Polatin (1949) to be representative of defensive efforts to neutralize the pain resulting from excessive emergency emotion that

was consequent to diminished neutralizing pleasure, whereas florid psychotic symptoms (hallucinations, magical or delusional thinking) were a complicating development due to further exacerbation of the emergency dyscontrol that resulted from the absence of stabilizing pleasurable emotion.

Information gathered from our therapeutic deep-electrode studies of schizophrenic patients was one source of data for our broader effort to establish the neural basis for emotion, sensory perception, and memory that we considered critical for relating mind to brain activity. In this section, in which I focus on the brain correlates of schizophrenia, I will necessarily refer to some of the same data previously cited, but in this limited context.

Identifying the Brain Pathophysiology in Schizophrenia

Although physiologic treatments for schizophrenic patients — particularly those involving extirpation of the cortex (lobotomy, topectomy) — influenced emotional behavior, they did not significantly affect the mechanism for emotional expression and, consequently, failed to affect core symptoms of schizophrenia. On the other hand, lesions at subcortical sites of animals (cats and monkeys), particularly of the septal region, severely impaired emotionality, producing behavior that resembled the aberrant behavior of the schizophrenic. Characteristic features were severe reduction in level of awareness and failure to respond appropriately to environmental stimuli. The animals were often catatonic. Similar but less profound changes occurred with lesions of the hippocampus and amygdala. These animal studies suggested involvement of the septal region in schizophrenia. Later, studies in patients clearly demonstrated that the septal region was anatomically connected and functionally related to the hippocampus and amygdala.

Results obtained with stimulation to numerous brain sites further focused our attention on the septal region as being critically implicated in the neural substrate for schizophrenia. Animals with electrodes implanted for long-term study became highly alerted and seemingly experienced pleasure with stimulation of the septal region, a response that contrasted sharply with the adverse responses produced by stimulation of several other subcortical sites within the so-called limbic lobe and, especially, of some deep temporal lobe structures, as well as the hypothalamus and much of the thalamus.

At the time we began our therapeutic deep-electrode studies in schizophrenic patients, some reports had indicated that the response of schizophrenic patients to stress was often diminished, as evidenced by certain biochemical markers (Pincus and Elmadjian, 1946; Pincus and Hoagland, 1950; Freeman and Elmadjian, 1950; Lee, Babcock, et al., 1951). In animals, lesions of the septal region often produced changes in stress indicators that resembled those associated with impairment of the pituitary adrenal axis, whereas stimulation of the septal region resulted in changes similar to those that occurred when the pituitary adrenal axis was activated.

Our findings in animals pointed to the septal region as the principal localized site for pleasure in the brain with the capability of influencing stress chemistry while raising the level of psychological awareness. Its malfunction, we postulated, would therefore result in impaired ability to experience pleasure, one of the two primary clinical features of schizophrenia described by Rado, and possibly in an impaired stress response. From these clinical and animal data, we hypothesized that schizophrenic patients, in the absence of a structural abnormality, had a functional abnormality of the septal region, a finding that we later demonstrated by use of deep-electrode techniques in patients. Subsequently, we also demonstrated a physiologic basis for Rado's other primary clinical feature of schizophrenia, the proprioceptive diathesis, in experiments in Harlow's monkeys. In those studies, the brain's pleasure system (septal region, lateral amygdala, interpeduncular nuclei of the mesencephalon) was shown to be in a direct and reciprocally functioning relationship with the vestibular proprioceptive system (deep nuclei of the cerebellum) (Harper and Heath, 1973, 1974; Heath, Dempesy, Fontana, et al., 1980; Heath and Harper, 1974, 1976). It was later demonstrated in psychotic patients that a recording abnormality appeared at deep midline cerebellar sites and the lateral amygdala concurrent with the recording abnormality in the septal region. These recording changes provide a physiologic basis for both the pleasure deficit and the proprioceptive diathesis.

In the intractably ill schizophrenic patients with deep electrodes, we demonstrated that the inverse relation between pleasurable and painful emotion observed clinically had a corresponding neural substrate. As a result of the defective function of his pleasure system, the schizophrenic's adverse system, as evidenced by deep recordings, was physiologically overactive. This finding substantiated Rado's conjecture that the schizophrenic's characteristic emergency emotional dyscontrol was a result of his malfunctioning pleasure system.

Rado's so-called developmental stages of schizophrenia — specifically, that increased intensity of emergency emotion was associated with the appearance of decompensating secondary symptoms — were also corroborated by our deep-electrode studies in patients. We first demonstrated direct monosynaptic connections between brain sites for pleasurable and painful emotion and sensory relay nuclei in anatomic studies in animals. Later, when patients had electrodes implanted into the sensory relay nuclei, as well as into sites for emotion, intensification of emotion was shown to correspond with a spread of activity to implicate the sensory relay nuclei. As patients hallucinated, recording changes that occurred at sites where activity correlated with emotion were often synchronous with the changes in recordings from sensory relay nuclei (Heath and Walker, 1985).

On the basis of data we have gathered thus far, we conclude that the septal region, the core of the brain's pleasure system, is the pivotal site of the neural substrate for schizophrenia. It is interconnected with the lateral amygdala and interpeduncular nuclei of the mesencephalon, other sites for pleasurable emotion, as well as with sites demonstrated for adversive emotion. Sites for pleasure and pain are in inverse relation. Further interconnections exist with the deep nuclei of the cerebellum (proprioception), the geniculates and lateral thalamus (sensory relay nuclei), the substantia nigra, locus ceruleus, and raphe nucleus (nuclei that are reservoirs for neurotransmitters), and with nuclei subserving function of the eyes, the cranial nerves (III, IV, and VI), and superior colliculus. (Data from animal studies substantiating these interconnections were presented previously.)

The Chemical Basis for Altered Brain Mechanisms in Schizophrenia

In the following section, I describe the progressive steps taken over the past forty years in our continuing efforts to identify the putative biochemical abnormality for schizophrenia. From time to time, attainment of our goal seemed imminent. But that anticipation would soon change to frustration when the results proved, at best, to be a stepping stone rather than an end point. The refusal to accept defeat may have seemed unwise in view of the controversy our studies often engendered, but at almost every step, provocative findings attesting to our concept of schizophrenia encouraged us to continue the quest.

In the early 1950s we speculated, in the absence of a manifest structural defect in the schizophrenic brain, that the unique recording abnormality was the result of impaired synaptic transmission in the septal region. Since aberrant activity was sometimes present at distal sites as well, two possibilities, alone or together, were considered:

(1) The abnormal activity was transmitted from the septal region to the distal sites.

(2) The distal sites, particularly the lateral amygdala and cerebellum that were most often implicated, might be affected by the same pathologic mechanism. About that time, Hoffer and co-workers (Hoffer, Osmond, and Smythies, 1954) advanced their adrenochrome-adrenolution hypothesis, in which it was assumed that schizophrenia resulted from altered catecholamine metabolism.

Catecholamine Oxidation and Ceruloplasmin

Our initial search for a chemical basis for the altered brain function in schizophrenia was influenced by the epinephrine hypothesis. We looked at catecholamine transmitters, noting in our tests that epinephrine and all catecholamines were metabolized by serum of acutely ill schizophrenics more rapidly than by serum of normal subjects. Results soon showed, however, that the increased speed of epinephrine oxidation was a nonspecific phenomenon that occurred in association with many illnesses — degenerative diseases, malignancies, and chronic and acute infections, including the common cold (Leach and Heath, 1956).

In attempts to understand the basis for the altered catecholamine metabolism in schizophrenics, we next turned our attention to ceruloplasmin, a known serum oxidase, and noted that ceruloplasmin levels correlated with the speed of oxidation of catecholamines (Leach, Cohen, Heath, et al., 1956; Angel, Leach, Martens, et al., 1957). When speed of oxidation increased, the ceruloplasmin level was elevated. Again however, it was soon apparent that an elevated level of ceruloplasmin and increased speed of oxidation of catecholamines were not demonstrable in all schizophrenic patients. Whereas the phenomenon was present in most patients with acute schizophrenic symptoms, it rarely occurred in chronically ill schizophrenics. Furthermore, this phenomenon, the elevated ceruloplasmin, like that of increased speed of epinephrine oxidation, also proved to be nonspecific, likewise occurring in association with other illnesses and during the second and third trimesters of pregnancy. Although ascorbic acid was shown on *in vitro* testing to inhibit the oxidation reaction, its intake did not reduce ceruloplasmin levels in patients.

Considerable interest was generated by the studies of ceruloplasmin. Shortly after we published our findings, Akerfeldt reported (in the lay press) a blood test for schizophrenia based on oxidation of catecholamines. We advised Akerfeldt of our findings — that the oxidation phenomenon was nonspecific and related to ceruloplasmin levels — and he included that information in a later scientific report (Akerfeldt, 1957).*

Our findings were generally supported by studies of other investigators (Gibbs, 1959). But one group of researchers who failed to show increased levels of ceruloplasmin in 20 chronic schizophenic patients did not cite the original reports and ignored those that concluded that increased levels occurred only in acutely ill schizophrenic patients (Clarke, Freeman, and Pryse-Phillips, 1970). The consistent finding was that the increased speed of oxidation occurring in many acutely ill schizophrenic patients was related to increased level of ceruloplasmin and that the reaction could be inhibited *in vitro* by ascorbic acid. While it is not clear why the phenomenon occurred only in acutely ill patients, it is noteworthy that those who showed a significant increase had a higher rate of spontaneous remission (Heath, Leach, Byers, et al., 1958).

Speculating that the phenomenon played a role in the body's defense against schizophrenia, we administered the crude ceruloplasmin fraction from sera of normal volunteers intravenously to a few acutely psychotic schizophrenic patients. Surprisingly, rather dramatic and immediate (within an hour) symptomatic improvement occurred in some of the recipients, but we could not be certain whether the improvement was produced by the injection or occurred spontaneously as the result of suggestion.

In an attempt to clarify the issue, Martens and associates (Martens, Vallbo, and Melander, 1959) obtained large quantities of a much purer ceruloplasmin and administered it intravenously in large doses and over prolonged periods, under carefully controlled conditions, to 30 schizophrenic patients. These Swedish investigators noted: "In confirmation of earlier work by Heath et al., we have observed certain biochemical and physiological changes following the administration of ceruloplasmin." Although their results were provocative, in that there were "favourable modifications in the clinical picture of 26 out of 30 cases," with acute and subacute cases responding more favorably than chronic cases, they did not warrant the conclusion that the effects were specific for schizophrenia.

* Letter dated November 27, 1956 from Dr. Heath to Dr. Akerfeldt, and, in reply, letter dated December 2, 1956 from Dr. Akerfeldt to Dr. Heath.

Isolation of a Psychotomimetic Serum Fraction (Taraxein)

In further investigations of the ceruloplasmin-oxidation phenomenon, we used the salting-out methods available at that time (1950s) to compare serum ceruloplasmin fractions from schizophrenic and control subjects, the latter group comprising healthy normal subjects and patients with illnesses other than schizophrenia. Our aim was to determine if ceruloplasmin of schizophrenics was qualitatively different and acting on catechol substrates to produce an abnormal (psychotomimetic) transmitter chemical.

The crude fractions from 400 ml of starting sera that had been pooled from several subjects of each category were tested intravenously in the monkey with deep electrodes. (This was the animal model we used consistently in association with our deep electrode studies in patients.) No behavioral or recording changes occurred with administration of the fractions from control subjects. In sharp contrast, administration of the fractions from sera of schizophrenic patients induced catatonic-like behavior and the kind of abnormal recording (spikes and slow-waves in the septal region) that was characteristic of the psychotic schizophrenic patient (Fig. 15). Although we determined very early that the active material was not ceruloplasmin, we were not able to identify the psychoactive component or how it acted to produce the aberrant brain activity.

To a large extent, the diagnosis of schizophrenia is based on the subjective reports of persons with the disease. Human testing was therefore required if we were to determine that effects in the monkey recipients of the fraction from schizophrenic serum were truly schizophrenic-like symptoms. After making certain the fractions would not be harmful to human subjects, we obtained authorization to conduct a double-blind study of the serum fractions (schizophrenic and control) in volunteers at the Louisiana State Penitentiary. The consent forms used for the study were prepared in collaboration with the office of the State Attorney General. Several psychiatrists took part in selecting appropriate participants from among the volunteers — all with negative histories for schizophrenia in themselves and their families — and in evaluating behavioral changes resulting from administration of the test substances.

Clinical signs and symptoms characteristic of schizophrenia developed in some of the volunteer subjects who received the active

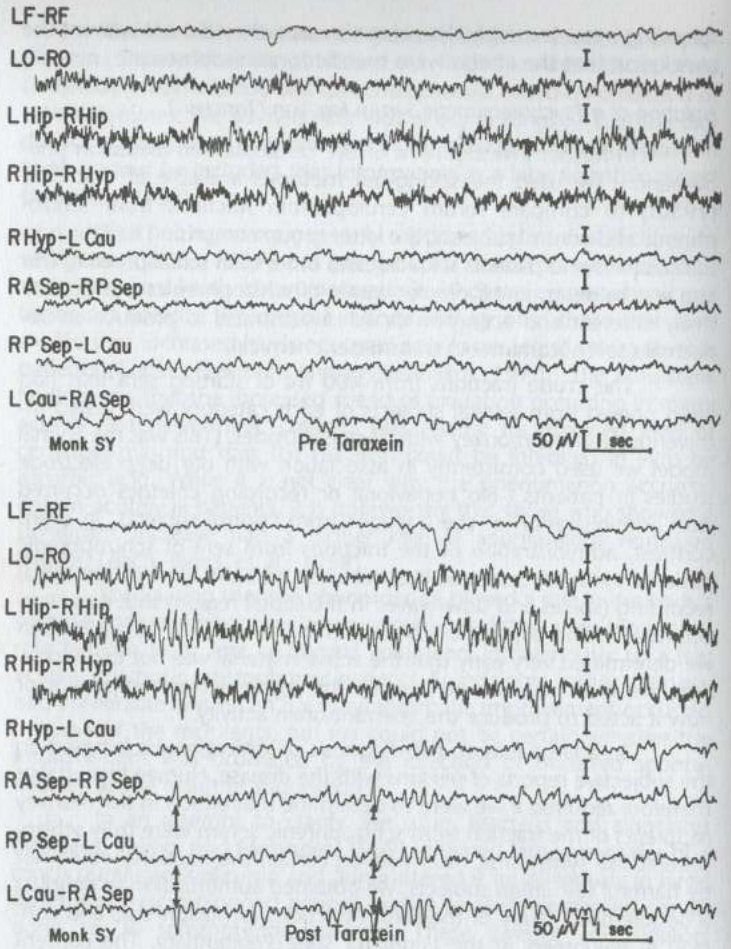

Figure 15. *Electroencephalographic recordings obtained from a rhesus monkey before and after intravenous administration of taraxein.*

schizophrenic serum fraction that we named taraxein. A consistent chronology occurred. About four minutes after intravenous administration of taraxein, blocking and thought-deprivation were manifest. Symptoms that later developed, usually peaking in about 20 minutes, included thought-disorder (overt delusions) and perceptual disturbance (usually auditory hallucinations). All symptoms invariably subsided in about an hour. (This was the same time sequence observed in monkey-recipients of taraxein.)

All clinical subtypes of schizophrenia occurred in the recipients — paranoid, catatonic, disorganized, and undifferentiated. The intensity of signs and symptoms varied considerably, some recipients showing minimal or no symptoms after receiving fractions that were active in the monkey assay. Since there was no precise quantification for the psychosis-inducing component, we attributed those responses to lower or subclinical levels of the active component in the test material.

The serum fractions obtained by the "salting-out" method inevitably contained minute quantities of ammonium sulfate, even after prolonged dialysis, resulting in flushing and increased pulse rate immediately after injection. This reaction always subsided within one to two minutes. It occurred to the same degree when fractions of sera of control subjects were tested.

When we presented the first report of our findings in May, 1956, at the annual meeting of the American Psychiatric Association, we described the clinical effects of taraxein in two volunteers, and the recording and behavioral effects in 11 monkeys with chronically implanted cortical and subcortical electrodes. By November, 1956, when we presented our next report (illustrated with 16-mm movie films) at a Divisional Meeting of the American Psychiatric Association in Montreal, 20 volunteers had participated in the double-blind studies of taraxein, some on more than one occasion (Heath, Martens, Leach, et al., 1957). Thirty-one intravenous injections had been given: 18 were active and two were inactive* taraxein fractions, five were the equivalent fraction from normal sera, three were ceruloplasmin, two were normal saline, and one was sodium amytal. The taraxein fraction had also been administered on 53 occasions to 20 monkeys.

---

* So-called inactive fractions were those that induced the characteristic behavioral and recording response when they were initially tested in the monkey, but were inert when they were later tested in volunteers and then retested in the monkey, evidently having lost activity during storage.

Identifying taraxein as gamma G immunoglobulin. — When the column fractionation method became available, the psychoactive material, taraxein, was shown to migrate with the gamma G immunoglobulin (IgG) fraction (Heath, Krupp, Byers, et al., 1967a). The serum fractions were electrophoresed against anti-human serum produced in rabbits or goats. Those containing only IgG were obtained by fractionating the sera over a diethylaminoethanol (DEAE) Sephadex A-50 column eluted with Trishydroxymethylaminomethane hydrochloride (Trizma Hydrochloride) buffer (pH 7.0, 7.5, or 8.0). Immunoelectrophoresis showed that the earlier preparations by "salting-out" methods contained many globulin fractions, including IgG.

Every fraction was first tested in the assay monkey, and judged to be active if it induced the septal recording abnormality and reduced behavioral awareness. Between 1955 and 1966, about two-thirds of the taraxein fractions that were active on monkey testing induced behavioral changes characterized by psychotic signs and symptoms in volunteers, whereas the others lost activity before being tested in human subjects five to 36 hours later. The fractions were always administered on a double-blind basis with the IgG fraction from nonschizophrenic human serum, ceruloplasmin, chemical psychotomimetics (d-LSD, mescaline), normal saline, and sodium amytal serving as control materials. With the improved column fractionation methods, taraxein extracted from 80 to 100 ml of schizophrenic serum was sufficient to demonstrate its psychosis-inducing activity. Furthermore, it did not produce in volunteers the undesirable side-effects of flushing, rapid breathing, and transient headache that sometimes occurred as a result of residual ammonium sulfate immediately after intravenous administration of the cruder fractions.

We have regularly pondered why taraxein activity was demonstrated in the monkey assay in only 25% of schizophrenic serum fractions we tested over the years. One observation was that the intensity of psychotic symptoms of the schizophrenic donors and the titer of antibody in their serum fractions seemed to correlate. The most active taraxein fractions were from patients who were floridly psychotic when blood was drawn, whereas activity was rarely demonstrated with fractions from patients whose psychotic symptoms were remitting, whether spontaneously or as a result of neuroleptic medication. With some patient donors, a few days of neuroleptic medication made a difference, in that their serum fractions were inactive on monkey testing before notable symptomatic improvement was clinically evident.

Problems with stability of the fractions. — On many occasions, schizophrenic serum fractions, especially those obtained by the early salting-out method, were active when tested in the assay monkey, but inactive when tested a few hours later in a human subject and, subsequently, when retested in the monkey.*

Taraxein fractions obtained by the "salting-out" method and maintained at room temperature deteriorated quickly. When stored at 4 degrees C, the fractions usually lost psychotomimetic activity within 24 hours. Those frozen at minus 20 degrees C, however, usually retained activity for as long as a month, and some stored at minus 70 degrees C retained activity as long as two months.

Sephadex column fractionation resulted in more stable taraxein fractions. If the fractions were kept frozen at minus 70 degrees C, they were demonstrated to retain activity for many months. When whole serum was frozen, full activity was usually maintained; indeed, some fractions obtained from whole serum that had been frozen as long as eight years tested active.

The Autoimmune Hypothesis

Having identified taraxein as a component of the IgG fraction, we postulated that it was antibody which, in the absence of structural change or cellular reaction, interfered with chemical transmission in the septal region by affecting a receptor or a second messenger for a transmitter chemical. Our continuing investigations were therefore based on the supposition that schizophrenia is an autoimmune disorder.

Creating antibodies to precise brain sites of animals. — One test of the concept that taraxein is antiseptal brain antibody was to produce antibrain antibody in animals and test its effect on brain function (Heath, Krupp, Byers, et al., 1967b). Homogenates of the septal region and other sites, prepared from brains of rhesus monkeys or humans that had been obtained no longer than eight hours after death and mixed with Freund's adjuvant, were used to create antibody in sheep (the animal we principally used) or rabbit. At the peak of antibody production, the animal was bled and its serum fractionated by the same methods used to obtain taraxein from schizophrenic serum.

---

* This sometimes happened when guest scientists were present and, needless to say, such failures to demonstrate taraxein activity in volunteer recipients contributed to the controversy over our findings.

Assaying and identifying the anti-brain IgG. — Our animal model, the rhesus monkey with deep brain electrodes, was critical for these studies. When the IgG serum fraction of sheep (or rabbit) that had been inoculated with septal region homogenate was tested intravenously or intraventricularly in the assay monkey, the same psychotic-like behavior and abnormal septal recordings were induced as with taraxein (Fig. 16). In contrast, IgG serum fractions from sheep immunized with other brain regions (hippocampus, cerebellum, cortex, brain stem) were inert on monkey testing. Monkey brain antigen and human brain antigen were equally effective in the production of antibrain antibody in the sheep (or rabbit).

Although the IgG fractions of anti-monkey brain sera (against all brain regions) contained antibody to antigens common to many brain regions, as demonstrated by crossed immunoelectrophoresis, only the anti-septal region fraction was psychoactive, and we therefore assumed it contained a unique additional antibody. In the absence of structural change or local cellular response, we further concluded it acted by changing the receptor in a reversible way. These results, in which known antibody fractions against the septal region induced recording and behavioral changes in the assay monkey closely resembling changes induced by taraxein, strongly suggested that taraxein acted as antibody against the septal region and further affirmed our contention that the septal region was the pivotal brain site implicated in schizophrenia. In a somewhat related experiment, Williams and Schupf (1977) produced antiseptal antibody in rabbits which, when administered to rats, induced transient behavioral changes. Mihailovic and Jankovic (1961), in another study, produced antibody against the caudate nucleus which, when injected into the ventricle of the cat, induced spiking in recordings from the caudate nucleus.

We know of no attempts by others for complete replication of our studies involving production and testing of antibodies to specific brain regions. The lack of interest in these findings was disappointing. Less complex methods were obviously necessary for our hypothesis of schizophrenia to have a hearing.

Studies to Replicate Taraxein Findings

At various times, studies have been undertaken in other laboratories to demonstrate psychotomimetic activity in sera of schizophrenic patients. Some have been successful, whereas others have not. Some investigators used the early salting-out procedures, and others later used the column-fractionation methods.

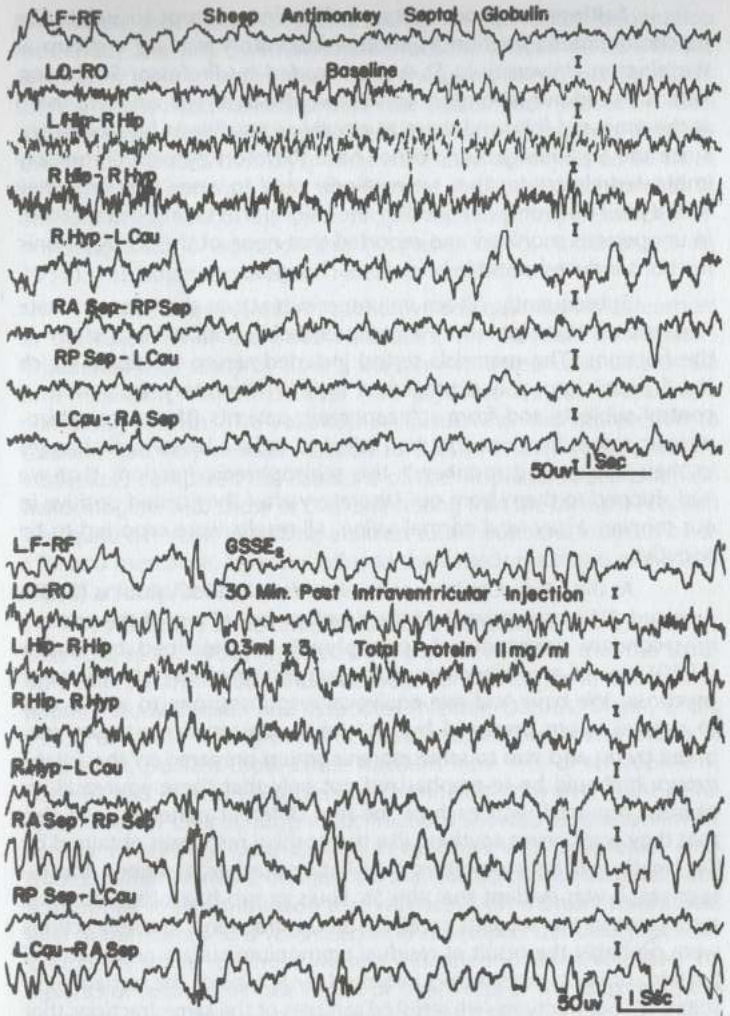

Figure 16. *Electroencephalographic recordings obtained from a rhesus monkey before and after intraventricular injection of sheep antimonkey septal globulin.*

Salting-out procedures. — The first attempt to isolate the psychotomimetic fraction in another laboratory was by a group at Washington University in St. Louis, headed by Professor Eli Robins. Robins visited our laboratory to observe the methods we were using at the time and followed them as closely as possible in his laboratory. Since the St. Louis group did not have the monkey with chronically implanted electrodes that we routinely used to assay fractions, they tested their fractions, obtained by the chloroform salting-out method, in unoperated monkeys and reported that none of the schizophrenic fractions induced notable behavioral changes.

Subsequently, fifteen volunteer subjects at the Missouri State Penitentiary participated in a comprehensive double-blind study of the fractions. The materials tested included serum fractions, which the St. Louis group had processed in their laboratory, from normal control subjects and from schizophrenic patients (the same schizophrenic serum fractions that had failed to induce behavioral changes in their unoperated monkeys), five schizophrenic fractions that we had shipped to them from our laboratory after they tested positive in our monkey assay, and normal saline. All results were reported to be negative.

At the Macy Conference in New York in 1957, Robins (1959) reported: "We have never had the development of any of the primary or secondary symptoms of schizophrenia as described by Bleuler (1950), nor of any other symptoms suggestive of any other kind of psychosis. We have had five equivocal responses: one to saline; one to normal serum prepared by us; one to schizophrenic serum prepared by us; and two to schizophrenic serum prepared by the Tulane group. It should be re-emphasized not only that these equivocal responses occurred with each of the four different materials, but also that they were never anything like the positive responses obtained by Dr. Heath and his co-workers." As Robins further described the responses, it was evident that the St. Louis group had observed toxic symptoms in the subjects receiving serum fractions. These reactions were probably the result of residual ammonium sulfate or denatured protein, or both. After being informed by Robins of the negative results with our fractions, we retested samples of the same fractions that had been psychoactive in our assay monkey before they were shipped to St. Louis and they were inert.

A replicative study was also undertaken in Stockholm by a group that included Martens, who had been a fellow in our laboratory when we began our studies of taraxein and who was therefore familiar with our procedures. The same salting-out method of fractionation was used. The first Swedish serum fractions proved to be inactive when they were tested in unoperated rhesus monkeys. In a careful review, Martens noted several errors in the fractionation procedure. Corrections were made and, on the next attempt, the fractions were active in unoperated monkeys. They were then administered to three volunteer subjects, all staff members of Beckomberga Hospital in Stockholm. In two of the three recipients, symptoms developed resembling those of schizophrenia (Martens, Vallbo, Andersen, et al., 1959). The descriptions of the reactions matched ours.

Since there were both qualitative and quantitative differences in the reactions of the three volunteers, the Swedish investigators broadened their study by having the same volunteers also take d-LSD and mescaline, chosen because their psychotomimetic effects were commonly known. The volunteer recipient who had no reaction to taraxein had only a weak reaction to d-LSD. In their report, the investigators compared the reactions of the recipients to the chemical hallucinogens with those of taraxein, noting that the taraxein reaction was quite different. In striking contrast to the euphoria induced by d-LSD and mescaline, taraxein induced the anhedonia that is characteristic of schizophrenia.

About the same time, Mekler and associates (Mekler, Lapteva, Lozovskii, et al., 1960) reported from the Soviet Union that the schizophrenic serum fraction induced behavioral changes in animals. In another study, Nelson and associates (Nelson, Daniels, Mann, et al., 1963) used the salting-out procedure and, in the second phase of their work, purified those crude fractions from sera of schizophrenic patients and normal volunteers by chromatography over DEAE cellulose. Many of their schizophrenic fractions showed psychotomimetic activity when they were assayed in monkeys with deep-brain electrodes, whereas none of their normal fractions was positive. One schizophrenic serum fraction that was active on monkey testing was later administered to a volunteer, who developed transient psychotic symptoms similar to those we had described in other volunteer recipients of taraxein. A case report of the effects of the taraxein in this recipient was published by his analyst (Lief, 1957).

When we later reviewed those replicative studies in light of information that accumulated, we speculated that the negative results of Robins and associates with their fractions may have been due to differences in the pH of the tap water used for the numerous dialyses in the fractionation procedure. At the time, tap water in New Or-

leans had a pH of more than 10, whereas the pH of the tap water in St. Louis was notably lower. Robins (1959 – page 32) also considered that the differences in pH of the water of the two cities might have been a critical factor. He also noted that psychotomimetic activity was demonstrated in only one-third of the fractions of schizophrenic sera in our test series.

Column fractionation. — Beginning in the late 1960s, Bergen and associates in Massachusetts, using our column fractionation procedure, undertook a serious attempt to replicate our studies. The studies involved staff and facilities of the Worcester Foundation for Experimental Biology, the New England Regional Primate Research Center, the Massachusetts Mental Health Center, and the Center for Blood Research. The group first submitted a report of their results to *Biological Psychiatry* in late August, 1974. The illness of a principal investigator-author, however, unavoidably delayed preparation of the requested revision. The revised manuscript was finally submitted to the journal in August, 1979, and published the next year (Bergen, Grinspoon, Pyle, et al., 1980). The Massachusetts group had spent considerable time in our laboratory to observe our procedures for selecting blood donors, fractionating sera, and implanting brain electrodes in the rhesus monkey. The IgG fractions from control subjects and acutely ill schizophrenic patients that they prepared were tested under double-blind conditions in rhesus monkeys with chronically implanted electrodes, but not in human subjects.

The results obtained by Bergen and associates were a partial confirmation of our findings. Of 107 serum fractions from 24 schizophrenic patients, 29 were shown to have psychosis-inducing activity, a ratio similar to ours. However, of 80 serum fractions from 30 control subjects, six induced a positive response in the assay monkey. Since none of our serum fractions from normal subjects ever showed activity according to our criteria, we questioned the brain site where septal electrodes were implanted in the monkeys used by the Massachusetts group. It was our impression that the septal placements were somewhat deep and rostral, and that the positive tests of normal fractions may have been the result of altered activity of the olfactory bulb. We had previously shown that the olfactory bulb was a sensitive region, responding even to intraventricularly administered normal saline. The question of electrode placement could not, however, be satisfactorily settled retrospectively.

Fluorescent antibody histologic studies. — One technique we used to test the autoimmune hypothesis of schizophrenia involved

reaction of fluorescent-tagged antihuman globulin with postmortem brain tissues of schizophrenic and control subjects (Heath, Krupp, Byers, et al., 1967b). Whereas a large percentage of schizophrenic brains showed antinuclear antibody that was often enhanced by the addition of schizophrenic serum before the tissue was reacted with the tagged antiserum, brain tissues of nonschizophrenic control subjects were negative for such antibody.

After some investigators reported their failure to show antinuclear antibody on neural cells of brains of schizophrenic patients (Logan and Deodhar, 1970; Whittingham, Mackay, Jones, et al., 1968), several reports appeared of the presence of antinuclear antibody on brain cells of schizophrenics as a result of Chlorpromazine medication (Alarcon-Segovia, Fishbein, Cetina, et al., 1973; Berglund, Gottfries, Gottfries, et al., 1970; Knowles, Saunders, and McClelland, 1970; Qusimorio, Bjarnason, Dubois, et al., 1972). We then realized that the finding we had reported was a "red herring." The postmortem schizophrenic brains we had studied were from patients who had been chronically ill in a custodial state facility and had been receiving large doses of Chlorpromazine for long periods. (In subsequent studies in our laboratory, we showed that administration of Chlorpromazine to cats often produced antinuclear antibody.*)

Critical commentary. — In 1957, we presented the results of our studies of ceruloplasmin and taraxein at the Fourth Conference of the Macy Foundation. Robins (1959), also a Conference participant, described the study of taraxein that he and his colleagues had undertaken in St. Louis and their failure to confirm our findings. Although data from initial experiments of the Swedish investigators were discussed, none of that group attended the Conference (Martens, Vallbo, Andersen, et al., 1959; Martens, Vallbo, and Melander, 1959). The ceruloplasmin and taraxein studies were cited extensively in a comprehensive two-part review article in *Science* by Kety (1959), who, at the time, was Chief of the Laboratory of Clinical Science of the National Institute of Mental Health.

As previously described, our attention had been directed to chemical transmitters because of the recording abnormality in the septal region that was uniquely associated with psychotic behavior. In the absence of a consistent structural defect at that brain site, or related sites, we had postulated that transmission was impaired at

---

* Study conducted in 1976 by CB Daul and RG Heath in the Tulane laboratory; results unpublished.

synapses of cells in the septal region. About the same time, other investigators were postulating that schizophrenia was the result of faulty metabolism of epinephrine (Hoffer, Osmond, and Smythies, 1954).

In contrast to what we considered was a rather orderly progression of studies of schizophrenia, Kety, in his review article in *Science*, described the sequence of studies we undertook, beginning with the oxidation test, as ". . . spurious or at least unrelated in any direct way to the schizophrenic process . . ." (page 1952). He further stated that ". . .bona fide discoveries have occasionally been made on the basis of erroneous leads; it does, however, reduce the probability of its occurrence from that involved in a logical interrelationship of sequential proven steps to the extremely small chance of selecting this particular and heretofore unknown substance [reference to taraxein] from the thousands of substances which occur in blood and which might have been chosen."

In his review, Kety did not cite our consistent observation of a functional abnormality focal in the septal region of psychotic patients. That finding was the starting point of our search for a mechanism, whereby synaptic transmission was impaired to produce a recording abnormality in the absence of a structural defect. Although our first hypothesis, which resulted in looking for changes in metabolism of catechol transmitters, failed to lead to an unequivocal answer, it led to the isolation of serum fractions and the formulation of the immune hypothesis of schizophrenia.

As fractionation techniques were improved, we demonstrated that taraxein activity was in the IgG fraction, and hence moved from the hypothesis of a faulty enzyme to the concept that taraxein is antibody affecting the brain. We further postulated that the septal region had a unique antigen that was in some way associated with a receptor (or second messenger), and that the action of taraxein (antibody) on the septal region (antigen) was such as to produce the recording abnormality and consequent psychotic behavior.

Difficulties in replicating taraxein. — In the mid-1950s, we were fortunate to have the resources that were then required to demonstrate taraxein. But most research groups were not in a position to undertake the required studies, and only a small number therefore made the attempt. Of the few investigators who, within the limitations of their resources, made conscientious efforts to reproduce our findings, some failed.

It was a complex undertaking that required a staff of diverse disciplines (psychiatry, neurophysiology, biochemistry) with sufficient interest to make it a major effort and with sufficient funds to support it. The researchers had to have access to a large group of blood donors, who were well evaluated and undeniably schizophrenic. Special equipment and qualified technical personnel were required for the complicated and tedious serum fractionation procedures. The assay monkey with chronically implanted brain electrodes was a constituent that most groups could not consider. Further, replication required a population of volunteer recipients to whom the serum fractions could be administered. Few organizations had or could obtain this combination of resources. Finally, psychoanalysis was the dominant orientation in the United States at that time and, consequently, there was little interest in a possible biological basis for schizophrenia.

Developments Toward a More Specific Serologic Test for Schizophrenia

Background. — In other laboratories, a large number of studies, with a variety of techniques, have been undertaken in attempts to demonstrate the immune hypothesis for schizophrenia. None of the studies has adequately considered our most important, basic observations: first, that the alteration in brain function of schizophrenic patients is very focal and, second, that the titer of antibody is evidently very low, since demonstration of psychotomimetic activity by passive transfer has required large amounts of starting sera, from which a relatively small, specific part of the IgG has been separated out and concentrated.

In nearly all studies carried out in other laboratories, whole brain has been used for antigen and whole sera for the antibody component (Ehrnst, Wiesel, Bjerkenstedt, et al., 1982; Roos, Davis, and Meltzer, 1985). One exception was a study by Baron and coworkers (Baron, Stern, Anavi, et al., 1977), who used whole serum but, for antigen, used septal brain in contrast to whole brain. Their study demonstrated, by radio immunofixation, that schizophrenic patients tend to have higher levels of brain-serum affinity than control subjects.

A major difficulty in trying to establish taraxein has been the insensitivity of passive transfer as an assay. To demonstrate the effects of taraxein in monkey or man has required a high titer of antibody. It was obvious that a much more sensitive and simple assay or test had to be developed for taraxein to be easily demonstrated and hence accepted. Based on the data that had accumulated in our laboratory over the past 40 years, it was our impression that an antigen-antibody interaction was occurring in the brain of the schizophrenic patient to

produce the psychotic behavior. We therefore directed our efforts toward the development of a simpler *in vitro* test.

Crossed immunoelectrophoresis. — The technique of crossed immunoelectrophoresis (CIE) offered a direct means for testing our hypothesis that serum of schizophrenic patients contained an antibody that reacted with a unique and discrete antigen which, by all indications, was present only in the septal region (Heath, McCarron, O'Neil, 1989). By the method of Weeke (1973), the antigen, after being treated with Triton x-100, was spread out by electrophoresis and then cross-electrophoresed against a gel containing the serum fraction. If antibody was present, an antigen-antibody reaction occurred to form a precipitin arc. For our procedure, antigens for CIE were prepared from tissues pooled from four or five rhesus monkeys' brains that were obtained when the animals were killed. Tissues from the septal region, hippocampus, vermal cerebellum, and frontal cortex were dissected for immediate use (Heath and Krupp, 1967a), or brains were frozen at -70° C for later dissection. Liver tissue was used for control. Since fresh monkey brain tissue was much more available than fresh human brain tissue, we standardized on it after determining that results were the same with monkey tissue as with similarly dissected tissues from a human brain obtained three to four hours after death.

We first used the CIE technique with sera from sheep immunized with brain homogenates of septal region or cerebellum and from non-immunized sheep. The sera were electrophoresed against homogenates* of monkey septal region, vermal cerebellum, hippocampus, and frontal cortex. Antigen-antibody was demonstrated with serum of immunized sheep, but not with serum of uninoculated sheep. Whereas whole serum of the immunized sheep produced no precipitin arc or, at best, only faint arcs, the gamma G immunogloublin (IgG) fraction from eight ml of serum concentrated to one ml produced one or more very distinct arcs. This was similar to our earlier experiences with passive transfer, in which psychosis-inducing activity was demonstrated in the assay monkey (rhesus monkey with deep and surface electrodes) only when concentrated IgG fractions of sheep anti-septal brain sera were tested.

Based on our hypothesis that the septal region contained a unique antigen, we reasoned that the fraction containing antibody against the septal region would have one or more precipitin bands

* Spread out by a first electrophoresis.

not present in antisera made against other brain parts. But the CIE technique was not precise enough to manifest discrete bands. Although qualitative demonstrations of an antibody-antigen reaction were consistent, the bands were not always of the same configuration or in the same place on repeated testing. Moreover, the precipitin arcs produced by reacting anti-septal serum fractions with septal brain homogenates were not notably different from those formed by reacting anti-cerebellar serum fractions with brain homogenates, and antisera against both brain regions produced multiple arcs when cross-immunoelectrophoresed against homogenates of several brain regions. Obviously, the brain homogenates used to innoculate the sheep had antigenic components common to all brain regions, in addition to the putative psychosis-inducing antigen to the septal region. Nonetheless, the anti-brain sera produced in animals have played a valuable role in the development of a procedure for testing human sera against brain homogenates, and for routine quality control of the homogenates that vary in antigenic activity.

When whole sera from acutely ill schizophrenic patients was cross-immunoelectrophoresed with septal brain homogenate (antigen), the tests were negative, that is, no precipitin arc formed. Whole sera had similarly produced negative results when it was used for the passive transfer test in the monkey assay. We therefore chose to concentrate the IgG fractions of schizophrenic serum from the DEAE cellulose column. Whereas negative results were obtained when a one ml concentrate of IgG from 8 ml of schizophrenic starting serum was cross-immunoelectrophoresed with septal antigen, a one ml concentrate of IgG from 16 ml of such sera produced one or more distinct precipitin arcs similar to those obtained when sheep antibrain serum fractions were tested (Heath, McCarron, and O'Neil, 1989).

We subsequently developed a protocol for testing sera of patients with schizophrenia (diagnosis based on DSM-III criteria, American Psychiatric Association, 1980) and, for control, sera of healthy normal subjects and of patients with a wide range of disease processes other than schizophrenia, including affective disorder, autoimmune disease (Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus), organic mental disorder, personality disorder, seizure disorder with or without psychosis, and substance abuse disorder. On the supposition that neuroleptic medication might influence results (based on previous experience with the passive transfer test), blood samples were obtained from *un*medicated schizophrenic patients (patients who had never had neuroleptics prescribed or who had been noncompliant for at least three weeks before sampling), as

well as from schizophrenic patients who were receiving neuroleptic medications.

Briefly summarized, our first results were from 66 schizophrenic spectrum patients (catatonic, disorganized, paranoid, and undifferentiated types, as well as schizoaffective and schizophreniform disorders) and 72 nonschizophrenic control subjects (Heath, McCarron, and O'Neil, 1989). The IgG fractions of 24 of 25 (96%) unmedicated schizophrenic spectrum patients and of six (100%) schizophrenic patients who had been on neuroleptic medication for less than 24 hours were positive (at least one precipitin arc was identified) when tested against septal region homogenate. In contrast, the fractions of only two of 35 (6%) schizophrenic patients who had been on neuroleptic medication for more than 24 hours showed precipitin arcs. Fractions of all 72 (100%) nonschizophrenic control subjects were negative when tested against septal region homogenate. With three exceptions,* fractions that had tested positive against septal region homogenate were negative when tested against similarly prepared homogenates of other tissues, including hippocampus, vermal cerebellum, frontal cortex, and liver.

Repeat blood samples were obtained from 11 of the 25 unmedicated schizophrenic patients after they had been receiving neuroleptic medication for at leasts one week and, in contrast to the original positive results, all 11 now tested negative against septal region antigen. Repeat blood samples were also obtained from two other patients in the original group of 25 unmedicated schizophrenics, when they returned to the clinic in a remitted state after neuroleptic medication had alleviated symptoms. Although both patients had stopped taking medication at least three weeks before the second testing, their repeat tests with the IgG fraction from 16 ml of serum were negative. Concentrated IgG fractions from 40 ml of serum (obtained by plasmapheresis) from each patient, however, were positive. When similarly concentrated IgG fractions of 40 ml of serum from seven nonschizophrenic control subjects and of two medicated schizophrenic patients were tested against septal region homogenate, the results were negative in every case.

Test results with CIE are not always reliable, principally because of problems with antigen. The crude brain homogenates contain considerable debris that can obscure the results. In addition, they

* The serum fractions from three schizophrenic patients were positive against homogenates of all brain tissue and liver.

are unstable, deteriorating at an unpredictable rate even when frozen, probably as a result of proteinase activity. Our only way to evaluate the antigenic activity of the homogenates was to test them against freshly fractionated sheep antimonkey brain antibody. However, the serum fractions are also unstable, losing activity within a few weeks even when frozen. This is in contrast to whole serum, which has been shown to retain psychotomimetic activity for several years.

From the collected data reviewed here, we postulate that the biologic process inducing changes in brain function in schizophrenic patients that correlates with their psychotic behavior represents an autoimmune disorder. Our latest approach is devised to identify the hypothetical specific antigen and antibody that produce the altered function. Toward this goal, a series of experiments, with use of a modified Western Blot technique (Laemmli, 1970; Harlow and Lane, 1988), have been designed by Henderson.* The aim is to identify components in homogenates of the septal region that are different from those in other brain sites (hippocampus, cortex, and cerebellum) since, we postulate, the septal region has a unique antigen. Homogenates of the four brain sites are being interacted with IgG serum fractions of schizophrenic patients and control subjects on the premise that the psychoactive IgG fractions from schizophrenics will react with the antigen unique to the septal region, whereas IgG fractions from control subjects will not.

Detection of retroviral serum antibodies in schizophrenics. — Other promising studies under way in the Tulane laboratory are being conducted by Dr. Darrenn Hart.* Anti-retroviral antibodies have recently been detected in a significant number of archived sera from patients with a variety of schizophrenic spectrum disorders. Preliminary data suggest that the titer of these antibodies may fluctuate during the course of the illness, with the stronger reactivity observed during the active phase. In an initial study of one patient, the presence of anti-retroviral antibodies also correlated with the presence of

* Lee A. Henderson, Ph.D., Collaborator and Principal Investigator for these studies. Formerly, Assistant Professor, Department of Pathology, Tulane University School of Medicine and now, Director of the Laboratory of Viral Immunology, Guthrie Foundation for Medical Research, Guthrie Square, Sayre, Pennsylvania 18840.

* Hart DJ, Heath RG, Sautter FJ Jr, Garry RF, and Beilke MA: Detection of retroviral serum antibodies in schizophrenics. Poster presentation (Abstract 254), 1995 Meeting of the Society of Biological Psychiatry, Miami, Florida.

antibodies that recognized antigens extracted from the septal region of rhesus monkeys. The titers of these antibrain antibodies paralleled those of the anti-retroviral antibodies during different phases of the illness. A comprehensive search is now under way for a retrovirus or a retroviral element associated with these disorders. Since previous studies that have failed to find evidence of a retrovirus associated with schizophrenia used detection methods of limited accuracy, we feel the viral hypothesis of schizophrenia remains viable.

Recent studies have also associated possible retroviral involvement in the etiology of certain autoimmune diseases. One attractive hypothesis is that of antigenic mimicry, in which a viral antigen resembles a normal host cell antigen in structure. The immune response directed against the viral antigen may then cross-react with the cellular component, resulting in a condition of autoimmunity. In light of the studies we conducted during the late 1950s and 1960s, it is possible that such cross-reactive antibodies constituted what we named "taraxein," the transient psychosis-inducing serum fraction obtained from schizophrenic patients. The search for a human retrovirus or retroelement, and associated autoimmunity in schizophrenia, is the focus of current research.

Therapeutic Attempts with Ceruloplasmin and Septal Extracts: Provocative Results for Future Considerations

Based on our findings that pointed to a chemical basis for schizophrenia, we devised two therapeutic trials in the late 1950s. The first, as described briefly in a previous section on catecholamine oxidation and ceruloplasmin, involved intravenous administration of large quantities of ceruloplasmin to schizophrenic patients with provocative, but equivocal, results.

In a second approach, first used in 1955, extracts of septal region of cattle brain* were administered intramuscularly to schizophrenic patients who had failed to respond to any therapy of that period (Heath, Leach, Byers, Martens, and Feigley, 1958; Heath, 1959; Heath, and Leach, 1962). Therapeutic results were favorable in some of the 38 severely ill patients to whom it was given, the longest trial in a patient having been 18 months. With the extracts, however, there was always concern that the recipient might become sensitized to possible protein residues in the extracts. Nonetheless, the beneficial effects prompted a major pharmaceutical house to undertake a larger study. But the results were essentially negative. Concerned about the possibility of sensitivity to protein in the preparations, they modified the procedure for preparing the extracts, and only very small molecules remained after the extracts had been passed over large columns. We did not have the resources to continue the studies, and the effort was therefore abandoned.

* Extracts were of acetone-dried powder after papain digestion into polypeptides (Heath and Leach, 1958).

Our rationale for use of septal extracts was based on the premise that the septal region, shown to be malfunctioning in the psychotic schizophrenic patient, might be secreting a peptide that needed to be restored. Since evolving our autoimmune hypothesis of schizophrenia, we reviewed our findings in the 1950s against newer data concerning autoimmune disease. In recent studies in animals, the administration of organ-specific antigens has been shown to be effective in preventing, and possibly treating, some autoimmune diseases (von Boehmer and Kisielow, 1991).

Brain Function and Epilepsy

As previously described, most of the 66 patients who participated in our therapeutic deep electrode studies had schizophrenia. A few patients intractably ill with disorders such as Parkinson's disease, cancer, or rheumatoid arthritis also participated. The data that accumulated from the first 30 of the patients, all of whom were schizophrenics who had failed to respond to conventional treatments, as well as from animals being used in concomitant studies, suggested the possibility of more effective treatments for epilepsy, and that was our rationale for including nine patients with that disorder in the special studies. Consistent with our interest in brain mechanisms in psychosis, seven of the nine epileptic patients were episodically psychotic. In association with the therapeutic procedures involving deep electrodes that were used in these patients over an extended period, we were also able to collect additional information regarding brain function as it correlated with emotion, sensory perception, and memory.

Since the epileptic patients with multiple implanted deep and surface electrodes were fully conscious between seizures (interictal periods), they were able to report their thoughts and feelings. Hence, it was possible to correlate their mental activity and observed behavior with activity at numerous brain sites, including those implicated in the seizural discharges. Furthermore, since most of these pa-

tients also had episodes of psychosis, we were able to correlate their psychotic behavior with associated changes occurring in recordings from numerous deep brain sites. These findings, augmenting data obtained by the same methods from patients with schizophrenia and other illnesses, thus afforded an opportunity to gain additional information concerning the relation between epilepsy and psychotic behavior.

Epilepsy, like the psychoses, is a syndrome or group of symptoms that can be attributed to a variety of causes. The data that follow indicate that the brain sites involved and the nature of the recording changes correlate with the onset and type of epileptic seizure, just as the sites involved and nature of the recording changes correlate with the appearance of psychotic behavior. When patients who presented with both epilepsy and psychosis were experiencing seizures, changes in their recordings corresponded to those in epileptics, and when they were psychotic, their recordings were similar to those of patients with psychoses of other origins, including schizophrenia (Mickle and Heath, 1957; Heath, 1986a). Thus, the site involved and nature of the recordings coincided with the prevailing clinical state.

Interictal Recordings

Our studies showed that the deep recordings of the epileptic patients displayed abnormal activity, in the form of intermittent spiking occurring principally in the amygdala and hippocampus, between seizures and between episodes of psychotic behavior (Fig. 17). These discharges at subcortical sites were present when cortical and conventional scalp EEG recordings were normal, or showing only minimal changes. If the abnormal activity was infrequent and confined to the amygdala and hippocampus, the patient was often asymptomatic.

At other times, when high-amplitude spike and sharp wave discharges of longer duration appeared in the amygdala or the hippocampus, with only the occasional appearance of a spike or sharp wave in cortical or scalp recordings, the patients experienced intense emergency behavior, in the form of anxiety, irritability, or unprovoked anger, that was unexplainable on the basis of psychodynamics or current events (Fig. 18) (Video tape). With development of aura, characterized by altered emotion in the form of visceral symptoms or alterations in sensory perception, recording abnormalities intensified at subcortical sites and appeared more often in surface recordings from the cortex and scalp.

Although the altered activity that occurred in recordings of

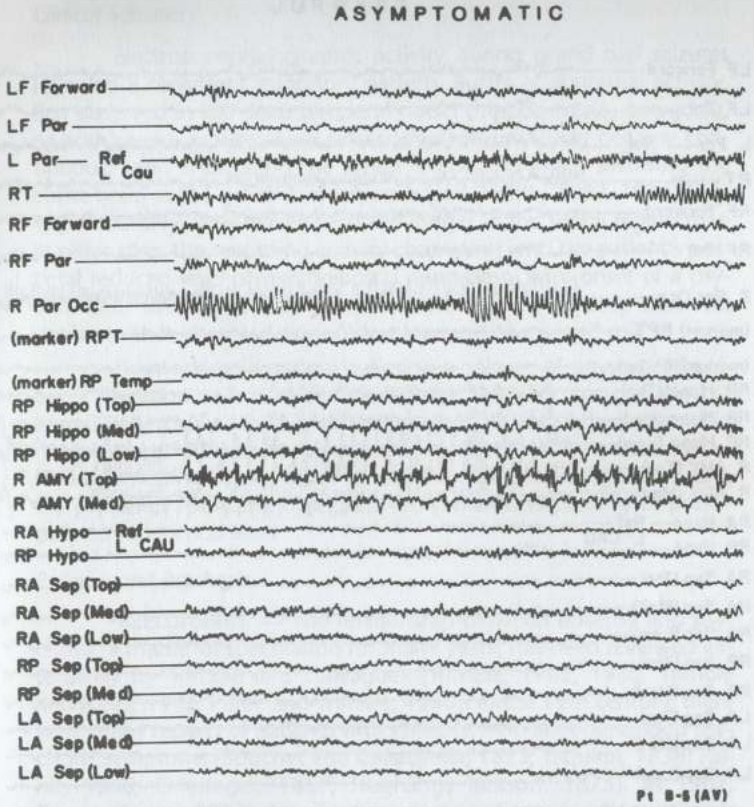

Figure 17. *Electroencephalographic recordings obtained from an epileptic patient when she was asymptomatic.*

epileptic patients during adversive emotion was at the same sites (principally the hippocampus and sites in the amygdala) at which it appeared in nonepileptic patients during states of emergency emotion, it had different characteristics. Sharp waves, spiking, and slow activity predominated, in contrast to bursts of high-amplitude spindling in the nonepileptic patients. The reporting of the epileptic pa-

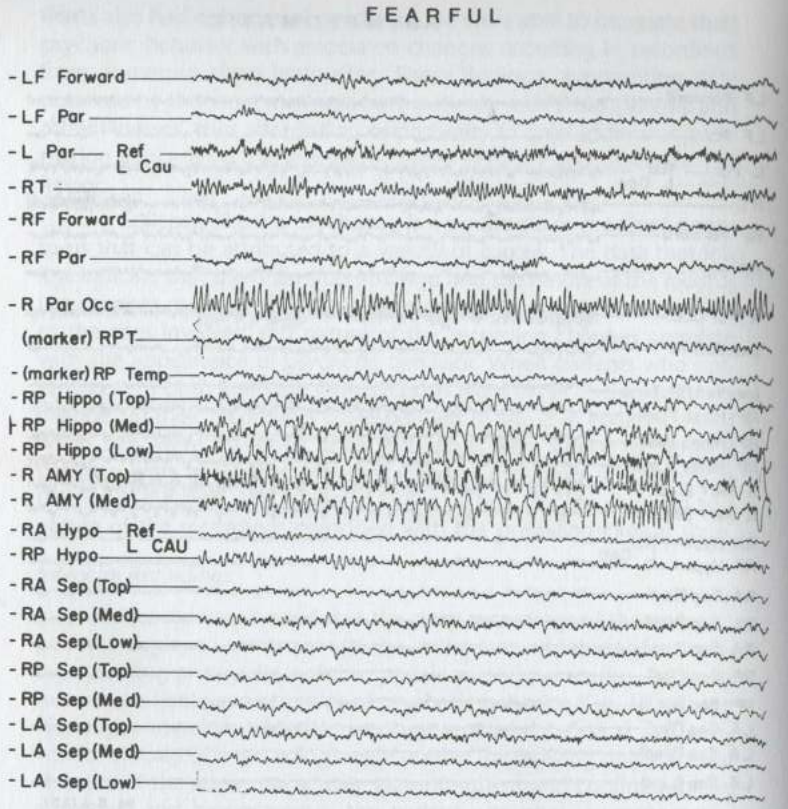

Figure 18. *Electroencephalographic recordings obtained from an epileptic patient when she was expressing anxiety and fear.*

tients indicated that their electrical discharges were initiated by the brain aberration responsible for their epilepsy (underlying organic abnormality), whereas the recording alteration of the nonepileptic patient, and associated altered emotion, was the result of current happenings related to his psychodynamic background (experiences).

Clinical Seizures

Electroencephalographic activity during grand mal seizures followed a consistent migratory pattern. Bursts of abnormal activity, first observed in the deep temporal nuclei (hippocampus, amygdala, or both), were progressively closer together, until they became continuous, soon implicating the septal region and finally involving the entire brain as the grand mal seizure began (Heath, 1982, 1986) (Fig. 19). Postictally, slow-waves persisted longer at the septal region than at other sites, the recording activity correlating with the patient's postictal reduced level of psychological awareness. With onset of a psychomotor seizure, buildup of epileptiform activity at deep sites was similar to that observed during development of a grand mal.

If an epileptic patient suffering a seizure of any type developed alteration or loss of consciousness, profound changes also occurred in cortical and scalp recordings. In contrast, if the patient did not lose consciousness during a period of inappropriate emotional behavior, including psychosis, or during the aura preceding the seizure, the profound recording changes were confined exclusively or principally to subcortical sites.

Epilepsy and Psychosis

Background. — The relationship between epilepsy and psychosis, a matter of speculation for many years, has been reviewed extensively by Trimble and colleagues (Trimble, 1982, 1986; Trimble and Perez, 1982; Perez and Trimble, 1980). In the 19th century, there were many reports of patients with epilepsy, who later developed psychotic symptoms (Bouchet and Cazauveilh, 1825; Esquirol, 1838; Falret, 1860; Griesinger, 1857; Hughlings Jackson, 1875). In 1907, Turner (Turner, 1907) described psychotic patients in whom seizures ultimately developed as well as patients who had had seizures and subsequently displayed psychotic behavior. None of these authors, however, detailed the type of seizure(s) most often associated with the psychotic behavior.

Bouchet and Cazauveilh (1825), in their report on patients with epilepsy, described a relationship between temporal lobe disorder and psychosis. It was not until the advent of the electroencephalogram, however, that sufficient evidence accumulated to establish a correlation between abnormal electrical activity over the temporal lobe of epileptic patients and pathologic behavior, including psychotic episodes.

In contrast to the reports that suggested the two syndromes

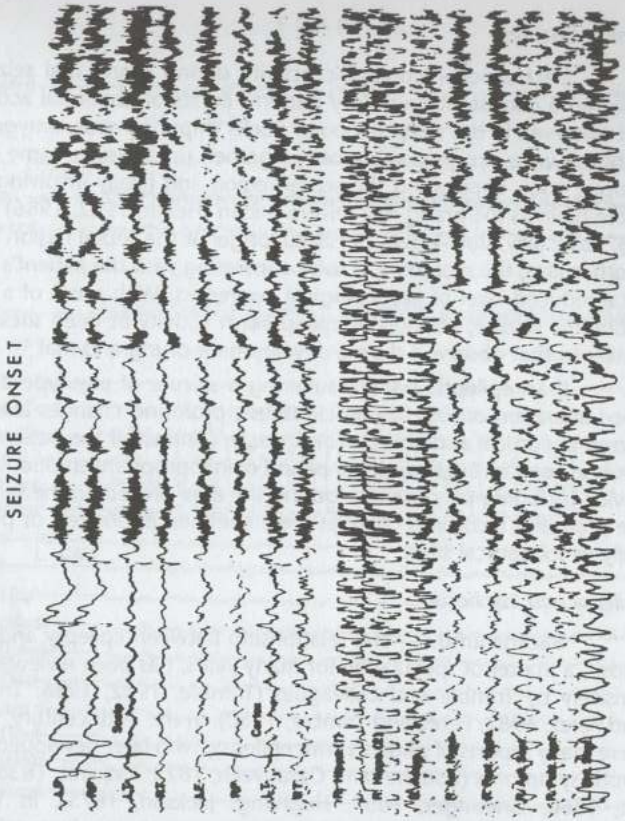

Figure 19 *Electroencephalographic recordings obtained from an epileptic patient during onset of a seizure.*

were interrelated and, in some instances, might be the result of a common brain disorder, reports appeared in the 1930s suggesting that the two syndromes were inversely related. Glaus (1931), pointing out that epilepsy and psychosis were found together less often than would occur by chance, hypothesized the two conditions were antagonistic. Von Meduna (1937) also postulated an inverse relation between the two disorders and, on that conjecture, introduced convulsive therapies for the treatment of psychoses, including schizophrenia, in the 1930s. After first using camphor as the convulsive agent, he changed to Metrazol. Electroconvulsive treatment was developed later by others.

In 1943, Hoch (1943) reported on his review of the records of 500 schizophrenic patients and 100 epileptic patients. Most of the schizophrenics had normal electroencephalograms. Only two had a history of convulsions, and one of them clearly had pseudo-seizures. In contrast to the schizophrenics, the majority of the epileptic patients had abnormal EEGs. Ten of the 100 epileptic patients had symptoms resembling schizophrenia. In fact, the behavior of three of the 10 was such that it was not possible clinically to differentiate them from schizophrenic patients. Hoch concluded that his data did not support the hypothesis that schizophrenia and epilepsy were interrelated. He also stated that the small number of schizophrenic patients with electroencephalographic abnormalities suggestive of epilepsy should be split off into a separate group.

The psychological symptoms of epilepsy are many and diverse. Although they sometimes closely resemble the picture seen in the functional psychoses, at other times, changes in the sensorium predominate. In 1937, Gibbs and associates (Gibbs, Gibbs, and Lennox, 1937) proposed the diagnostic category of "psychomotor epilepsy" for the patient group with temporal lobe EEG abnormalities and a clinical picture in which psychotic symptoms were prominent, and it was generally accepted.

In the psychomotor epileptic group, there is a high incidence of abnormal behavior between seizures (interictal), as well as during a seizure. Presenting symptoms of some patients in this group are often the same as those presented in patients diagnosed as schizophrenic. In describing the electroencephalographic patterns associated with these clinical symptoms, Gibbs and coworkers (1937) noted that abnormal electrical activity was characteristically recorded from the temporal leads of these patients, and for that reason, the terminology "temporal lobe epilepsy" is used interchangeably with "psychomotor epilepsy."

In spite of the common symptoms sometimes presented by epileptic and schizophrenic patients, schizophrenia has its own characteristic syndrome. The constellation of symptoms in schizophrenia is such that trained psychiatrists agree on diagnosis in most cases. Although the electroencephalogram of the schizophrenic subject is characteristically normal, some electroencephalographers have noted

a slightly increased incidence of recording abnormality in the schizophrenic group, as compared to the nonschizophrenic group (Pond, Rey, and Hill, 1950; Ostrow, 1952; Rodin, DeJong, Waggoner, et al., 1957). However, the feature is not unique to schizophrenia; it occurs with similar incidence in certain other disease states (Hill, 1948).

In a few patients, differential diagnosis between the syndromes of schizophrenia and psychomotor epilepsy can be a problem. The confusion usually occurs when interictal behavioral abnormalities of the epileptic are prolonged, rather than being circumscribed or episodic. In view of the very similar symptoms, Perez and Trimble (1980) used the Present State Examination (PSE) on 24 patients with psychosis and epilepsy, in whom the psychosis occurred in a setting of clear consciousness and persisted for at least a month. Twelve of the 24 patients were categorized as having a schizophrenia-like psychosis, and 98% of them, a profile of nuclear schizophrenia. All those identified as having nuclear schizophrenia had temporal lobe abnormalities in their electroencephalogram, whereas psychotic patients with generalized epilepsy and generalized electroencephalographic changes had a variety of psychopathologic presentations. Trimble considered the findings confirmation of a direct link between patients with epilepsy, who had seizures originating in the temporal lobes, and patients with a clear presentation of nuclear schizophrenia. Trimble and associates (Gallhofer, Trimble, Frackowiak, et al., 1985), using positron emission tomography (PET), also reported changes in decrements of oxygen metabolism in the temporal lobe of patients with epilepsy and psychosis.

In our earliest deep electrode patients with schizophrenia (beginning in 1950), in whom recordings were obtained from precise regions of the brain for long periods, abnormal electrical activity was consistently focal in the septal region when they were psychotic, although clinical scalp electroencephalograms were normal. Since we also had a number of psychotic epileptic patients with temporal lobe electroencephalographic abnormalities on our inpatient service, we initiated several studies in an attempt to shed light on the question of an interrelationship between the psychoses of schizophrenia and of epilepsy.

One study was an in-depth clinical evaluation (psychiatric and psychological) of psychotic patients with temporal lobe abnormalities who had disturbances in affect and thought. The picture they presented was very similar to that of psychotic schizophrenic patients when the same criteria were used for evaluation (Ervin, Epstein, and

King, 1955). Results that Perez and Trimble (1980) obtained with Present State Examination (PSE) corresponded to those we obtained in our early study.

With chronically implanted electrodes, we also explored activity at predetermined sites deep in the brain and on the surface of patients with epilepsy, who, while in a state of clear consciousness, had interictal psychotic episodes, as well as of patients with epilepsy who did not have psychotic behavior. The data from these two groups of patients were compared with those from the psychotic schizophrenic patients.

Recordings in epileptic patients during psychotic episodes. — In epileptic patients, onset of psychotic behavior consistently correlated with onset of abnormal EEG activity, in the form of spikes or slow-waves, or both, from septal leads, which persisted as long as the patient showed psychotic behavior (Fig. 20). As psychotic behavior remitted, recordings from the septal region returned to baseline, whereas abnormal recordings at other sites usually continued. The septal spiking was a phenomenon in common in epileptic and schizophrenic patients during episodes of psychotic behavior.

Differences between recordings from the epileptic patients and from the overtly psychotic schizophrenic patients are noteworthy. The septal spiking of the episodically psychotic epileptic patient was usually more pronounced. The spikes were sharper, of higher amplitude, and occurred more often. Septal slow-wave activity was also more pronounced. Moreover, spike and slow-wave activity in recordings from the deep temporal lobe nuclei, both the amygdala and hippocampus, was much more pronounced in the epileptic patients when they were episodically psychotic than in the psychotic schizophrenic patients, who usually showed minor changes, if any, in recordings from the deep temporal lobe structures. Associated abnormal recordings from the cortex and scalp, especially over the temporal regions, were frequent in the epileptic patients and rare in the schizophrenic patients.

Relation Between Schizophrenia and Epilepsy

Abnormal septal activity was present in all our deep electrode patients, not just the schizophrenics and epileptics, in association with psychotic behavior, regardless of its cause (structural abnormality affecting the septal region as the consequence of a degenerative process, vascular disease, or trauma, or the ingestion of a psychotomimetic). Aberrant septal activity also occurred if psychotic be-

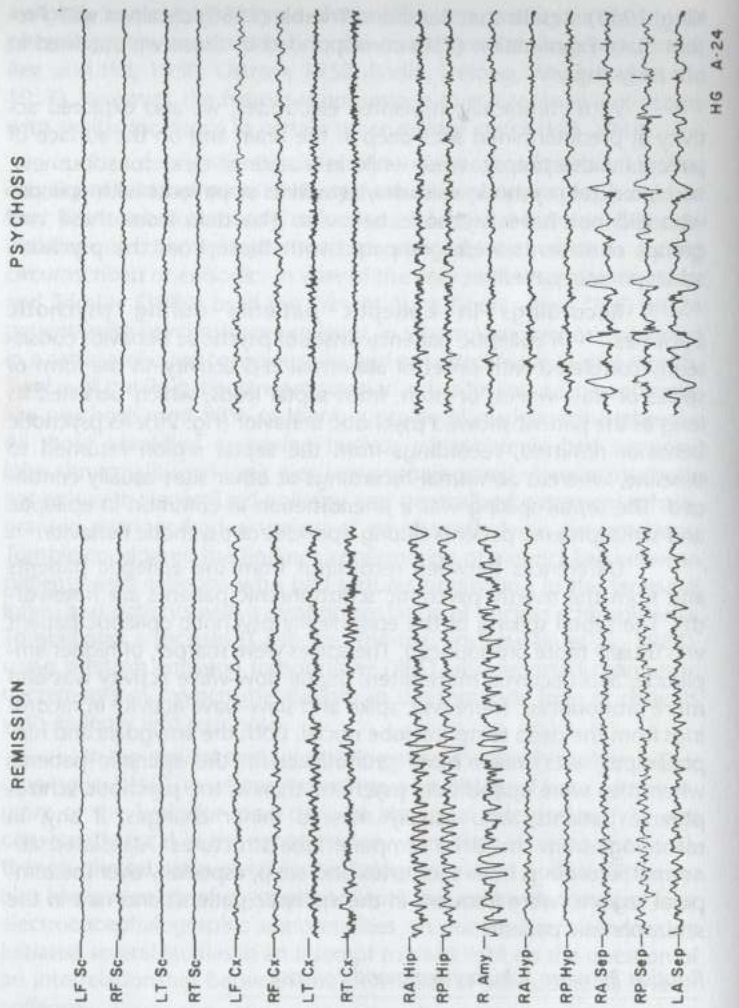

Figure 20. *Electroencephalographic recordings from Patient A-24, an epileptic, when he was in a state of remission and later, psychosis.*

havior developed as a result of the induction of septal spiking by electrical stimulation at slow frequencies of a directly connected site (hippocampus) (Heath, 1964). We thus concluded that psychotic behavior, a syndrome or group of symptoms, can result from a variety of factors if the effect on the brain is to induce the physiologic aberration in the septal region.

On the basis of our data, we have hypothesized that the EEG dysrhythmia in the septal region of schizophrenic patients results from an immunologic disorder, as previously described, quite different from the various underlying disturbances that produce seizures, as well as episodic psychotic behavior, in epileptic patients.

A recent report that the temporal lobe is smaller in some schizophrenic patients than in control subjects may further confuse the issue (Johnstone, Cowens, Crow, et al., 1989). The shrunken temporal lobe may result from a focal cellular abnormality that generates an abnormal focus, which, secondarily, through a direct anatomic connection, induces a dysrhythmia in the septal region, thereby causing the psychotic symptoms. If that is the case, the disorder in patients with smaller temporal lobes may be more closely related to that of patients with psychomotor epilepsy than patients with schizophrenia. Until there is a specific biologic marker for schizophrenia, however, it will not be possible to determine whether this group of patients, considered by Johnstone and coworkers to be a subgroup of schizophrenia, indeed has schizophrenia, or is suffering from a cellular disorder that induces a dysrhythmia in the temporal lobe and directly connnected septal region, thereby producing the psychotic behavior that is often clinically indistinguishable from schizophrenic psychosis.*

Animal Models of Epilepsy

Our use of animal models of epilepsy was based on observations in our early temporal lobe epileptic patients, who were being treated with deep electrode techniques. It was generally believed that seizures emanating from temporal lobe foci were confined to the con-

---

* The discovery of a biologic marker for schizophrenia will be comparable to the serologic test for syphillis. That test made it possible to segregate the psychosis of general paresis, which, like the psychosis of epilepsy, was often clinically indistinguishable from schizophrenia. Similarly, a biologic marker, the urine or blood test, has made it possible to distinguish the psychosis of psychotomimetic ingestion from that of schizophrenia.

ventional limbic system (MacLean, 1970; Collins, Tearse, Lothman, 1983; Crandall and Sutherling, 1988). Our patients, however, had symptoms that suggested that additional structures were involved. During an episode, they not only displayed emotional dyscontrol similar to that of patients with other disorders in which activity of deep temporal lobe nuclei were altered, but had changes in sensory perception associated with distinct changes in expression of the face and eyes. In some patients in whom electrodes were implanted into one or more sensory relay nuclei, epileptiform activity occurred in the sensory relay nuclei during seizures, as well as in limbic structures. Furthermore, the patient data indicated that sites implicated in the propagation of an epileptic seizure were the same sites where activity had been shown to correlate with emotion.

Hence, the data from epileptic patients, as well as from patients with other disorders, provided impetus for our animal studies aimed at demarcating the neural basis for both emotion and seizures. In addition to the limbic forebrain, the monosynaptically connected nuclei and pathways implicated were those subserving sensory perception, facial and eye expression, and nuclei for chemical transmitters. As discussed in a previous section, electrodes could be implanted at sites in the animals that would have been too risky to implant in patients. The most effective technnique for determining functional relationships proved to be implantation of the irritant, cobalt, into the several sites in the circuitry that were shown, by anatomic studies, to be connected. We demonstrated that initiation of an epileptiform focus at one nuclear site within this neural network resulted in activity throughout the entire network (Fig. 4). We also found, as other investigators had, that once distal foci were generated away from the primary site where the irritant was implanted, they continued to discharge after the preliminary site was extirpated. These observations highlight some of the difficulties and shortcomings of clinical techniques for treatment of epilepsy that involve the search for a primary focus by insertion of electrodes only into the deep temporal lobe.

Treatment of Epilepsy: Evolving Methods and Results

As new data were generated from our patient and animal studies, we modified our methods for treating epilepsy. Our original rationale for the use of deep electrodes was to demarcate the focus from which the seizure emanated and remove it by ablation. About that time, reports appeared that indicated that removal of the anterior temporal region in patients experiencing psychomotor seizures was effective in significantly reducing or eliminating seizures in almost

half of them (Bailey, Green, Amador, and Gibbs, 1953). However, those patients all had demonstrable anterior temporal foci on their EEGs, whereas none of the patients in our group had well-defined temporal lobe foci. Recordings of our patients revealed that seizures did not always originate from the same site. But even with multiple deep and surface electrodes in place, we failed to pinpoint the site of a discharging focus.

More recent reports support the early observations that epileptic patients, in whom a well-defined focus has been established, benefit significantly from surgical removal of the site of the focus. Norman and associates (1989) reported that 40% of a group of 48 patients with defined foci were greatly improved as a result of temporal lobe resection and 29% became seizure-free. It is noteworthy, however, that the unilateral temporal lobe resections involved subcortical temporal lobe nuclei, as well as temporal cortex.

Our animal models for epilepsy, in which primary seizural foci were initiated by implantation of an irritant, also influenced our approach in treating intractable epilepsy.

Electrical stimulation to subcortical sites of epileptic patients. — Our experience in recording from, and stimulating, deep brain sites in epileptic patients was a determinant in our first therapeutic efforts. The various deep sites into which electrodes were implanted were stimulated, as they had been in schizophrenic patients and in patients with other intractable illnesses. It was notable that the pleasurable emotional response of the epileptic patients (as of other nonschizophrenic patients) was much more intense than that of the schizophrenic patient, suggesting the schizophrenic, as a result of his still undefined disorder, had impaired activity at these sites. In the epileptic patients, we also observed that the threshold for inducing seizures with stimulation of deep temporal lobe structures was much lower than in patients with other disorders.

The reponse of the epileptics to stimulation of specific brain sites contributed to our efforts to identify the circuitry for pleasurable and adversive emotions. When pleasure was induced, it was the result of activation of the same sites that produced a pleasurable response in patients with other disorders. Likewise, an adversive emotional response with stimulation resulted from activation of the same sites that induced unpleasant emotion in other groups of patients. In our epileptic patients, stimulation never elicited memories of previous episodes of past life that Penfield and associates (Penfield and Jasper, 1954; Penfield and Perot, 1963) cited. When our patients, at times,

recalled previous experiences, it was the consequence of the emotional state induced by the stimulation. For example, if the patient became rageful with stimulation, he likened his feelings to those elicited by a specific event in the past.

The finding that particularly influenced our therapeutic approach, however, was that stimulation of pleasure sites, specifically of the septal region, tended to reduce the frequency of seizures. We postulated that by a process akin to kindling, activity in the discharging focus was thereby permanently inhibited. Unfortunately, with longer follow-up, the effect proved to be transitory. When, after a few weeks or months, seizures recurred at their prestimulation level, we turned to other therapeutic approaches, including introduction of chemical transmitters directly into deep brain sites.

Chemical stimulation to subcortical sites of epileptic patients. — Whereas introduction of catecholamine transmitters into the hippocampus lowered seizure threshold, resulting in increased frequency of seizures, introduction of acetylcholine into the cholinergic cells of the septal region (basal forebrain) induced prolonged activation of epileptiform discharges there, resulting in significant inhibition of activity at deep temporal lobe structures where seizures originated. The clinical consequence was a notable reduction in the incidence of seizures for an appreciable period.

Use of acetylcholine in a 33-year-old woman (Patient B-5) with epilepsy was briefly described in a previous section ("Pleasure induced by direct chemical stimulation of the brain"). Except for borderline mental retardation (I.Q. 75), this patient's development was normal until, at the age of 22, she began to have partial complex and grand mal seizures, as well as episodes of status epilepticus lasting as long as six hours. During the year preceding her admission to our service and stereotaxic implantation of electrodes and cannulas, the patient's seizures, which usually occurred immediately before and during menstruation, had averaged eight per week despite various combinations of anticonvulsant drugs. During previous hospitalizations, her EEGs were often abnormal, with maximal dysrhythmia over the temporal region.

Before treatment with acetylcholine was begun, deep and surface recordings were obtained in association with a variety of emotional states and during many seizures. Interictally, spike and slow-wave activity, or both, occurred principally in the hippocampi and amygdalae; these deep recording abnormalities correlated with her emotional state and were often present even when cortical and scalp EEGs were normal. With clinical seizures, epileptiform recordings developed first in one amygdala or hippocampus and then spread to the opposite side and to the septal region before encompassing the cortex, at which time the clinical seizure began (Heath, 1982) (Fig. 19).

With introduction of acetylcholine directly into the septal region, the patient became euphoric (often experiencing sexual orgasm) in association with continuous bursts of high-amplitude spindling focal in the septal region, activity that diminished gradually over a thirty-minute period (Heath, 1972). While the profound recording changes were occurring focally in the septal region, the cortical and scalp recordings were usually normal, showing a shift toward lower amplitudes, and high-amplitude slowing and frequency of spiking in the hippocampus were reduced (Fig. 8). After the first acetylcholine treatment, the patient's seizures stopped and all anticonvulsant medications were discontinued. For ten weeks, she was given 70 lambda acetylcholine (467 micrograms) weekly into the septal region. For six months thereafter, she remained seizure-free. She then developed several seizures, and Dilantin (100 mg t.i.d.) was resumed. During a ten-year follow-up period, the patient continued to take Dilantin, and averaged only one to two seizures a year.

When the patient died of pulmonary emboli in 1974, an autopsy was performed in her home community, and her brain was placed in 10% formalin and sent to our laboratory for study. On gross sectioning, the brain was essentially normal, the only finding being suggestive evidence of one cannula track in the septal region, and four small silver-ball electrodes, and there was a small area of gliosis at the presumed site of one of the cannula tracks. Otherwise, cellular structure throughout the septal region appeared normal.

Another patient (B-22), who occasionally showed temporal lobe abnormalities on scalp electroencephalograms but who had no clincial seizures, was treated with introduction of acetylcholine into the lateral amygdala. When she was referred to us, she had been ill without significant remission for six years. In consulting numerous psychiatrists throughout the country, she had been variously diagnosed as having chronic anxiety neurosis, latent schizophrenia, schizoaffective disorder, or temporal lobe epilepsy (based on electroencephalographic recordings). Different psychotherapeutic attempts by her physicians, including numerous psychotropic medications and two courses of electroconvulsive treatment, failed to relieve her signs and symptoms. Early in 1971 she gained relief for ten days after receiving a bimedial tractotomy (conservative lobotomy), but

the symptoms recurred. At the time of that operation, ventriculography showed her ventricles to be minimally enlarged.

When we first saw the patient in mid-1972, she was tense and anxious, but there was no evidence of looseness of associations, delusions, or hallucinations. Scalp electroencephalograms showed abnormalities over the temporal lobes. Large doses of tranquilizing medications were required even to reduce her agitation and sleeplessness. A trial using the monoamine oxidase inhibitor, tranylcypromine (Parnate), the only antidepressant medication that had not been tried previously, was unsuccessful and complicated by development of orthostatic hypotension. On one occasion after her discharge from the hospital, the patient made a serious attempt at suicide, requiring a week of recovery in an intensive care unit. At the end of 1972, she returned to our program for implantation of electrodes and cannulas.

Introduction of acetylcholine into the lateral amygdala on two occasions, at an interval of two days, induced pleasurable feelings and focal spindling in recordings from that site that lasted an hour. During a third treatment three days later, however, seizural activity that first developed in the lateral amygdala spread to the cingulate gyrus, and then, with onset of a grand mal convulsion, involved the whole brain. Following this, the patient's psychiatric symptoms remitted. During a follow-up period of 20 years, she remained out of the hospital and made no more suicidal attempts. Occasional electroencephalograms over those years showed fewer abnormalities or were normal.

We have no satisfactory explanation for the prolonged therapeutic effects of chemical stimulation in epileptic patients. The recording change that was focal in the septal region with introduction of acetylcholine was epileptiform and similar to those recorded from the scalp during an actual seizure. Yet the patients were mentally clear, more alert than usual, and felt good. Our animal experiments have shown that activation of the septal region inhibits unit activity in the hippocampus (Heath, Dempesy, Fontana, and Fitzjarrell, 1980). Since clinical seizures were associated with activation of the hippocampus, we postulate that the beneficial effects associated with chemical stimulation of the septal region resulted from inhibition of hippocampal cells. Despite the successes we had with the procedure, we have not used it in epileptic patients since the early 1970s.

Continuous cerebellar stimulation. The last therapeutic approach we used in epileptic patients was initiated in 1976, when we implanted electrodes over the vermis of the cerebellum for delivery of

an ongoing stimulus (Heath, 1977; Heath, Llewellyn, and Rouchell, 1980; Heath, Rouchell, and Llewellyn, 1981). Cooper and associates (Cooper, Amin, Riklan, et al., 1976), on the basis of findings obtained by Snider (1967) in animal experiments, were the first to use cerebellar stimulation for the treatment of epilepsy. Our rationale for its use was based on a series of studies in our laboratory, beginning with use of deep electrodes in the Harlow monkeys, in which stimulation of the midline cerebellar structures was shown to inhibit cellular activity in the hippocampus, as described in a previous section (Heath, 1972b; Heath, Dempesy, Fontana, Myers, 1978; Heath, Dempesy, Fontana, Fitzjarrell, 1980). Since activity of the hippocampus intensified immediately preceding the onset of a seizure and during adversive emotional states, we postulated that cerebellar vermal stimulation would control the seizures, as well as associated adversive symptoms, particularly violent behavior. Like the patients in the earlier series with epilepsy and intractable behavioral disorders in whom deep electrodes were implanted, these patients did not show a temporal lobe focus on repeated electroencephalograms.

The results obtained in nine patients with this syndrome have been gratifying. When the first patient in this series was referred to us, he had been continuously hospitalized for seizures and violent behavior for many years. He has had a stimulator since 1976. As of this writing, 19 years later, he continues to live outside the hospital without seizures or violent behavior.

The seizures and violent behavior of another patient, who was first equipped with a stimulator in 1977, were well controlled for ten years, at which time the incidence of seizures with episodes of psychotic behavoir gradually increased. In two other patients, the duration of beneficial effects was shorter. We postulated that the scar tissue that had built up between the electrodes and the arachnoid of one of them, noted when his stimulator was removed from the surface of the cerebellum, was responsible for the diminished effectiveness of the stimulation (Heath, 1992).

The contribution of the cerebellar stimulator, in terms of the theme of this monograph, has been to demonstrate the functional relationship postulated from animal studies, namely, the manner in which the cerebellum is involved in the neural mechanism for emotion. Other recent studies have also implicated the cerebellum in the mechanism for memory (McCormick and Thompson, 1984a, 1984b; Steinmetz, Logan, Rosen, Thompson, Lavond, and Thompson, 1987; Thompson, 1988).

Comment

The methods used in these studies provide significant information about the brain's neural network for emotion, sensory perception, and memory, findings that constitute a basis for relating brain function and mental activity. Newer techniques give promise of extending our findings. We hope that our data will furnish guidelines for conducting sophisticated studies with PET, single photon emission computer tomography (SPECT), and the highly promising magnetic resonance spectography.

A few studies have been reported in which PET has shown a correlation between activity focal at precise brain sites and emotion. Some of the findings correspond with data we gathered in our studies with implanted deep electrodes and cannulas. In one study a few years ago, in collaboration with Bhacca* and with use of a 4.0 Tesla magnetic resonance spectrometer, focal changes were seen in the spectrum recorded from the septal region of monkeys after intravenous administration of delta 9-THC. The changes with this technique were at the same site at which we had demonstrated changes in deep electrode recordings following administration of delta 9-THC to monkeys in a large series of experiments. Because NMR spectroscopy is more precise than PET scanning and does not require administration of labeled metabolites, it probably offers a greater potential at present for extending our studies to demonstrate the relationship between mind and brain.

Although our data relating brain function to mind will unquestionably be expanded or modified through use of these newer techniques, the principal application of our findings, at least for the immediate future, will probably be limited to providing direction for more effective treatment of schizophrenia and other major mental illnesses, epilepsy, and Parkinsonism, and to the understanding and treatment of intractable pain. These data also suggest procedures to ameliorate specific symptoms, such as violence and aggression, in individual patients.

Relatively recent evolutionary changes in the human brain have made possible complex memory, the acquisition and storage of new information, and advanced planning. This has resulted in explosive technologic advances and the potential for man to have a more

* Unpublished study with Norman Bhacca, Ph.D., Louisiana State University, Baton Rouge.

comfortable and productive life. But the organization of the human brain, and hence the mind, is unfortunately such that primitive drives and emotions can nullify reason and logic. Greed, envy, and hostility often hold sway, culminating in social unrest and crime and war. Indeed, this maladaptive behavior, amplified by modern technology, approaches the point of threatening the survival of man and even that of the planet.

Because neurobiologic techniques increasingly demonstrate the brain mechanisms for mental activity — particularly the neural circuitry for pain and pleasure, the basic moving forces in behavior — there is increasing curiosity over the possibility of altering social behavior by biologic methods. Will it be possible to control minds? Will ruthless leaders be able to inflict their wills? We have already had experiences of large populations being affected deleteriously through biologic methods (abuse of pleasure-inducing chemicals; experimental use of mind-disrupting chemicals — for instance, d-LSD dispersed through drinking water). Or can we hope for the development of biologic methods that can be applied for improving the human condition universally?

For adaptive behavior (whether individual or group) to predominate, reward (pleasure) is required for laudable behavior and punishment (pain) for detrimental behavior. In order to modify man's behavior at the social level, it is necessary to establish more effective moral codes, a function which has fallen traditionally to religion. But religions have shortcomings. They are often fractionated and competitive, provoking the very violence and destruction they are designed to prevent. If one day a common moral code evolved, and biologic methods applied so as to imprint firmly the memories of that code, it might be possible for man to live in harmony with his fellowman, as well as with other species. We might then be able to work together to conserve our resources and safeguard our planet.

References

Adams RD, Victor M: *Principles of Neurology*, New York, McGraw Hill, 1977. Chapter 12 - "Deafness, dizziness, vertigo, and disorders of equilibrium," pp 185-187, and Chapter 19 - "Neurological disorders caused by lesions in particular parts of the cerebrum," p 295.

Adams, RD, Victor M: *Principles of Neurology*, New York, McGraw Hill, 1985. Chapter 21 - "Neurologic disorders caused by lesions in particular parts of the cerebrum," pp 323-350.

Akerfeldt S: Oxidation of N, N-dimethyl-p-phenylenediamine by serum from patients with mental disease. *Science 125*:117-119, 1957.

Alarcon-Segovia D, Fishbein E, Cetina JA, Raya RJ, Berrera E: Antigenic specificity of chlorpromazine-induced antinuclear antibodies. *Clin Exp Immunol 15*:543-548, 1973.

Alexander F: Psychosomatic specificity. *Psychosom Med 24*:13, 1962.

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM-III). Washington DC, 1980.

Andreasen NC, Olsen S: Negative v positive schizophrenia: definition and validation. *Arch Gen Psychiatry 39*:789-794, 1982.

Angel CA, Leach BE, Martens S, Cohen M, Heath RG: Serum oxidation tests in schizophrenic and normal subjects. *Arch Neurol Psychiatry 78*: 500-504, 1957.

Ariens-Kappers CU: The development of the cortex and the function of its different layers.

Acta Psychiatrica et Neurologica Scandinavica 3:115-132, 1928.

Armstrong E: Enlarged limbic structures in the human brain: the anterior thalamus and medial mammillary body. *Brain Res 362*:394-397, 1986.

Bailey P, Green JR, Amador L, Gibbs FA: Treatment of psychomotor states by anterior temporal lobectomy. A report of progress. In, *Psychiatric Treatment.* Research Publication of the Association for Research in Nervous and Mental Disease. Vol XXXI, ed by Wortis SB, Herman M, and Hare CC. Baltimore, Williams & Wilkins, 1953, pp 341-346.

Ballantine TH, Cassidy WL, Flanagan NB, and Marino R: Stereotaxic anterior cingulotomy for neuropsychiatric illness and intractable pain. *J Neurosurg 26*:488-495, 1967.

Bard P: A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. *Am J Physiol 84*:490-516, 1928.

Bard P: Central nervous mechanisms for emotional behavior patterns in animals. *Res Publ Assoc Res Nerv Ment Dis 19*:190-218, 1939 (quotation, page 190).

Bard P, Mountcastle VB: Some forebrain mechanisms involved in expression of rage with special reference to suppression of angry behavior. *Res Publ Assoc Res Nerv Ment Dis 27*:362-404, 1948.

Baron M, Stern M, Anavi R, Witz IP: Tissue-binding factor in schizophrenic sera: A clinical and genetic study. *Biol Psychiatry 12*:199-219, 1977.

Bear DM: The temporal lobes: An approach to the study of organic behavioral changes. In, *Handbook of Behavioral Neurobiology*, Vol 2, ed by Grazzaniga MS. New York, Plenum, 1979, pp 75-95.

Becker HC, Founds WL, Peacock SM, Heath RG, Llewellyn RC, Mickle WA: A roentgenographic stereotaxic technique for implanting and maintaining electrodes in the brain of man. *Electroencephalogr Clin Neurophysiol 9*:533-543, 1957.

Bergen JR, Grinspoon L, Pyle HM, Martinez JL, Pennell RB: Immunologic studies in schizophrenic and control subjects. *Biol Psychiatry 15*:369-379, 1980.

Berglund S, Gottfries CG, Gottfries I, Stormby K: Chlorpromazine-induced antinuclear factors. *Acta Med Scand 187*:67-74, 1970.

Bishop MP, Elder ST, Heath RG: Intracranial self-stimulation in man. *Science 140*:394-396, 1963.

Bleuler E: *Dementia Praecox or the Group of Schizophrenias.* Translated by Zinkin J. New York, International Universities Press, 1950.

Bouchet D, Cazauveilh M: De l'epilepsie considere dans ces rapports avec l'alienation mentale. *Archives General de Medicine 9*:512-542, 1825.

Brady JV: Emotional behavior. In, *Handbook of Physiology - Section I, Neurophysiology*, Vol III, ed by Field J., Magoun HW, Hall VE. Washington DC, American Physiological Society, 1960, pp 1529-1552.

Brenner C: A psychoanalytic theory of affects. In, *Emotion - Theory, Research, and Experience*, Vol I, ed by Plutchik R, Kellerman H. New York, Academic Press, 1980, pp 341-348.

Breuer J, Freud S: *Studien uber Hysterie*, Vienna, 1895.

Broca P: Anatomie comparee des circonvolutions cerebrales, Le grand lobe limbique et la scissure limbique dans la serie des mammiferes. *Rev Anthrop 1*:385, 1878.

Cannon WB: The James-Lange theory of emotions: A critical examination and an alternative theory. *Am J Psychol 39*:106-124, 1927.

Cannon WB: Again the James-Lange and the thalamic theories of emotion. *Psychol Rev 38*:281-295, 1931.

Cannon WB: *The Wisdom of the Body*. New York, Norton, 1932.

Carpenter WT, Heinrichs DW, Wagman AMI: Deficit and nondeficit forms of shizophrenia: The concept. *Am J Psychiatry 145*:578-583, 1988.

Clark GA, McCormick DA, Lavond DG, Thompson RF: Effects of lesions of cerebellar nuclei on conditioned behavioral and hippocampal neuronal responses. *Brain Res 291*:125-136, 1984.

Clark GM: Some afferent connections of the septal region of the cat: A study using the horseradish peroxidase retrograde transport method. Unpublished dissertation, Department of Anatomy, Tulane University School of Medicine, New Orleans, Louisiana, 1976.

Clarke HGM, Freeman T, Prysе-Phillips W: Quantitative immunoelectrophoresis of serum from hospitalized chronic schizophrenic and epileptic patients. *J Neurol Neurosurg Psychiatry 33*:694-697, 1970.

Collins R, Tearse R, Lothman E:

Functional anatomy of limbic seizures: Focal discharges from medial entorhinal cortex in rat. *Brain Res 280*:25-40, 1983.

Cooper IS, Amin I, Riklan M, Waltz JM, and Poon TP: Chronic cerebellar stimulation in epilepsy. *Arch Neurol 33*:559-570, 1976.

Cooper IS and Bravo GJ: Chemopallidectomy and chemothalamectomy. *J Neurosurg 15*:244-250, 1958.

Cowan WM, Guillery RW, Powell TPS: The origin of the mammillary peduncle and other hypo-thalamic connexions from the midbrain. *J Ant 98*: 345-363, 1964.

Crandall PH, Sutherling W: Tactical considerations leading to surgical treatment of the partial epilepsies. In, *Mechanisms of Epileptogenesis - The Transition to Seizure*, ed by Dichter MA. New York, Plenum Press, 1988, pp 255-279.

Crow TJ: Molecular pathology of schizophrenia: more than one disease process. *Br Med J 1*:66-68, 1980.

Crow TJ: The two-syndrome concept: origins and current status. *Schizophr Bull 11*:471-486, 1985.

deBruin JPC, Van Oyen HGM, Van de Poll N: Behavioral changes following lesions of the orbital prefrontal cortex in male rats. *Behav Brain Res 10*:209-232, 1983.

Denny-Brown D, Meyer, DS, Horenstein S: Significance of perceptual rivalry resulting from parietal lesions. *Brain 75*:433, 1952.

Dietrichs E: Cerebellar autonomic function: Direct hypothalamocerebellar pathway. *Science 223*:591-593, 1984.

Egger MD, Flynn JP: Effects of electrical stimulation of the amygdala on hypothalamically elicited attack behavior in cats. *J Neurophysiol 26*:705-720, 1963.

Ehringer H, Hornykiewicz O: Verteilung von noradrenalin and dopamin (3-hydroxytyramin) im gehirn des menschen und ihr verhalten bei erkrankungen des extrapyramidalen systems. *Klinische Wochenschrift 38*:1238-1239, 1960.

Ehrnst A, Wiesel FA, Bjerkenstedt L, Tribukait B, Jonsson J: Failure to detect immunologic stigmata in schizophrenia. *Neuropsychobiology 8*:169-171, 1982.

Ervin F, Epstein AW, King HE: Behavior of epileptic and nonepileptic patients with "temporal spikes." *AMA Arch Neurol & Psychiatry 74*:488-497, 1955.

Esquirol JED: Des maladies mentales considerees sous les rapports medicale, hygienique et medico-legal. *Balliere, Paris*, 1838.

Falret J: De l'etat mental des epileptiques. *Archives Generales de Medicine 16*:661-679, 1860.

Ferenczi S: Stages in the development of the sense of reality. *Z*:1:124-138, 1913.

Fitzjarrell AT, Heath RG: Vasopressin: Immunohistochemical localization in brains of cats and monkeys. Unpublished manuscript.

Fox JL: Debate on learning theory is shifting. *Science 222*:1219-1222, 1983.

Freeman H, Elmadjian F: Carbohydrate and lymphoid studies in schizophrenia. *Am J Psychiatry 196*:660-667, 1950.

Freeman W, Watts JW: Psychosurgery during 1936-1946. *Arch Neurol Psychiatry 58*:417-425, 1947.

Freud S: *Introductory Lectures to Psychoanalysis*. New York, Boni and Liveright, 1920.

Freud S: Fragment of an analysis of a case of hysteria. In, *Collected Papers*, Vol III, London, Hogarth Press, 1925, pp 13-146.

Freud S: *New Introductory Lectures on Psychoanalysis*. New York, Garden City Publishing Company, 1933.

Freud S: *The Problem of Anxiety* (Translated from the German by HA Bunker). The Psychoanalytic Quarterly Press and WW Norton & Company, Inc., New York, 1936.

Fuster JM: *The Prefrontal Cortex*. New York, Raven Press, 1980.

Gallhofer B, Trimble MR, Frackowiak R, Gibbs J, Jones T: A study of cerebral blood flow and metabolism in epileptic psychosis using positron emission tomography and oxygen. *J Neurol Neurosurg Psychiatry 48*:201-206, 1985.

Gibbs FA (ed): *Molecules and Mental Health*. Philadelphia, JB Lippincott Co, 1959.

Gibbs FA, Gibbs EL, Lennox WG: Epilepsy: A paroxysmal cerebral dysrhythmia. *Brain 60*:377-388, 1937.

Glaus A: Uber combinationen von schizophrenie und epilepsie. *Zeitschrift fur Diegesante Neurologies und Psychiatrie 135*:450, 1931.

Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S: The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Ann Neurol 12*:129-144, 1982.

Goldberg SC: Negative and deficit symptoms in schizophrenia do respond to neuroleptics. *Schizophr Bull 11*:453-456, 1985.

Griesinger W: Mental pathology and therapeutics, (Translation Lockhart-Robertson C, Rutherford J), New Syndenham Society, London, 1857.

Guerrero-Figueroa R, deBalbian Verster F, Heath RG: Mirror focus in specific subcortical nuclei. *Trans Am Neurol Assoc 87*:207-209, 1962.

Guillery RW: Degeneration in the post-commissural fornix and the mammillary peduncle of the rat. *J Anat 90*:350-370, 1956.

Guillery RW: Degeneration in the hypothalamic connexions of the albino rat. *J Anat 91*:91-115, 1957.

Hamilton NG, Frick RB, Takahashi T, Hopping MW: Psychiatric symptoms and cerebellar pathology. *Am J Psychiatry 140*:1322-1326, 1983.

Harlow E, Lane D: *Antibodies, a Laboratory Manual*, a Cold Spring Harbor Laboratory publication, 1988, pp 471-510.

Harlow HF, Harlow MK: Social deprivation in monkeys. *Sci Am 207*: 137-146, 1962.

Harlow HF, Harlow MK, Suomi SJ: From thought to therapy: Lessons from a primate laboratory. *Am Sci 58*:538-549, 1971.

Harlow HF, Mears CE: Emotional sequences and consequences. In, *Emotion: Theory, Research, and Experience*, Vol II, ed by Plutchik R, Kellerman H. New York, Academic Press, 1983.

Harper JW, Heath RG: Anatomic connections of the fastigial nucleus to the rostral forebrain in the cat. *Exp Neurol 39*:285-292, 1973.

Harper JW, Heath RG: Ascending projections of the cerebellar fastigial nuclei: Connections to the ectosylvian gyrus. *Exp Neurol 42*: 241-247, 1974.

Head H: *Studies in Neurology*. New York, Frowde, Hodder & Stoughton, 1920 (II), p 620.

Heath RG: Definition of the septal region. In, *Studies in Schizophrenia*, Heath RG, and the Tulane University Department of Psychiatry and Neurology. Cambridge, Massachusetts, Harvard University Press, 1954a, pp 3-5.

Heath RG: Behavioral changes following destructive lesions in the subcortical structures of the forebrain in cats. In, *Studies in Schizophrenia*, Heath RG, and the Tulane University Department of Psychiatry and Neurology. Cambridge, Massachusetts, Harvard University Press, 1954b, pp 83-84.

Heath RG: Clinical studies with taraxein. In, *Neuropharmacology Transactions of the Fourth Conference*, ed by Abramson HA. New York, Josiah Macy Jr Foundation, 1959, pp 37-151.

Heath RG: Physiological and biochemical studies in schizophrenia with particular emphasis on mind-brain relationships. *Int Rev Neurobiol 1*:299-331, 1959.

Heath RG: Common characteristics of epilepsy and schizophrenia: Clinical observation and depth electrode studies. *Am J Psychiatry 118*: 1013-1026, 1962.

Heath RG: Electrical self-stimulation of the brain in man. *Am J Psychiatry 120*:571-577, 1963.

Heath RG: Pleasure response of human subjects to direct stimulation of the brain: Physiologic and psychodynamic considerations. In, *The Role of Pleasure in Behavior*, ed by Heath RG. New York, Hoeber Medical Division, Harper & Row, 1964a, pp 219-243.

Heath RG: Developments toward new physiologic treatments in psychiatry. *J Neuropsychiatry 5*:318-331, 1964b.

Heath RG: Schizophrenia: Biochemical and physiologic aberrations. *Int J Neuropsychiatry 2*:597-610, 1966.

Heath RG: An antibrain globulin in schizophrenia. In, *Biochemistry, Schizophrenias, and Affective Illnesses*, ed by Himwich HE. Baltimore, Williams & Wilkins, 1970, pp 171-197.

Heath RG: Pleasure and brain activity in man: Deep and surface electroencephalograms during orgasm. *J Nerv Ment Dis 154*:3-18, 1972a.

Heath RG: Electroencephalographic studies in isolation-raised monkeys with behavioral impairment. *Dis Nerv System 33*:157-163, 1972b.

Heath RG: Physiologic basis of emotional expression: Evoked potential and mirror focus studies in rhesus monkeys. *Biol Psychiatry 5*:15-31, 1972c.

Heath RG: Marihuana: Effects on deep and surface electroencephalograms of man. *Arch Gen Psychiatry 26*:577-584, 1972d.

Heath RG: Fastigial nucleus connections to the septal region in monkey and cat: A demonstration with evoked potentials of a bilateral pathway. *Biol Psychiatry 6*:193-196, 1973.

Heath RG: Brain function and behavior: Emotion and sensory phenomena in psychotic

patients and in experimental animals. *J Nerv Ment Dis 160*:159-175, 1975.

Heath RG: Correlation of brain function with emotional behavior. *Biol Psychiatry 11*:463-480, 1976a.

Heath RG: Brain function in epilepsy: Midbrain, medullary, and cerebellar interaction with the rostral brain. *J Neurol Neurosurg Psychiatry 39*: 1037-1051, 1976b.

Heath RG: Modulation of emotion with a brain pacemaker: Treatment for intractable psychiatric illness. *J Nerv Ment Dis 165*:300-317, 1977.

Heath RG: The neural basis for violent behavior: Physiology and anatomy. In, *Aggression and Violence: A Psycho-biological and Clinical Approach*, ed by Valzelli I, Morgese I. Italy, Edizioni Centro Culturale E Congress Saint Vincent, 1981, pp 176-194.

Heath RG: Psychosis and epilepsy: Similarities and differences in the anatomic-physiologic substrate. In, *Temporal Lobe Epilepsy, Mania, and Schizophrenia, and the Limbic System*, ed by Koella WP, Trimble MR. Basel, S Karger, 1982, pp 106-116.

Heath, RG: Studies with deep electrodes in patients intractably ill with epilepsy and other disorders. In, *What is Epilepsy?*, ed by Trimble MR, Reynolds EH. London-New York, Churchill Livingstone, 1986, pp 126-138.

Heath RG: The neural substrate for emotion. In, *Emotion: Theory, Research, and Experience*, vol III, ed by Plutchik R, Kellerman H. New York, Academic Press, 1986, pp 3-35.

Heath, RG: Correlation of brain activity with emotion: A basis for developing treatment for violent-aggressive behavior. *J Amer Acad Psychoanal 20*:335-346, 1992.

Heath RG, Cox AW, Lustick LS: Brain activity during emotional states. *Am J Psychiatry 131*:858-862, 1974.

Heath RG, deBalbian Verster F: Effects of chemical stimulation to discrete brain areas. *Am J Psychiatry 117*:980-990, 1961.

Heath RG, Dempesy CW, Fontana CJ, Myers WA: Cerebellar stimulation: Effects on septal region, hippocampus, and amygdala of cats and rats. *Biol Psychiatry 13*:501-529, 1978.

Heath RG, Dempesy CW, Fontana CJ, Fitzjarrell AT: Feedback loop between cerebellum and septal-hippocampal sites: Its role in emotion and epilepsy. *Biol Psychiatry 15*:541-556, 1980.

Heath RG, Fitzjarrell AT: Chemical stimulation to deep forebrain nuclei in Parkinsonism and epilepsy. *Int J Neurol 18*:163-178, 1984.

Heath RG, Fitzjarrell AT, Fontana CJ, Garey RE: Cannabis sativa: Effects on brain function and ultrastructure in rhesus monkeys. *Biol Psychiatry 15*:657-690, 1980.

Heath RG, Founds WL: A perfusion cannula for intracerebral microinjections. *Electroencephalogr Clin Neurophysiol 12*:930-932, 1960.

Heath RG, Freedman DA, Mettler FA: Striatal removal without previous cortical ablation: Release, disorientation, metabolic disturbance. *Fed Proc 6*:126, 1947.

Heath RG, Gallant DM: Activity of the human brain during emotional thought. In, *The Role of Pleasure in Behavior*, ed by Heath RG. New York, Hoeber Medical Division, Harper & Row, 1964, pp 83-106.

Heath RG, Guerrero-Figueroa R: Psychotic behavior with evoked septal dysrhythmia: Effects of intracerebral acetylcholine and gamma aminobutyric acid. *Am J Psychiatry 121*:1080-1086, 1965.

Heath RG, Harper JW: Ascending projections of the cerebellar fastigial nucleus to the hippocampus, amygdala, and other temporal lobe sites: Evoked potential and histological studies in monkeys and cats. *Exp Neurol 45*:268-287, 1974.

Heath RG, Harper JW: Descending projections of the rostral septal region: An electrophysiological-histological study in the cat. *Exp Neurol 50*: 536-560, 1976.

Heath RG, Hodes R: Effects of stimulation with electrodes chronically implanted in rhesus monkeys. In, *Studies in Schizophrenia*, Heath RG, and the Tulane University Department of Psychiatry and Neurology, Cambridge, Massachusetts, Harvard University Press, 1954, pp 109-111.

Heath RG, Hodes R, Peacock SM: Cortical stimulation of induced motor activity. *Trans Am Neurol Assoc 76*:70, 1951.

Heath RG, John SB, Fontana CJ: Stereotaxic implantation of electrodes in the human brain: A method for long-term study and treatment. *IEEE Trans Biomed Eng BME-23*:296-304, 1976.

Heath RG, Krupp IM: The biological basis of schizophrenia: An autoimmune concept. In,

Molecular Basis of Some Aspects of Mental Activity, Vol II, ed by Walaas 0. New York, Academic Press, 1967a, pp 313-344.

Heath RG, Krupp IM: Schizophrenia as an immunologic disorder: Demonstration of antibrain globulins by fluorescent antibody techniques. Arch Gen Psychiatry 16:1-9, 1967b.

Heath RG, Krupp IM, Byers LW, Liljekvist JI: Schizophrenia as an immunologic disorder: Effects of serum protein fractions on brain function. *Arch Gen Psychiatry 16*:10-23, 1967a.

Heath RG, Krupp IM, Byers LW, Liljekvist JI: Schizophrenia as an immunologic disorder: Effects of antimonkey and antihuman brain antibody on brain function. *Arch Gen Psychiatry 16*:24-33, 1967b.

Heath RG, Leach BE: Multidisciplinary research in psychiatry. In, *Changing Concepts of Psychoanalytic Medicine*, ed by Rado S, Daniels G. New York, Grune & Stratton, 1956, pp 201-224.

Heath RG, Leach BE: Therapeutic agent for treatment of mental illness and method for preparation thereof - Patent 3,047,465 (Cushman, Darby & Cushman, Attorneys), July 31, 1962 (Filed November 14, 1958).

Heath RG, Leach BE, Byers LW, Martens S, Feigley CA: Pharmacological and biological psychotherapy. *Am J Psychiatry 114*:683-689, 1958.

Heath RG, Leach BE, Monroe RR, Mickle WA, Strohmeyer FB: Immediate chemical and behavioral effects with stimulation of chronically implanted electrodes in rhesus monkeys and in patients. In, *Studies in Schizophrenia*, Heath RG, the Tulane University Department of Psychiatry and Neurology. Cambridge, Massachusetts, Harvard University Press, 1954, pp 555-564.

Heath RG, Llewellyn RC, Rouchell AM: The cerebellar pacemaker for intractable behavioral disorders and epilepsy: Follow-up report. *Biolog Psychiat 15*:243-256, 1980.

Heath RG, Martens S, Leach BE, Cohen M, Angel CA: Effect on behavior in humans with the administration of taraxein. *Am J Psychiatry 114*:14-24, 1957.

Heath RG, Martens S, Leach BE, Cohen M, Feigley CA: Behavioral changes in nonpsychotic volunteers following the administration of taraxein, the substance obtained from serum of schizophrenic patients. *Am J Psychiatry 114*:917-919, 1958

Heath RG, McCarron KL, O'Neil CE: Antiseptal brain antibody in IgG of schizophrenic patients. *Biol Psychiatry 25*:725-733, 1989.

Heath RG, Monroe RR, Mickle WA: Stimulation of the amygdaloid nucleus in a schizophrenic patient. *Am J Psychiatry 111*:862-863, 1955.

Heath RG, Peacock SM, Monroe RR, Miller WH: Electroencephalograms and subcorticograms recorded since the June 1952 meetings. In, *Studies in Schizophrenia*, Heath RG, the Tulane University Department of Psychiatry and Neurology, Cambridge, Massachusetts, Harvard University Press, 1954, pp 573-608.

Heath RG, Rouchell AM, Llewellyn RC, Walker CF: Cerebellar pacemaker patients: An update. *Biolog Psychiat 16*:953-962, 1981.

Heath RG, the Tulane University Department of Psychiatry and Neurology: *Studies in Schizophrenia*. Cambridge, Massachusetts, Harvard University Press, 1954.

Heath RG, Walker CF: Correlation of deep and surface electroencephalograms with psychosis and hallucinations in schizophrenia: A report of two cases. *Biol Psychiatry 20*:669-674, 1985.

Heath RG, Weber JJ, Hogan C, Price TD: Metabolic changes following destructive lesions in the forebrain in cats. In, *Studies in Schizophrenia*, Heath RG, and the Tulane University Department of Psychiatry and Neurology, Cambridge, Massachusetts, Harvard University Press, 1954, pp 61-81.

Heath RG, Weber JJ, Crandell A: Psychiatry. In, *Selective Partial Ablation of the Frontal Cortex*, ed by Mettler FA. New York, Paul B. Hoeber, Harper & Bros, 1949, pp 315-429.

Heilman KM, Scholes R, Watson RT: Auditory affective agnosia. Disturbed comprehension of affective speech. *J Neurol Neurosurg Psychiatry 38*: 69-72, 1975.

Herrick CJ: *An Introduction to Neurology*. Philadelphia, WB Saunders, 1924, p 179.

Hess WR, Brugger M: Das subkortikale Zentrum der affectiven Abwehrreaktion. *Helv Physiol Pharmacol Acta 1*:33-52, 1943.

Hoch PH: Clinical and biological interrelations between schizophrenia and epilepsy. *Am J Psychiatry 99*: 507-512, 1943.

Hoch P, Polatin P: Pseudoneurotic forms of schizophrenia. *Psychiatr Q 23*: 248, 1949.

Hodes R, Heath RG, Founds WL, Llewellyn RC: Implantation of subcortical electrodes in man by a stereotaxic method. In, *Studies in Schizophrenia*, Cambridge, Massachusetts, Harvard University Press, 1954, pp 141-150.

Hodes R, Peacock SM, Heath RG: Somatic and visceral effects from stimulation of the forebrain of the cat. *Trans Am Neurol Assoc 75*:194-198, 1950.

Hodes R, Peacock SM, Heath RG: Influence of the forebrain on somatomotor activity. *J Comp Neurol 84*: 381-408, 1951.

Hoffer A, Osmond H, Smythies J: Schizophrenia: A new approach. II. Result of a year's research. *J Ment Sci 100*:29-45, 1954.

Hughlings Jackson J: On temporary mental disorders after epileptic paroxysms. In Taylor J (ed), *Selected Writings of John Hughlings Jackson*. Vol 1, London, Staples Press, 1875, pp 119-134.

Ito S-I: Prefrontal unit activity in macaque monkeys during auditory and visual reaction in time tasks. *Brain Res 247*:39-47, 1982.

James W: *Principles of Psychology*, Vols I and II, complete and unabridged. New York, Dover Publications, 1950 (by special arrangement with Henry Holt & Co., who did the original publication in 1890).

Johnstone EC, Cowens DG, Crow TJ, Frith CD, Alexandropolis K, Bydder G, and Colter N: Temporal lobe structure as determined by nuclear magnetic resonance in schizophrenia and bipolar affective disorder. *J Neurol Neurosurg Psychiatry 52*:736-741, 1989.

Jones EG, Burton H, Saper CB, Swanson LW: Midbrain, diencephalic and cortical relationships of the basal nucleus of Meynert and associated structures in primates. *J Comp Neurol 167*:385-398, 1976.

Kandel ER, Schwartz JH: *Principles of Neural Science*. New York, Elsevier-North Holland, 1981.

Kety SS: Biochemical theories of schizophrenia. *Science 129*:1528-1532; 1590-1596, 1959.

Kievet J, Kuypers HGJM: Basal forebrain and hypothalamic connections to the frontal and parietal cortex in the rhesus monkey. *Science 187*: 660-662, 1975.

Kling A, Steklis HD: A neural substrate for affiliative behavior in nonhuman primates. *Brain Behav Evol 13*:216-238, 1976.

Kluver H, Bucy PC: An analysis of certain effects of bilateral temporal lobectomy in the rhesus monkey, with special reference to "psychic blindness." *J Psychol 5*:33-54, 1938.

Kluver H, Bucy PC: Preliminary analysis of functions of the temporal lobe in monkeys. *Arch Neurol Psychiatry 42*:979-1000, 1939.

Knowles M, Saunders M, McClelland HA: Effects of phenothiazine therapy on lymphocyte transformation in schizophrenia. *Acta Psychiatr Scand 46:* 64-70, 1970.

Koella WP, Trimble MR (eds): *Temporal Lobe Epilepsy, Mania, and Schizophrenia, and the Limbic System*. Basel, S Karger, 1982.

Kojima S: Prefrontal unit activity in the monkey: Relation to visual stimuli and movements. *Exp Neurol 69*:110-123, 1980.

Kolb B, Nonneman AJ: Frontolimbic lesions and social behavior in the rat. *Physiol Behav 13*:637-643, 1974.

Kraepelin E: *Dementia Praecox and Paraphreni*. Translated by Barclay RM. Edinburgh, E & S Livingstone, 1919.

Laemmli UK: Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature 277*:680-688. 1970.

Landis C: Psychology. In, *Selective Partial Ablation of the Frontal Lobe*, ed by Mettler FA. New York, Paul B. Hoeber, Harper & Brothers, 1949, pp 306-312.

Lange CG: *Ueber Gemuthsbewegungen*. Leipzig, Germany, Uebersetzi von H Kurell, 1887.

Lange CG, James W: *The Emotions*. Baltimore, Williams & Wilkins, 1922.

Leach BE, Byers LW, Heath RG: Methods for isolating taraxein: A survey of results. In, *Serological Fractions in Schizophrenia*, ed by Heath RG. New York, Hoeber Medical Division, Harper & Row, 1963, pp 7-22.

Leach BE, Cohen M, Heath RG, Martens S: Studies of the role of ceruloplasmin and albumin in adrenaline metabolism. *Arch Neurol Psychiatry 76*:635-642, 1956.

Leach BE, Heath RG: The in vitro oxidation of epinephrine in plasma. *Arch Neurol Psychiatry 76*:444-450, 1956.

Lee RE, Babcock L, Reilly R, Schlann L, Pfeiffer CG: Thorn test on institutionalized schizophrenic patients. *Fed Proc 10*:318, 1951.

Lewis PR, Shute CCD: The cholinergic limbic system: Projections to hippocampal formation, medial cortex, nuclei of the ascending cholinergic reticular system, and the subfornical organ and supra-optic crest. *Brain 90*:521-539, 1967.

Lief HI: Effects of taraxein on a patient in analysis. *Arch Neurol Psychiatry 78*:624-627, 1957.

Lindsley DB: Emotion. In, *Handbook of Experimental Psychology*, ed by Stevens, SS. New York, Wiley, 1951, pp 473-516.

Logan DG, Deodhar SD: Schizophrenia, an immunologic disorder? *JAMA 212*:1703-1704, 1970.

Lorenz KZ: The companion in the bird's world. *The Auk 54*:245-273, 1937.

Luria AR: *The Mind of a Mnemonist: A Little Book About a Vast Memory*. New York, Basic Books, Inc, 1968, pp 77-78.

MacLean PD: Psychosomatic disease and the "visceral brain." Recent developments bearing on the Papez theory of emotion. *Psychosom Med 11*:338-353, 1949.

MacLean PD: New findings relevant to the evolution of psychosexual function of the brain. *J Nerv Ment Dis 135*:289-301, 1962.

MacLean PD: The limbic and visual cortex in phylogeny: Further insights from anatomic and microelectrode studies. In, *Evolution of the Forebrain*, ed by Hassler R, Stephan H. Stuttgart, G Thieme, 1966, pp 443-453.

MacLean PD: The triune brain, emotion and scientific bias. In, *The Neurosciences*, ed by Schmitt FO. New York, Rockefeller Press, 1970, pp 336-349.

MacLean PD: A triune concept of the brain and behavior. In, *The Hincks Memorial Lectures*, ed. by Boag T, and Campbell D, Toronto, University of Toronto Press, 1973, pp 6-66.

MacLean PD: Sensory and perceptive factors in emotional functions of the triune brain. In, *Emotions: Their Parameters and Measurement*, ed by Levi L. New York, Raven Press, 1975, pp 71-92.

MacLean PD: *The Triune Brain in Evolution: Role in paleocerebral functions*, New York, Plenum Press, 1990.

Mark VH, Ervin FR: *Violence and the Brain*. New York, Harper & Row, 1970.

Martens S, Vallbo S, Andersen K, Melander B: A comparison between taraxein and some psychotomimetics. *Acta Psychiatrica et Neurologica Scandinavica (Suppl 136) 34*:361-368, 1959.

Martens S, Vallbo S, Melander B: An approach to biochemical therapy in schizophrenia. *Acta Psychiatrica et Neurologica Scandinavica (Suppl 136) 34*:349-360, 1959.

Mason WA, Davenport RK Jr, Menzel EW Jr: Early experience and the social development of rhesus monkeys and chimpanzees. In, *Early Experience and Behavior*, ed by Newton G. Springfield, Illinois, Charles C Thomas, 1968, pp. 1-41.

Masserman JH: *Behavior and Neurosis*. Chicago, University of Chicago Press, 1943.

McCormick DA, Thompson RF: Cerebellum: Essential involvement in the classically conditioned eyelid response. *Science 223*:296-299, 1984a.

McCormick DA, Thompson RF: Neuronal responses of the rabbit cerebellum during acquisition and performance of a classically conditioned nictitating membrane-eyelid response. *J Neurosci 4*:2811-2822, 1984b.

Mekler LB, Lapteva NN, Lozovskii DV, Balezine TI: On the chemical and biological properties of taraxein, a toxic protein observed in the blood serum of schizophrenic patients. *Dokl Akad Nauk SSSR 139*: 1148-1151, 1960.

Mesulam M-M: Patterns in behavioral neuroanatomy: Association areas, the limbic system, and hemispheric specialization. In, *Principles of Behavioral Neurology*, ed by Mesulam M-M. Philadelphia, FA Davis Company, 1985, pp 1-70.

Mettler FA: Extracortical connections of primate frontal cerebral cortex: corticofugal connections. *J Comp Neurol 86*:119-166, 1947.

Mettler FA (ed): *Selective Partial Ablation of the Frontal Cortex*. New York, Paul B Hoeber, Harper & Bros, 1949.

Mettler FA, Mettler CC: Effects of striatal injury. *Brain 65*:242-255, 1942.

Meyer A: *Psychobiology: A Science of Man*. Springfield, Illinois, Charles C Thomas, 1957.

Mickle WA, Heath RG: Electrical activity from subcortical, cortical, and scalp electrodes before and during clinical epileptic seizures. *Trans Am Neurol Assoc 82*:63,1957.

Mihailovic L, Jankovic BD: Effects of intraventricularly injected anti-N caudatus antibody on the electrical activity

of the cat brain. *Nature 192*:665-666, 1961.

Milner B: Psychological aspects of focal epilepsy and its neurosurgical management. *Neurology 8*:299-321, 1975.

Nakai M, Iadecola C, Reis DJ: Global cerebral vasodilation by stimulation of rat fastigial cerebral nucleus. *Am J Physiol 243*:H226-H235, 1982.

Nauta WJH: Hippocampal projections and related neural pathways to the mid-brain in the cat. *Brain 81*:319-340, 1958.

Nauta WJH, Kuypers GJM: Some ascending pathways in the brain stem reticular formation. In, *Reticular Formation of the Brain*, ed by Jasper HH, Proctor LD, Knighton RS, Noshay WC, Costello RT. London, Churchill, 1957, pp 3-30.

Nelson JW, Daniels EG, Mann KM, Hinman JW: Studies of extraction and purification of taraxein. In, *Serological Fractions in Schizophrenia*, ed by Heath, RG. New York, Harper & Row, 1963, pp 43-55.

Niedermeyer E, Uematsu S: Electroencephalographic recordings from deep cerebellar structures in patients with uncontrolled epileptic seizures. *Electroencephalogr Clin Neurophysiol 37*:355-365, 1974.

Norman S, Olivier A, Andermann F, Gloor P, Quwaney LF: Results of surgical treatment in patients with bitemporal epileptiform abnormalities. *Ann Neurol 25*:432-439, 1989.

Novelly RA, Augustine EA, Mattson RH, Glaser GH, Williamson PD, Spencer DD, Spencer SS: Selective memory improvement and impairment in temporal lobectomy for epilepsy. *Ann Neurol 15*:64-67, 1984.

Olds, J: Hypothalamic substrates of reward. *Physiol Rev 42*:554, 1962.

Olds, J, Milner P: Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol 47*:419-427, 1954.

Olds J, Olds ME: The mechanisms of voluntary behavior. In, *The Role of Pleasure in Behavior*, ed by Heath RG. New York, Hoeber Medical Division, Harper & Row, 1964, pp 23-53.

Ostrow M: Psychodynamic disturbances in patients with temporal lobe disorders. *Trans Amer Neurol Ass 79*:79-83, 1952.

Owens DGC, Johnstone EC, Crow TJ, Frith CD, Jagoe JR, Kreel L: Cerebral ventricle enlargement in schizophrenia: Relationship to the disease process and its clinical correlates. *Psychol Med 15*:27-41, 1985.

Papez JW: A proposed mechanism of emotion. *Arch Neurol Psychiatry 38*: 725-743, 1937.

Paul SM, Heath RG, Ellison JP: Histochemical demonstration of a direct pathway from the fastigial nucleus to the septal region. *Exp Neurol 40*: 798-805, 1973.

Peacock SM: Physiological responses to subcortical stimulation. In, *Studies in Schizophrenia*, Heath RG, the Tulane University Department of Psychiatry and Neurology. Cambridge, Massachusetts, Harvard University Press, 1954, pp 235-248.

Penfield, W: *The Mystery of the Mind. A Critical Study of Consciousness and the Human Brain*. Princeton, Princeton University Press, 1975.

Penfield W, Jasper H: *Epilepsy and the Functional Anatomy of the Human Brain*. Boston, Little, Brown, 1954, pp 113-143; 438-469.

Penfield W, Perot P: The brain's record of auditory and visual experience. A final summary and discussion. *Brain 86*:595-696, 1963.

Perez MM, Trimble MR: Epileptic psychosis. A psychopathological comparison with process schizophrenia. *Br J Psychiat 137*:245-249, 1980.

Pincus G, Elmadjian F: The lymphocyte response to heat stress in normal and psychotic subjects. *J Clin Endocrinol 6*:295-300, 1946.

Pincus G, Hoagland H: Adrenal cortical responses to stress in normal men and in those with personality disorders; some stress responses in normal and psychotic subjects. *Amer J Psychiatry 106*:641-650, 1950.

Pond DA, Rey JH, Hill D: Biological correlates of constitutional EEG abnormalities of the temporal lobes. *Electroenceph Clin Neurophysiol 2*:111-112, 1950.

Proust M: *Remembrance of Things Past*, vol. 1. New York, Random House, 1934, pp 34-36.

Quismorio FP, Bjarnason DF, Dubois EL, Friou GJ: Chlorpromazine-induced antinuclear antibodies. *Arthritis Rheum 15*:451 (Abstract), 1972.

Rado S: Unpublished lectures, Columbia Psychoanalytic Clinic, 1946-1965.

Rado S: Emergency behavior - With an introduction to the dynamics of conscience. In,

Psychoanalysis of Behavior - The Collected Papers of Sandor Rado, New York, Grune & Stratton, 1956, pp 214-234.

Rado S: Schizotypal organization - Preliminary report on a clinical study of schizophrenia. In, *Psychoanalysis of Behavior - The Collected Papers of Sandor Rado, Volume Two: 1956-1961*, New York, Grune & Stratton, 1962 pp 1-10.

Rado S: Theory and therapy: The theory of schizotypal organization and its application to the treatment of decompensated schizotypal behavior. In, *Psychoanalysis of Behavior - The Collected Papers of Sandor Rado, Volume Two: 1956-1961*, New York, Grune & Stratton, 1962, pp 127-140.

Restak RM: *The Brain: The Last Frontier*, New York, Warner Books, 1979 (pages 38; 266-270).

Roberts WW, Kiess HO: Motivational properties of hypothalamic aggression in cats. *J Comp Physiol Psychol 58*:187-192, 1964.

Robins E: Clinical studies with taraxein. In, *Neuropharmacology-Transactions of the Fourth Conference* (September, 1957), ed by Abramson HA. New York, Josiah Macy, Jr Foundation, 1959, pp 124-125.

Rodin EA, DeJong RN, Waggoner RW, Bagchi BK: Relationship between certain forms of psychomotor epilepsy and "schizophrenia." *Arch Neurol Psychiat 77*:449-463, 1957.

Roos RP, Davis K, Meltzer HY: Immunoglobulin studies in patients with psychiatric disease. *Arch Gen Psychiatry 42*:124-128, 1985.

Ross ED: The aprosodias: Functional-anatomical organization of the affective components of language in the right hemisphere. *Arch Neurol 38*:561-569, 1981.

Schaltenbrand G, Bailey P (Eds). *Introduction to Stereotaxis with an Atlas of the Human Brain*, New York, Grune & Stratton, 1959.

Shelton RC, Weinberger DR: X-ray computerized tomography studies in schizophrenia: A review and synthesis. In *The Neurology of Schizophrenias*, ed by Nasrallah HA, Weinberger DR. Amsterdam, Netherlands, Elsevier, 1986, pp 207-250.

Sherrington, Sir Charles. *The Brain and Its Mechanism*, London, Cambridge, 1937.

Shirer WL: *The Rise and Fall of the Third Reich*, New York, Simon and Schuster, 1960, p 236.

Shute CCD, Lewis PR: The ascending cholinergic reticular system: Neocortical, olfactory and subcortical projections. *Brain 90*:497-520, 1967.

Snezhnevsky AV: The symptomatology, clinical forms, and nosology in schizophrenia. In, *Modern Perspectives in World Psychiatry*, ed by Howells JG. New York, Brunner/Mazel, 1971, pp 425-447.

Snider RS: Functional alterations of cerebral sensory areas by the cerebellum. In, *The Cerebellum*, ed by Fox CA, and Snider RS. Amsterdam, Netherlands, Elsevier, 1967, pp 322-333.

Spalding DA: Instinct, with original observations on young animals. *British Journal of Animal Behavior. 2*:2-11, 1954.

Steinmetz JE, Logan CG, Rosen DJ, Thompson JK, Lavond DG, Thompson RF: Initial localization of the acoustic conditioned stimulus projection system to the cerebellum essential for classical eyelid conditioning. *Proc Natl Acad Sci USA 894*:3531—3535, 1987.

Thompson RF: The neural basis of basic associative learning of discrete behavioral responses. *Trends in Neurosciences 11*:152-155, 1988.

Thorpe SJ, Rolls ET, Maddison S: The orbitofrontal cortex: Neuronal activity in the behaving monkey. *Exp Brain Res 49*: 93-115, 1983 .

Trimble MR: Phenomenology of epileptic psychosis: A historical introduction to changing concepts. *Adv Biol Psychiat 8*:1-11, 1982.

Trimble MR: Radiological studies in epileptic psychosis. In, *The Limbic System: Functional Organization and Clinical Disorders*, ed by Doane DK, Livingston KE. New York, Raven Press, 1986, pp 195-200.

Trimble MR, Perez MM: The phenomenology of the chronic psychoses of epilepsy. *Adv Biol Psychiat 8*:98-105, 1982.

Turner WA: *Epilepsy — A Study of the Idiopathic Disease*. London, Churchill, 1907.

von Boehmer H, Kisielow P: How the immune system learns about self. *Sci Am 265*: 74-81, 1991.

von Meduna L: *Die Konvulsionstherapie der Schizophrenie.* Halle, Carl Marhold, 1937.

Wasman M, Flynn JP: Directed attack elicited from hypothalamus. *Arch Neurol 6*: 220-227, 1962 .

Weeke B: Crossed immunoelectrophoresis. In, *A Manual of Quantitative Immunoelectrophoresis*, ed by Axelson NH, Kroll J, Weeke B. Oslo,

Universitets Forlaget, 1973, pp 47-56.

Weinberger DR: Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry 44*:660-669, 1987.

Whittingham S, Mackay IR, Jones IH, Davies B: Absence of brain antibodies in patients with schizophrenia. *Br Med J 1*:347-348, 1968.

Williams CA and Schupf N: Antigen-antibody reactions in rat brain sites induce transient changes in drinking behavior. *Science 196*:328-330, 1977.

Wilson SAK: *Neurology*, Vol 1, Baltimore, Williams & Wilkins Co., 1940. Chapter 8, pp 130-133.

Wing JK: Clinical concepts of schizophrenia. In, *Schizophrenia - Towards a New Synthesis*, ed by Wing JK. New York, Grune & Stratton, 1978, pp 1-30.

Zanchetti A: Subcortical and cortical mechanisms in arousal and emotional behavior, In, *The Neurosciences*, ed by Quarton GC, Melnechuk T, Schmitt FO. New York, Rockefeller University Press, 1967, pp 602-614.

ABBREVIATIONS FOR FIGURES

A	
A	anterior
Amy	amygdaloid nucleus
C	
C	cortex
Cau	caudate nucleus
Cbl	cerebellum
Cin	cingulate gyrus
C med	centro median
Col	colliculus
Cuneif	cuneiform
Cx	cortex
D	
Den	dentate nucleus
E	
Ecg)	
Ekg)	heart rate
F	
F	frontal
Fas	fastigial nucleus
G	
Gen)	
Genic)	geniculate
H	
Hip)	
Hippo)	hippocampus
Hyp)	
Hypo)	hypothalamus
I	
Inf	inferior
L	
L	lateral
M	
M	medial
Mes ret	mesencephalic reticulum
Mot	motor
N	
Nigra	substantia nigra
Nu	nucleus
O	
O	occipital
P	
P	posterior
Pall	globus pallidus
Par	parietal
Post	posterior
Pvl	posterior ventral lateral thalamus
R	
R	right
Raphe	raphe
S	
Sc	scalp
Sep	septal region
Sub	substantia nigra
Sup	superior
T	
T)	
Temp)	temporal
Tha)	
Thal)	thalamus

ABOUT THE AUTHOR

Educated at the University of Pittsburgh (B.S., M.D.), The Neurological Institute in New York (Neurology), the Pennsylvania Hospital in Philadelphia (Psychiatry), and the Columbia University College of Physicians and Surgeons in New York (Psychoanalysis, D.M.Sci. in Neurophysiologic Research), Dr. Robert G. Heath is Board-certified in both Psychiatry and Neurology. In 1949 he was appointed the founding Chairman of the Tulane University Department of Psychiatry and Neurology and continued to lead the Department until he retired from the post in 1980. During the 45 years he headed Tulane's brain research program, he wrote more than 400 articles for scientific journals and was the principal author and editor of three books. He received a variety of awards during his career, including a D.Sci. (Hon.) from Tulane, the Gold Medal Award for research from the Society of Biological Psychiatry, and the Frieda-Fromm Reichman Award from The American Academy of Psychoanalysis. A University Chair and an Endowed Lectureship have been established in his name at Tulane University, where he is currently an Emeritus Professor.

Exploring the Mind-Brain Relationship

Robert G. Heath, M.D., D.M.Sci.