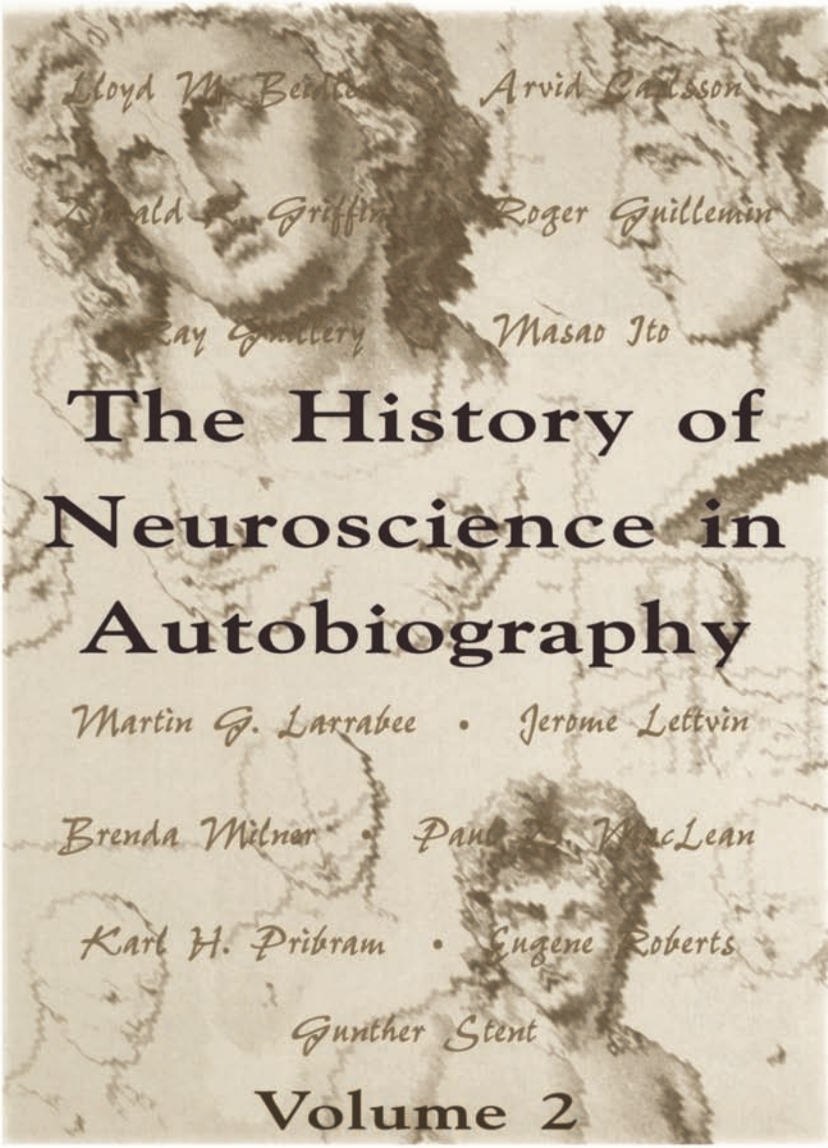

The History of Neuroscience in Autobiography

Volume 2

Edited by Larry R. Squire

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Contents

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May 1, 1913

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Paul MacLean is best known for his formulation and elaboration of the concept of the limbic system, which is based on relationships between the "visceral brain" and psychosomatic disease.

Paul D. MacLean

Introduction

This autobiographical sketch will be limited to tracing the experiences and ideas that led me into brain research and the kinds of experiments I did thereafter. After all, without a history of the products of our subjective experience, there is little to link the formulation and evolution of ideas from generation to generation. The mention of subjective experience requires that I state right at the start what I mean by that expression.

Neurologically speaking, subjective experience boils down to psychological forms of information and, as Norbert Wiener (who coined the word *cybernetics*) cogently expressed it, "Information is information, not matter or energy" (Wiener, 1948, p. 155). Regarding the immateriality of his definition, an argument by Neils Bohr about the existence of the particle and wave of quantum mechanics offers a kind of parallel: "A particle in *reality* has *neither* a position nor momentum. It has only the *potential* to manifest these complementary properties. . . ." (Bernstein, 1991, p. 48). In thinking of Wiener's definition of information in light of Bohr's comment, it must be emphasized at the same time that there can be no communication of information without an expenditure of energy. This might be regarded as a law of communication. The word *potential* calls to mind Aristotle's "potential," applying in his philosophy to different forms of nothingness, which would compare to the use of our word *information.* The so-called law of communication would seem to be incompatible with Cartesian dualism, which proposes that brain matter and the operations of the mind are independent of one another.

Although it can be argued that there is no certainty of knowledge, it does not deny our subjective feelings of certainty that none of us would be engaged in human endeavors without the diversity of our subjective experience. Certainly without it, there could hardly exist the commonly expressed questions such as, "Why are we here?"; "Where are we going?"; and "What is the meaning of life?" And the same reasoning could be applied to such everyday things as colors and other qualia which, except for their subjective generation in our brain, do not exist in the entire universe.

Since there are indications that the brain provides the algorithms capable of leading to solutions for everything we do (Vandervert, 1988), there could hardly be any more important investigation than the discovery of the neuroanatomical and chemoarchitectonic connectivity of the brain which allows it to create its particular species of algorithms (MacLean, 1997). In one of his informal writings, Santiago Ramón y Cajal (1966) stated, in effect, that everything that goes on in our perceived universe is but a reflection of the structure of the brain.[1]

Epistemology deals with the origin, nature, limits, and validity of knowledge. It represents a collective public approach that attempts to find what can be publicly agreed upon on the basis of what is observable, that is, "facts." In a word, epistemology seems to disregard the realization that everything "selected for study, every observation, and every interpretation, require subjective processing by an introspective observer" [*The Triune Brain in Evolution* (TBE); MacLean, 1990, p. 5). The irony of the purely objective approach is that there is no logical way of circumventing the realization "that the cold, hard facts of science, like the firm pavement underfoot, are informational transformations by the software of the brain, the physical properties of which are defined as 'viscoelastic'" (MacLean, 1990, p. 5). As a complementary term for that branch of epistemology that deals with the body of knowledge and the collective disciplines concerned with clarifying the nature and limitations of the subjective brain, I have used the expression "epistemics" (MacLean, 1975, 1990, p. 4). Later, I shall have occasion to mention some of the limitations that may be expected even if we were able to discover the detailed connectivity that accounts for the brain's particular species of algorithms.

Childhood Influences

The background for my growth and development was that of a Presbyterian minister's family. I was born on May 1, 1913, in Phelps, New York, which is in the Finger Lakes region near the head of Lake Seneca. My parents, along with my two older brothers, had moved to Phelps the previous year from the town of Naples, where my father had begun his ministry in 1904. The youngest of a large family living at Lake Ainslie, Nova Scotia, my father was influenced by his oldest sister, Euphemia, the widow of a minister, to pursue the same profession. After obtaining his education locally and in the nearby city of Sydney, he completed his education for the ministry at Auburn Seminary in Auburn, New York, near the head of Lake Owasco. While at the seminary, he helped to support himself by substituting for ministers on summer vacation. Preaching in Delhi, New York, on one of these occasions, he fell in love at first sight with a beautiful young woman in the choir, Eliza Dreyfus, who was to become his wife and mother of four sons.

[1] I am grateful to Miguel Marin-Padilla for this difficult-to-obtain reference.

The manse where I was born was on the north side of a red brick, paved main street, located a few houses east of the red brick Presbyterian church with a lovely, towering steeple. The manse itself was also brick, but painted yellow and faced with a low, white porch. The fields, gentle hills, woods, and streams surrounding Phelps were a veritable wellspring for a child's imagination. Indeed, one had only to go down to the foot of East Main Street to follow a stream that led to pussy willows in spring, or a stunning nest of speckled pheasant's eggs in the leaves at the edge of the woods. In the fall, there was raking of leaves, running and jumping into the piles, then the smell of burning leaves with chestnuts exploding from deep within. In winter, there was plenty of snow with hillside sledding, horses with jingle bells pulling sleighs, or bobsleds filled with hay.

I'll mention just a few childhood incidents that might have influenced my career. Because my father was in the pulpit on Sundays and my mother and two older brothers sang in the choir, it seemed quite natural that I was encouraged to attend Sunday School as early as possible. Sometime between the age of three and four, we were learning the Ten Commandments when someone indicated that you might be struck dead if you took the Lord's name in vain. This led to what might be described as my first experiment. The assertion continued to bother me because I had heard the Lord's name taken in vain and had never seen anyone struck dead. So, one day, when the manse was empty, I went into a closet, closed the door, and shouted at the top of my lungs, "JESUS CHRIST!" I waited for lightning to strike, and nothing happened. I was to learn later that this experiment was counterproductive. Whoever had said that one might be struck dead if you took the Lord's name in vain had not qualified whether it would occur immediately or sometime in the future. Hence, I have been waiting ever since.

The next incident occurred sometime after I was considered old enough to go to church. Again, because my father was in the pulpit, and my mother and brothers were in the choir, I had to fend for myself and was advised to sit in the back of the church where my presence would be less conspicuous. One warm spring Sunday I rode my tricycle to church and parked it in a safe place far from the door. I walked up the steps, and once inside, chose an empty pew just to the right of the central aisle. My father was not far into the sermon when a little girl a few pews ahead of me began to giggle uncontrollably while alternately looking up at the ceiling and covering her mouth to suppress her giggles. Finally, I could not resist my curiosity to see what was amusing her. To do this, I had to climb over the partition between the pews. At the instant I stood up to make this move, I heard a voice from the pulpit shout, "PAUL!" I spent the rest of the sermon figuring out what I should do. I decided to run away from home and, right after the Benediction, slipped out quietly and rode my tricycle down the next street toward the flour mill by the Canadaigua outlet. I was seeking refuge in the house of Anna Kent, the dressmaker, whom I had gotten to know and love when she came to our house to sew for my mother. She had the soothing, deep voice of a quietly playing organ.

When I failed to return home after the service, my two older brothers were sent out to search for me, and it was not long before I was brought home, expecting a thrashing. But there was not even a scolding. If there was, it had come from just the sound of my name, Paul, shouted from the pulpit. But ever after that, I kept wondering to myself, "Why do people who know better do things that they also know may get them in trouble?" In retrospect it would seem I was perseverating on the question raised by Spinoza's statement to the effect that all people are driven by their emotions. The persistence of that question seems to have been instrumental in steering the direction of my interests when I engaged in brain research 30 years later at the Massachusetts General Hospital (MGH).

World War I

After the church incident, there was a concatenation of world events triggered by the assassination of the Archduke of Austria and his wife at Sarajevo, Bosnia, on June 28, 1914, and Austria's declaration of war on Serbia. The Germans, who sided with the Austrians, declared war on Russia and soon opened a second front in Belgium, where, to everyone's horror, they were depicted as cutting off the breasts of Belgian women. Eventually, the reticence of the United States to engage in worldwide conflict was overcome. We were to learn via telegraph and newspaper that our government had declared war on Germany on April 15, 1917. Thereafter, I found my 4-year-old mind swimming in a sea of war-related events—my father's donning a uniform to serve as chaplain at Camp Merritt, New Jersey (and eventually returning with uniforms to fit me and my three brothers); my watching the burning embers of the logs in the fireplace and imagining the back and forth lighting-up of sparks as soldiers fighting in the trenches of France; the hanging of an effigy of the Kaiser, followed by its burning in the town park on a mountain-high pile of potato crates; a movie at the town theater showing fighting against the Germans and an officer with a spiked helmet flying 40 feet into the air after being hit by a single bullet. Then there was the surprise false armistice, when we as children were awakened at four in the morning and given hot cocoa. And finally, on November 11, 1918, the daytime telegraphing of the real armistice, with all except my youngest brother, Burton, going our separate ways with neighbors in open cars to spread the word of victory to the outlying farmers. That was an unbelievably warm and sunny day!

During the war, I had my first introduction to a medical condition. I first heard the word "germ" in Phelps when I contracted German Measles. When I asked why I was sick, it was explained to me that germs had gotten into my system. I mistook the term "system" for the word "cistern" which, in those days, were located in the cellars of houses to collect a supply of rainwater from the roof. My room was on the second floor of the manse and on a balmy spring day during the height of the war, I had the window wide open so I could look out onto the street. A good friend of the family walked by and called up, asking why I was in bed. I was reported as saying, "I have too many Germans in my cistern!"

Not long after the war my father received a "call" from the Presbyterian church in the small city of Hornell, New York, some 60 miles southwest of Phelps in the foothills of the Allegheny Mountains. As a six-year-old, there were many reasons for my disliking Hornell. Apart from its atmosphere of manufacturing, the location of the manse was just around the corner from the business district, and there were no nearby inviting streams to play in. Most disturbing to me was the closed-in feeling produced by the surrounding hills and my inability to see the horizon from any spot. The absence of a horizon as a reference point was particularly disrupting to my current preoccupation with trying to discover how Columbus concluded that the earth was round. I was partially reconciled when, one day while sitting on the steps of the gray stone Presbyterian church where I had a sweeping view of the sky, it suddenly occurred to me that the heavens were rounded like a tremendous dome.

But these dislikes were nothing compared with the anxiety generated by the renowned flu epidemic that later crept into Hornell and, in our own house, threatened my mother's life. The dread that she might die brought back one of my earliest memories from Phelps. One morning at get-up time, I had scampered across the bed and asked her, "How long will you live, Mother?" She did not answer, and when I asked again, she pretended to swat me so as to get me to move along. I was to wait a long time before my brain research gave me some evolutionary insight into why separation—or even the threat of separation—is such a painful condition for mammals.

I think we were all happy when, three years later, my parents decided to accept an attractive call to the Presbyterian church in Batavia, New York. The gray stone church with the bell tower topped by four pinnacles was at the corner of Main and Liberty Streets. Our large brick manse with high ceilings was next door on Liberty Street.

In some respects, Batavia was a larger edition of Phelps. The towering elms of East Main Street gave such a lovely, cathedral-like appearance that Thomas Moore described them in a poem when he visited there in the early 19th century. Like Phelps, the city was edged by surrounding farms that could be reached by bicycle and where one could hear the sounds of crows and chickens, delight in the familiar smells of horses and cows, and inhale the fragrance of new-mown hay.

With experiences like these, my childhood years in Batavia, punctuated by two-month-long summer vacations at the Thousand Islands, were hardly more notable than a long, quiet, organ prelude. One of my most enduring childhood influences was a cultivation of a love of painting, triggered by the gift of a box of oil paints and brushes from my oldest brother. I found that once I started a picture on a Saturday, I could not leave it all day. Another enduring influence occurred in eighth grade. A lovely older teacher once said to me, "noblesse oblige." I did not know what it meant at the time, but along with the golden rule, I have been thinking about it ever since.

The approach of high school brought with it a real fracture in my way of life. My oldest brother, Charles, had attended Hamilton College for a year and then transferred to Yale College. In his letters to the family, he successfully conveyed his impression that students who went to Yale were far better off if they had attended a preparatory school. That was enough to get me looking, and I turned up one in the Adirondacks that sounded like a real resort where one rode horses, played tennis, and so on. But the hammer came down quickly on that notion, and I was advised to apply for a school that prepared particularly for a college like Yale. I was fortunate to learn of the Taft school, where I applied and, probably thanks to my being a minister's son, was awarded a full scholarship of $1600 a year for four years.

Steps toward Medical School

Perhaps one disadvantage of a preparatory school is that it overprepares you for what to expect in the first year or two of college, when one is presumed to be getting steamed up for selecting a major. I attended Yale as an undergraduate but, without the exhilaration of novelty, I found the first two years rather humdrum. All of that changed in the third year when, along with honors work in English, I discovered F.S.C. Northrop's course called Philosophy of Science. At our home the emphasis had been on English literature. Hence, at Yale, I took a minimum of courses required in science and chose biology and geology to satisfy science requirements. At that time, Northrop had the reputation of being one of the few people who could understand Einstein's theories of relativity. The subject captured my imagination, and after taking his courses in my junior and senior years, I decided to pursue a career in philosophy. My friend and classmate, Steve Crary, who was going to study divinity at New College, Edinburgh, suggested that I go along with him to satisfy my ambition to study philosophy under the Plato scholar, A.E. Taylor.

But no sooner had I purchased a steamship ticket than I began to have second thoughts. How, by reading and rereading what philosophers had already said, could I derive any substantial new ideas about the "why" of life? In September 1935, not long before my scheduled departure for Scotland, an alarming incident occurred at home that was to change the whole course of my career. My mother was suddenly taken ill with what was presumed to be a heart attack. But when the number-one doctor of Genesee County was called in, he dismissed it as a probable passage of a stone in the duct of the gall bladder. It was a tremendous relief to everyone, and after he departed, I thought how wonderful it must be to belong to a profession where one could relieve such anxiety. I decided almost immediately that by going into medicine I could satisfy two aspirations—to help people, and to learn about the psychological functions of the brain. I would still go to Edinburgh, but with the alternate purpose of obtaining the accreditation in physics and chemistry required for entrance to a medical school.

When I arrived in Edinburgh I found that I had not taken into account the accreditation I would need to take courses in physics and chemistry at the university. Most students, I discovered, already had eight years of experience in both subjects. Professor Charles Barkla, who had won the Nobel prize for his work on X ray, gave the first part of the physics course beginning in October. He was an imposing, stout person and wore a swallow-tailed coat and striped trousers. When I was ushered in to ask if I could take his course, the first thing he did was ask for my credentials. Upon telling him, he leaned back in his swivel chair, and holding his hands on his round belly, began to guffaw like Santa Claus. Finally, when he was able to control himself, he asked me if I had had trigonometry. When I replied with a slow, side-to-side "no" with my head, he let out such a loud whoop that one might have thought he was going to have a convulsion. When it seemed he would never stop laughing, I went up to him and, patting him softly on his shoulder as though to soothe him said, "Here, here, this is really serious. I don't have enough money to return to the States." With that he suddenly stopped laughing, turned toward me and, looking me straight in the eye said, "There's a week before classes start. Here, take this little book on trigonometry and if you read it, you can take my course." My accreditation for medical school was completed the following summer when I sailed through organic chemistry at Cornell University in Ithaca, New York.

My first choice for medical school was Yale, where Dean Milton Winternitz had introduced many interesting innovations. After my admission, he winkingly showed me the recommendation that he said had been the deciding factor. It was from Chauncey Brewster Tinker, who had a legendary reputation as professor of English at Yale. He had been sent a questionnaire about me. On it he had written, "I never fill out questionnaires. MacLean is a good man, and you had better take him without more ado."

All four years during medical school I earned a bedroom and small study in the Dana House at 24 Hillhouse Avenue, which was owned by a gracious, elderly lady, Amy Dwight Dana, the daughter of James Dwight Dana, the geologist, and the granddaughter of Benjamin Silliman, who had introduced the teaching of science at Yale. The house was on a large corner lot, and I earned my living quarters by sweeping a wide macadam sidewalk and its connecting walks. Winternitz gave an early morning course of introductory lectures, and sometimes my broom sweeping and long walk to the school were not always conducive to my arriving on time. He lectured while walking back and forth and twirling a gold watch at the end of a long gold chain. I sensed that it broke the tension when I would walk in late and he would stop, draw himself up to his full height and say, "Good morning, MacLean!" Everyone seemed to enjoy this.

The Yale system had many built-in freedoms, and as every citizen learns, freedom has many constraints. There was the freedom to take periodic examinations which were purported to be for the student's benefit and which were presumably never graded. A wonderful feature of the system was the opportunity to delve into a subject as deeply as you wanted. There was the challenge, too, of writing a thesis. I started off particularly enjoying the study of the nervous system, but the more we read and were lectured to, the more it seemed that its functions were mainly to regulate reflexes, posture, and all kinds of motor performance. It was a period when people joked that, as far as psychological functions were concerned, the skull might as well be filled with cotton wadding. At any rate, my disappointment was such that I decided I might as well settle down to being a real physician specializing in cardiovascular disease. My thesis was concerned with an attempt to produce cardiovascular disease with antisera.

When it was time to apply for internships, I discovered that there existed a kind of Ivy League competition among eastern medical schools. I was leaning toward an internship in medicine in one school where my good friend (and, later, best man), David Crocker, had wanted to go. But when I returned from an interview there, I was called in by Dr. Francis G. Blake, the dean and professor of medicine at Yale, who was well known for his research on pneumonia. He told me that he had received a letter from Professor Warfield Longcope, the head of medicine at Johns Hopkins University, who wished to meet me and could do so during one of his periodic visits to the Rockefeller Institute in New York. I told Dr. Blake of my leaning for the place I had just visited. "No," he said, "you've got to go to New York for an interview with Professor Longcope." He stated this in his usual clipped speech, and it was clearly an order. I was fortunate to be accepted into the program, and I learned later that at that time, Johns Hopkins provided a position for only one outsider, and Yale had never had a candidate accepted. Medically speaking, it was one of the most rewarding experiences I've ever had. One was expected to be on call 7 days a week, and the day you were assigned to the Accident Room, you could expect to be up all night. Being on call around the clock acquainted one with all phases of a disease requiring hospital treatment.

World War II

I had fully intended to keep a diary my first year at Johns Hopkins, but the only entry I made was when I was hospitalized for a brief respiratory illness. The entry read, "I expect that we'll be at war with Japan by the end of the year." At the end of my internship, I returned to Yale as an assistant resident on Dr. Blake's service, and on December 7th, when Pearl Harbor was bombed, I was in Batavia visiting my parents. I had received an appointment as assistant resident in medicine at the Peter Bent Brigham Hospital for the following year. After the declaration of war, I wanted to join the war effort and decided to sign up with the Yale Unit, which was to become the 39th General Hospital. While waiting for activation, I continued in my position as assistant resident, and also held a research position with Winternitz's group, which was concerned with treating the effects of exposure to war gas.

It so happened that one day, while tearing up the steps to the wards, I tripped on the steps upon seeing a beautiful girl waiting with classmates to get into the amphitheater for a lecture. Her name, I learned later, was Alison Stokes. She was a Quaker, graduate of Bryn Mawr College, and was studying for a degree in nursing. After our first social occasion, I decided that she was the one person in this world I wanted to marry. We became engaged, and on July 16, 1942, we were married at Camp Edwards on Cape Cod, shortly after hearing the rumor that the Yale Unit would be departing for Europe in three days.

Just as abruptly, the word circulated that our mailing address would be APO San Francisco, and we were issued mosquito netting and snow boots and told to purchase winter overcoats. Where else but Alaska? We did not entrain until the middle of September, and after a mysterious, roundabout, transcontinental crossing, arrived at Pittsburg, California. Here we had orientation classes which included instructions to shoot ourselves if we were ever taken captive, and there were almost daily 20-mile hikes in dry, 90 to 100° heat. The ship on which we were to sail arrived in San Francisco so heavily covered with barnacles that the hull had to be scraped and painted, and it was another six weeks before we set sail with some of the shipmates sarcastically cheering "Golden Gate in '48" as we went under the famous bridge.

I include more of this history because of subsequent experiences that got me back on track to my original aspirations to learn about psychological functions of the brain. Despite our presumed preparation for an Alaskan assignment, our unescorted vessel kept sailing in a southwesterly direction, and after three weeks, we docked at Auckland, New Zealand, where we learned that a 1000-bed hospital was being built for soldiers evacuated from the Solomon Islands. At that time, a large number of our troops were on Guadalcanal undergoing a six-week bombardment by Japanese ships firing 16-inch shells. The food supplies of our troops were so reduced that the soldiers were living on rice and maggots.

I could not believe it, but I discovered that I was the only person in the unit who had experience in bacteriology. Consequently, I was assigned to work with Averill Liebow, a pathologist and one of my teachers at Yale, who had responsibility for the laboratory. Together, Liebow and I showed that the diphtheria bacillus caused tropical ulcers that were disabling our troops. This discovery led to effective treatment and prophylaxis.[2]

Our 1000-bed hospital filled up and emptied about once a week. About a third of the casualties were surgical, a third malaria, and a third psychiatric. For whatever reasons, two of our three psychiatrists chose to accept positions of advancement in the office of the hospital commander. This left Merrill Moore, a psychiatrist from Boston (and also a poet who had published a book of a thousand sonnets titled "M"), in an intolerable situation. When the searchlight circled for replacements it found my friend, David Crocker, and me. This was because when our hospital personnel were bivouacked 30 miles south of Auckland, we became restive in our bucolic surroundings and volunteered to help out at the naval station, whose temporary buildings were on the Auckland cricket field. There, every patient from Guadalcanal, in addition to having malaria and an enlarged liver, suffered from a psychoneurosis.[3] So, overnight, because of that experience and a short tutelage by a Navy psychiatrist, I was taken by the scruff of the neck, lifted out of bacteriology, and put in charge of the psychotic ward. At the far end of the ward was a padded cell with a refrigerator-thick door, and a small, thick-glassed window for looking in on the patient. One of my first patients was a six-foot, four-inch Marine who, when not grimacing and playing with his toes, became alternately self-destructive or attacked others. Major Moore advised me to strip him of his clothes and place him in the padded cell. After three days he became so quiet and seemingly affable that, on rounds, I suggested to the nurse and the two corpsmen that I go in alone and talk with him. Everything seemed to be going well when suddenly I felt a tightening sensation around my neck and my head beginning to burst. The patient had taken each end of my tie and was choking me. Luckily, one of the corpsmen had stayed nearby, saw what was going on, and rushed in to save me. These experiences with patients suffering from psychiatric illness got me thinking again that the mind must be in the head, that it was just not an epiphenomenon.

[2] I had read that garage mechanics did not get infections on their hands because of the antibacterial effect of pyocyanase from the bacillus *Pseudomonas aeruginosa* living in a tarry environment. Hence, I grew this organism in an appropriate broth until it acquired the typical bluish color of the bacteria's secretions. The broth was filtered, concentrated, and mixed into a salve. Amazingly, when applied to tropical ulcers, they healed rapidly. Not long after a Grand Rounds reporting its effectiveness, I was put out of business by the availability of penicillin.

[3] Every time a little airplane would fly over, a whole ward of patients would "hit the deck" and crawl under the bed. When I got down on my hands and knees to reassure one of them, I discovered fruit jars containing things such as cut off ears and gold teeth under the head of almost every bed.

Postwar Interim

The just-mentioned impression was clinched during a short period of the practice of medicine after the war. I was separated from the Army on New Year's Day, 1946, at the Brooke General Hospital, San Antonio, Texas. Eyeing the future, I suggested to my wife, Alison, that we head for Seattle, which a friend at Yale had described as a "brave new world." So as to avoid expensive rented office space, I initiated practice in the lower half of our house and also attended in the hospital outpatient clinic of the new medical school where my former teacher, Theodore Ruch, had been appointed head of the department of physiology. Owing to that connection, I was recruited to give the lectures on electrocardiography to the students comprising the first class at the school.

In my private practice I often found that after taking a complete history and doing a complete physical examination in the classical manner, I was unable to uncover anything except psychological symptoms and found it unconscionable to send such patients away with nothing but a sedative. At the same time, it was frustrating not to have any idea where in the brain these symptoms were generated. Consequently, I wrote Dr. Stanley Cobb at MGH in Boston, whose writing on psychosomatic illness had appealed to me, and inquired about the possibility of a fellowship for studying with him. It turned out that a U.S. Public Health Service fellowship would be available in September and I was invited to Boston for an interview. It was the most impressive and wisest interview I ever had. I did not know then that he had a notorious stammer and would not have guessed it until toward the end of the interview when there was every indication I could have the job. Dr. Cobb went on to say, "MacLean, I want you to know that if you come here, you can have the freedom to just sit on your . . . ah . . . ah . . . ah . . . ah." He couldn't get the word out. He leaned back in his chair, and continued to go on with his mouth wide open, saying, "ah . . . ah . . . ah . . . ah . . . ah" for what seemed an eternity. I knew of course what he wanted to say but did not help him. Finally, his head came forward and he explosively let out the one syllable word—adding, "and think." Subsequently I learned from a friend that he hated to be helped and that my not doing so was probably a good thing.

The following August found us leaving Seattle and driving east to Boston with our young sons, Paul and David, and their baby brother, Alexander. On the way, we spent a reviving vacation in a rented cottage near my family's summer place on Murray Isle in the Thousand Islands. Through a college friend, my wife had already found us an early 19th century house on Monument Street in Concord, Massachusetts, about a half mile beyond Old North Bridge where the first shot of the Revolutionary War was "heard 'round the world." Living in Concord made it an easy commute to North Station in Boston, where I would walk along a back street with markets to the MGH, often enjoying the company of the neuropathologist, Dr. Charles Kubik, who boarded the train at Lincoln.

At the MGH, 1947–1949

For my research I wanted to record the bioelectrical activity of structures at the base of the brain that possibly fed into the hypothalamus, which was known to be important for the expression of emotion. I therefore devised improved nasopharyngeal electrodes that could be slipped easily through each side of the nose and lie comfortably in the posterolateral part of the nasopharynx on each side. X rays showed the tips to be about 2 cm from the medial surface of the temporal lobe toward the rostral end of the hippocampus.

As I will explain, this proved to be a timely endeavor because of increased interest in a form of epilepsy that Gibbs and colleagues in 1938 called "psychomotor epilepsy." This type of epilepsy commonly occurs without convulsions. During the aura at the beginning of an epileptic storm, the patient's mind may light up with one or more of a wide range of emotions. Of great epistemological significance is that some patients experience an altered sense of self, or an exaggerated, free-floating feeling of what is real, true, and important. Afterwards, they engage in various forms of behavior for which they have absolutely no memory. In 1948, Gibbs and colleagues published a report indicating that, in most cases, the epileptic focus was in the anterior temporal region.

These landmark studies, combined with the localizing neurosurgical findings of Penfield and Jasper (1954) (see MacLean, 1990, pp. 419–420) led to the best evidence and, indeed, the only subjective evidence, that structures seemingly in the temporal lobe were involved in the elaboration and expression of emotional feelings.

The electroencephalography laboratory where I worked was headed by the well-known neurologist, Robert Schwab. It was close to Cobb's department in the Ether Dome Building. There I was joined by A. Arellano, a research fellow from Lima, Peru. The opportunity arose to examine 12 patients with symptoms of psychomotor epilepsy, whose standard EEGs had shown neither a general nor localized disturbance. For this study Arellano devised an extra basal electrode that had a felt tip which, when wetted in saline, could be placed next to the tympanic membrane, about a half centimeter below the fusiform gyrus of the temporal lobe. Leads from the ear lobes served as two extra monitors of activity in the basal EEG. With simultaneous recording of the standard and basal EEGs, and using the sleep-activated method described by Gibbs and colleagues in 1948, we found in a majority of cases that spiking activity appeared and that the negative component reached greatest amplitude at the site of the left or right nasopharyngeal electrodes—the electrodes nearest the hippocampal formation, a supposedly rhinencephalic structure (MacLean and Arellano, 1950).

How would such an epileptogenic focus account for the emotional symptomatology of such patients, and more incomprehensible still, the symptoms involving the visual, auditory, or somatic sensory systems? In searching for an answer at the Boston Medical Library, I stumbled upon a paper by James W. Papez titled "A Proposed Mechanism of Emotion" in the 1937 volume of *Archives of Neurology and Psychiatry* and was immediately struck by its relevance to our findings. Taking into account what was then known about the role of the hypothalamus in emotional expression, Papez pointed out that the so-called rhinencephalon was the only part of the hemisphere known to be strongly connected with the hypothalamus. In citing case material to support his argument he summed up his view of the underlying mechanism as follows (Papez, 1937, p. 728):

> The central emotive process of cortical origin may then be conceived as being built up in the hippocampal formation and as being transferred to the mammillary body and thence through the anterior thalamic nuclei to the cortex of the gyrus cinguli. The cortex of the cingular gyrus may be looked on as the receptive region for the experiencing of emotion as the result of impulses coming from the hypothalamic region, in the same way as the area striata is considered the receptive cortex for photic excitations coming from the retina.

The serially connected structures just mentioned have since become known as "the Papez circuit."

But if the emotive process was originally built up in the hippocampal formation, it still left open the question of how emotions generated by exterosensory information got into these particular structures. When I went to Dr. Cobb with this question, he suggested I go to Cornell, where Papez taught, to ask the Odyssean navigator of the brain. A nice letter from Papez suggested that I come during the spring break of 1948, during which I was treated to a concentrated three-day course in comparative neuroanatomy. Papez seemed so dedicated and saintlike that I still have the feeling of remembering everything he said. In answer to my question about visual, auditory, and somatic inputs into the hippocampal formation, he showed me in a fixed human brain possible association pathways from the respective sensory areas.

Following my visit I began working on a paper titled, "Psychosomatic Disease and the 'Visceral Brain.' Recent Developments Bearing on the Papez Theory of Emotion." I used the term "visceral brain" instead of rhinencephalon as a means of reducing the previous accent on olfactory functions. In its original 16th century meaning, visceral applied to strong inward feelings and implicitly to accompanying visceral manifestations.

The visceral brain paper was perhaps significant in introducing a few new ideas. First of all, it suggested that a phylogenetically old part of the brain occurring as a common denominator in all mammals might receive information from all the sensory systems. With respect to the hippocampus itself, this would indicate that "it was not an autonomous little factory of its own, manufacturing the raw materials of emotion out of thin air" (MacLean, 1990, p. 266). Figure 3 of that paper schematized the overlapping of interoceptive and exteroceptive systems in the hippocampal formation which, because of the analyzing mechanism of the evolutionarily primitive cortex, might account for the seemingly paradoxical overlapping of affective experience whereby primitive peoples and those with psychoneurotic and so-called psychosomatic conditions, appear to experience outside conditions as though they were happening inside.[4] In terms of Freudian psychology, I suggested that the visceral brain is not at all "unconscious (perhaps not even in certain stages of sleep) but rather eludes the grasp of the intellect because its animalistic and primitive structure makes it impossible to communicate in verbal terms" (MacLean, 1949). In conclusion, I made the suggestion that, although our intellectual functions are mediated in the newest and most highly developed part of the brain, "our affective behaviour continues to be dominated by a relatively crude and primitive system. This situation provides a clue to understanding the difference between what we 'feel' and what we 'know'" (MacLean, 1949, p. 351).

I presented my paper on the visceral brain at a staff meeting on January 11, 1949, and it was published in late 1949. In the meantime, my curiosity had developed a mounting interest in a whole series of anatomical and neurobehavioral questions raised in the paper that could only be answered in an experimental laboratory. The opportunity came when I received an invitation from my friend, John Fulton, professor and head of the department of physiology at Yale Medical School, with whom I had become well-acquainted while there as a student. I held a combined research–teaching appointment in physiology and psychiatry, starting at the rank of assistant professor in 1949 and then became associate professor in physiology in 1957.

Research at Yale, 1949–1956, and Development of the Limbic System Concept

Curiously enough, Papez in his 1937 paper does not even refer to Broca's famous paper of 1878. It had become, so to speak, part of the public domain, and everyone was assumed to know about it. But it can hardly be overem-

[4] For example, I examined a patient in the Hopkins accident room who came in complaining of cats and dogs fighting in his stomach. When I placed my stethoscope on his abdomen during the examination, he said, "Can you hear them, Doc?"

phasized that from the standpoint of the evolution of mammals and their culmination thus far in human beings, it represents a historic milestone. Giving recognition to earlier descriptions of the same structure by Gerdy (1838) and Foville (1844), Broca drew attention to a large, cerebral convolution which he called the great limbic lobe because it surrounded the brainstem. It was Broca's special contribution to identify the limbic lobe in a large variety of mammals and infer on that basis that it was a part of the brain common to all mammals. For function, Broca's comparative findings led him to infer that the limbic lobe operated at an animalistic level (cerveau brutal), whereas the rest of the cortex subserved intelligence (cerveau intellectuel). Being impressed by the robust connections of the olfactory bulb with the forward part of the limbic lobe, Broca speculated that the entire limbic convolution was involved in olfactory functions. This notion gained wide appeal, and textbooks appeared in the 1890s referring to the entire limbic lobe as the rhinencephalon (MacLean, 1990, p. 263). Because olfaction was regarded as an unimportant sense in human beings, "the rhinencephalon was treated like an unwanted child" in the teaching of brain anatomy (MacLean, 1990, p. 263). As one author of a book on human evolution wrote, "[the rhinencephalon] probably has not contributed greatly to the evolution of the human brain and will, therefore, not be considered further" (MacLean, 1990, p. 263).

Although not known at the time of Broca's paper, cytoarchitectural studies have since shown that the limbic lobe is enveloped by two concentric rings of cortex—the inner ring, usually referred to as archicortex and the outer ring, as mesocortex of M. Rose. As Rose points out, the mesocortex appears for the first time in mammals and is transitional in type between the archicortex and the outer evolving neocortex (MacLean, 1990, pp. 252–256).

When I joined the department of physiology at Yale in 1949, I became aware that the term *visceral brain* seemed to create misunderstanding because, in physiological parlance, the word visceral applies only to the glands and hollow organs, including the blood vessels. As a way around this, I found myself referring to the limbic cortex and its primary brainstem connections as the *limbic system*. Broca originally chose the word *limbic* because it is purely descriptive and implies no theory about function. At any rate, that is how the term limbic system was introduced into the literature in 1952 (MacLean, 1952, 1990, p. 267).

It is the expression "primary brainstem connections" that gives the cutting edge to Occam's razor for defining the limbic system in a modular sense. Another reinforcement of the term is the interconnectivity within the limbic lobe itself. In addition, there are other illustrative reasons for the designation. First, nothing serves so well to illustrate that the limbic cortex and its primary brainstem connections constitute an anatomically and functionally integrated system than to map the propagation of neuronal after discharges induced in limbic structures by electrical stimulation (MacLean, 1990, Chapter 19). Time after time, one finds that the propagating nerve impulses stay within the confines of limbic circuitry. Parallel observations have been made during therapeutic neurosurgical procedures. Second, of biochemical distinctions, I found it of particular interest that our autoradiographic study on rats showed that, following the parenteral injection of ^{35}S-labeled L-methionine, there was a high uptake of the agent in both the archicortex and the mesocortex that distinguished the limbic cortex from the neocortex (MacLean, 1990, pp. 361–362). Third, as will be summarized later, both experimental and clinical findings provide evidence that the three main subdivisions of the limbic system derive information in terms of affective feelings that guide behavior required for self-preservation and preservation of the species.

The limbic system concept leads to the often overlooked recognition that the history of the evolution of the limbic system represents the history of the evolution of mammals and their distinctive family way of life.

Experimental Work

The first experiment on my agenda at Yale was a strychnine neuronographic study with Karl Pribram to learn whether or not there were association pathways from visual, auditory, and somatic cortical areas to the hippocampal gyrus, as Papez had suggested. The findings in cats and rhesus monkeys did provide evidence of such stepwise connections.

For neurobehavioral studies, I developed an electrode that could be chronically fixed for recording electrical activity while performing either electrical or chemical stimulation in freely moving cats. A long, semicircular viewing box with a clear plastic front allowed the behavioral responses to be recorded by motion picture while the subject was always in focus of a camera rotating on a central post. The leads to and from the subject traveled along a track above it, and moving panels along the back provided immediate access to the subject. The stage also permitted observations of the effects of brain stimulation on conditioned avoidance behavior. For chemical stimulation, we employed primarily cholinergic agents because, ostensibly, they avoid complication of excitation of fibers of passage (MacLean, 1990, p. 64). With different collaborators (MacLean, 1990, Chapter 19), I explored the amygdala and related cortex, the hippocampus, the cingulate gyrus, the hypothalamus, and other structures. I will summarize the main findings later when, after citing the work done at the National Institute of Mental Health (NIMH), I will consider the functions of the three main subdivisions of the limbic system.

A Sabbatical Followed by a National Institutes of Health Appointment

In 1956, in addition to my promotion to associate professor of physiology, I was given a year's leave of absence for study in Europe made possible by the award of a National Science Foundation Senior Postdoctoral Fellowship. During that time I was affiliated with the Institute of Physiology at the University of Zürich. We rented a house in Thalwil, on the west bank of Lake Zürich, 11 miles south of the city. If I were to dwell on the wealth of experiences both I and my family enjoyed that year, there would be space here for little else.

When we sailed for Europe in 1956 the outlook at Yale was such that I thought I would be there the rest of my life. But in the spring of 1957, while in Zürich, I had an inviting letter from Robert B. Livingston, who had succeeded Seymour Kety after his highly successful launching of the intramural research program at the NIMH and the National Neurological Institute. With Wade Marshall, chief of the laboratory of neurophysiology, I had been invited to establish a new section in the Marshall Laboratory. The new section would be named The Section on Limbic Integration and Behavior.

I had shied away from previous opportunities to go to the National Institutes of Health because during World War II, I had grown wary of government-operated institutions. But the record of the NIH in the meantime had melted away all such concerns, and I would like to express my profound gratitude for the opportunity to do full-time research with such marvelous support.

The Marshall Laboratory was on the third floor of the Clinical Center in Bethesda, Maryland. Except for rabbits, animals larger than rats and mice had to be transported back and forth to a neighboring animal building. Since a main purpose of my research was to investigate how vision influenced limbic functions, I decided that I would no longer use cats, but rather employ a primate, such as the small South American squirrel monkey (*Saimiri sciureus*), with which I had had experience at Yale. Moreover, for obtaining a complete description of their behavior (a so-called ethogram), I hoped to recruit an ethologist.[5] Also for that purpose, I wanted the animals to be housed across the hall from my office where records of observation could be made around the clock.[6] There was no administrative precedent

[5] In the 1950s the European enthusiasm for ethology had hardly reached our shores. Through Richard Jung, the well-known German electrophysiologist, I was introduced to Detlev Ploog, who had spent a year in Jung's laboratory and, in addition, had a special interest in ethology. Arrangements were made for him to join our section as a visiting scientist. During the 2-year period (1958–1960) that he was with us, he collaborated with me in electrophysiological studies, and together we also obtained a well-defined ethological picture of the behavior of squirrel monkeys as the behavior occurs in captivity.

[6] In running the animal quarters opposite from my office, it was kept foremost in mind that in neurobehavioral studies the health, care, and surroundings of the animals are of utmost importance. Most important, it was necessary to have a full-time animal caretaker with a kindly disposition that the animals learned almost immediately to recognize. We made rounds at scheduled times and in following the health of the monkeys, weighed them weekly, and inspected them closely. Special cages were made to satisfy their needs for exercising and for viewing everything that was going on. An extra large, two-story cage with four accessible compartments was constructed for observation of four or five monkeys living together.

for this and, moreover, fear was expressed that a monkey might escape and get on a patient corridor. But after devising a monkey escape control system, I was granted permission.

One of the main purposes of our section was to obtain electrophysiological and anatomical information about the connections of the limbic cortex with the various sensory systems. I was aware from experience that macroelectrodes would be unsatisfactory for this work because volume-conducted potentials generated in visual structures were manifest in the hippocampus. Moreover, anaesthesia was known to block nerve conduction in certain pathways. I therefore modified the system that I had used at Yale, whereby a light plastic stereotaxic platform could be permanently fixed above the scalp and provide a closed system for exploring the brain with metal or glass microelectrodes. The same device also provided exploration of the brain with stimulating electrodes in experiments where that was required (MacLean, 1990, pp. 333–336).[7] For the microelectrode recording, it was a special advantage that the Marshall Laboratory possessed as much expertise and apparatus for recording bioelectrical activity as could be found anywhere.

One module of our section was set aside for purely anatomical work and the staining of serial sections of brains of experimental and control animals. John Gergen (a research associate) and I prepared a stereotaxic brain atlas based on serial sections of the brains of 30 squirrel monkeys (Gergen and MacLean, 1962).

The most complete review of the microelectrode findings on more than 14,000 units recorded while in the Marshall Laboratory and later at the Poolesville facility is to be found in Chapter 26 of *The Triune Brain in Evolution* (MacLean, 1990). In a word, we found that stimulation of all the exteroreceptive systems evoked unit responses in respective limbic areas of the fronto-insulo-temporal cortex and in the occipital, parasplenial, and posterior cingulate cortex. Surprisingly, the unit responses were modality-specific. A finding of special interest was that photic stimulation evoked both phasic and sustained unit responses in the posterior hippocampal gyrus as well as unit spike potentials in the adjoining parasplenial limbic cortex and neocortical fusiform cortex. An anatomical study showed that when lesions were placed in the lateral geniculate body, degeneration could be traced in Meyer's temporal loop into the posterior cortex of the hippocampal gyrus. The posterior parahippocampal cortex caudal to the rhinal fissure is a major source of hippocampal afferents. Phasic spike discharges were elicited in the hippocampus only by vagal and olfactory stimulation. These observations may be relevant to mechanisms involved in conditioning and memory.

[7] See these pages also in regard to humane experimental conditions.

Another major undertaking in our section was the investigation of brain structures and pathways involved in primal sexual functions. It is curious that little knowledge had existed about the representation of such pivotal functions above the level of the hypothalamus. The major findings and associated collaborators in these studies are summarized in Chapter 20 of *The Triune Brain in Evolution* (MacLean, 1990).

A Triune Concept of the Brain and Behavior

In February 1969, I gave the Clarence Hincks Memorial Lectures at Queens University, Kingston, Ontario. In keeping with the overall theme of the three lectures—The Brain and Behavior—I explained that the human forebrain evolved to its great size while retaining features of three basic formations that reflect an ancestral relationship to reptiles, early mammals, and recent mammals. The three neural assemblies, I pointed out, are radically different in structure and chemistry, and in an evolutionary sense, countless generations apart. Based on these features alone, I said, it might be surmised that psychological and behavioral functions depend on the interplay of three quite different mentalities. The three evolutionary formations might be popularly regarded as three interconnected biological computers, each having its own special intelligence, its own subjectivity, its own sense of time and space, and its own memory, motor, and other functions.

What I did not realize until afterward was that if you speak publicly in Canada, the communication ties within the British Commonwealth are such that there may be a period when the sun will never set on what you say. The underlying theme of my lectures—the three-brain concept—gained rather wide circulation, but in the abbreviated reports, one got the impression that we behaved as though under the direction of three separate brains. I realized that what I needed was a word so definably tight that there could be no possible confusion on that score. Despite its other connotations, I liked the word "triune" because its letter-by-letter spelling was so close to the Greek term meaning, literally, three-in-one. If the three main evolutionary assemblies were pictured as intermeshing and functioning together as a triune brain, they could hardly be completely autonomous, but would be able to operate somewhat independently. Moreover, the word triune also implies that the whole is greater than the sum of its parts because, with the exchange of information among the three main assemblies, each derives a greater amount of information than if it were acting alone. Consequently, I explained in the published version why I changed the title to "A Triune Concept of the Brain and Behavior."

The Laboratory of Brain Evolution and Behavior

Bob Livingston, director of the Intramural Research Program, and I had frequently discussed the advantages of having a satellite field laboratory for conducting certain neurobehavioral studies. The reasons for having such a facility were many, but the main thrust of the argument may be found in the writings of C. Judson Herrick, who said in effect, that there is no experiment that Nature has not done for us.[8] In my entry titled "Triune Brain" in the *Encyclopedia of Neuroscience* (1987), I cited some of the advantages of the comparative, evolutionary approach at both the molecular and macroscopic levels.

In 1959, Livingston learned of the NIH plan to obtain a 1000-acre farm to support the clinical and research needs of the Clinical Center. Mindful of our foregoing discussions, he applied for and obtained a sector of 30 acres for a field laboratory. Economic considerations required the purchase of a farm 30 miles from the Clinical Center, near the Potomac River, 7 miles south of Poolesville, Maryland. Because our facility was part of the overall plan for the farm, including the architecture, the laboratory was not ready for occupancy until May 1971. In the meantime, John E. Eberhart, who had succeeded Livingston as director of the NIMH Intramural Research Program, and who shared a like enthusiasm for the facility, thoughtfully asked me to be with him every time there was a meeting with the architects.

Goals and Outcome of Research at Poolesville

The Poolesville facility was built to serve as another means of broadening the evolutionary approach in finding the roots of human subjective experience and behavior. Evidence continues to accumulate that in all animals there are molecular commonalities that apply to genetic coding and enzymatic reactions that carry over to complex cellular assemblies. "Nowhere is the uniformity of complex cellular assemblies more striking than in the cerebral evolution of vertebrates both as it applies to similarities within classes and to certain commonalities across classes" (MacLean, 1987, p. 1235).

We intended to focus on the anatomy and functions of cerebral commonalities of animals belonging to the three classes of terrestrial vertebrates: reptiles, birds, and mammals. All land vertebrates derive from the stem reptiles. Continuing fossil discoveries are adding to the evidence that birds evolved from dinosaurs. The fossil record, on the contrary, provides numerous examples linking the lineage of human beings and other mammals to the mammal-like reptiles (therapsids) that lived in Permian times, some 250 million years ago when there was but one giant continent known as Pangaea. Providing a remarkable illustration of directional evolution, several lines of the therapsids were approaching the mammalian condition so that finally the most reliable distinction was the retention in the jaw joint of two small bones which, in mammals, migrate and become the malleus and incus of the middle ear.

[8] In correspondence about this matter, Herrick could cite no particular aphoristic statement to this effect.

There are no living reptiles directly in line with mammals, but one of the primitive therapsids had an auditory apparatus and skeleton so similar to lizards that paleontologists gave it the name Varanosaurus, after the Varanus (monitor) lizard, of which the Komodo dragon is an example. Therefore, I decided to use lizards in our comparative neurobehavioral studies. If one does a behavioral analysis (ethogram) of the three classes of land vertebrates, one finds about 25 forms of behavior common to all three (MacLean, 1990, p. 100). In one category are behaviors that comprise their daily master routine and subroutines. In the other category are displays used in social communication. In all three classes, the displays can be grouped into four main types—greeting displays, aggressive displays, courtship displays, and submissive displays.

Given the list of the basic forms of behavior in the three classes of land vertebrates, what brain structures might account for the shared similarities? Classical experiments had shown that the neural chassis in the lower brainstem and spinal cord was somewhat comparable to a vehicle without a driver (MacLean, 1990, Chapter 3). This would indicate that structures responsible for directive behavior must be looked for in the forebrain. Given the small representation and archicortical resemblance of the cortex in reptiles and birds, the most likely place to look for the driver was those parts of the basal ganglia having both an anatomical and chemical resemblance to those in mammals. These comprise the so-called striatal complex and include the olfactostriatum (olfactory tubercle and nucleus accumbens), corpus striatum (caudate nucleus and putamen), globus pallidus, and satellite collection of gray matter (MacLean, 1990, pp. 37–43). In a comparative context, I refer to them as the R-complex. Clinically, they have been regarded as part of the motor apparatus under the control of the motor neocortex, having, so to speak, no mind of their own.

Years before in Boston, on one of our walks from North Station to the MGH, I asked Charles Kubik, "Charlie, what do the basal ganglia do?" Because he had seen so many cases with large cavities in the corpus striatum without a history of motor symptoms, he jokingly replied, "Hunh, they don't do nuttin': They just hold up the rest of the brain."

Experimental Findings on Display Behavior

Squirrel Monkeys. In 1964 I described two varieties of squirrel monkeys, one of which would consistently display to its reflection in a mirror, whereas the other showed little or no interest in its reflection. I referred to the mirror-displaying monkey as the gothic type because the ocular patch formed a peak over the eye like a gothic arch, while the other variety was called roman because the arch was rounded like a roman arch (see MacLean, 1990, pp. 172–173, for facial, vocal, and karyotypic differences). The main features of the gothic-type mirror display comprise vocalization, spreading of the thigh, and full penile erection. In year-round testing of 105 monkeys, these manifestations were shown to occur 82% of the time in sets of 30 trials. Systematic observations of the effects of brain lesions of various neocortical, limbic, and striatal structures were made on more than 115 monkeys (MacLean, 1990, Chapters 13 and 14).

The main outcome of the study showed that the rostromedial part of the globus pallidus (MacLean, 1978) is a site of convergence of neural systems involved in the species-typical expression of the mirror display. Since the same features of the display occur in both aggression and courtship, the findings would imply that the same cerebral structures are also implicated in these displays.

Lizards. With Neil Greenberg, we studied the effects of forebrain lesions on the challenge display of the green Anolis lizard (MacLean, 1990, p. 153). In this kind of an experiment, it is essential not to interfere with thermoregulation. Since the optic nerves of the lizard are almost completely crossed, it is possible to place a lesion in only one side of the brain and then test the lizard's behavior with either of its eyes covered when it looks at a rival male lizard living side-by-side in a like vivarium with a removable screen in between. Serial brain sections showed that only the lizards with lesions of the R-complex failed to display when looking with the eye projecting to the injured hemisphere. Lesions elsewhere, including the dorsal ventricular ridge, were ineffective.

Routines. There seems to be a tendency not to think about the complicated kind of neural apparatus required to maintain a daily master routine, and at the same time brook the interruptions of emergencies and other factors that precipitate a variety of subroutines. The master routine of lizards is quite similar for various species, including (1) cautious morning emergence; (2) basking; (3) defecation; (4) drinking; (5) morning hunting within territory; (6) period of inactivity; (7) afternoon hunting farther afield; (8) late afternoon basking near shelter; and (9) retirement to roost.

We never completed a neurobehavioral study on how different cerebral lesions affected the daily master routine in mammals. However, with Michael Murphy, a research associate, we found that neonatal hamsters that were completely deprived of neocortex but with an intact limbic system and striatal complex developed normally and manifested all forms of hamster-typical behavior along with the usual daily master routine.

In my study of the effects of pallidal lesions on the mirror display of squirrel monkeys, I reported that each monkey had a subroutine for approaching a mirror during the control preoperative period. Although not displaying after surgery, the former preoperative manner of looking into the mirror was altered.

Perhaps the most telling observations on the probable role of the basal ganglia in affecting the daily master routine and subroutines derived from clinical case reports. Caine and colleagues (MacLean, 1990, p. 220) observed a group of 18 patients at the NIH Clinical Center with a diagnosis of Huntington's disease, which primarily affects the corpus striatum. Although the authors do not mention the word *routine,* what they actually described as one of the earliest symptoms of the illness was an inability to initiate and carry out a daily master routine. In some cases, long-accustomed subroutines were also affected. A dentist, for example, was no longer able to perform the familiar step-by-step sequence of filling a tooth.

Patients with Sydenham's chorea, often attributed to an irritative condition of the corpus striatum, may spend their days, as reported so vividly by Osler (MacLean, 1990, p. 221), engaged in repeated performance of bizarre subroutines that allowed them little time for an orderly, daily master routine.

In summary, there are indications that the R-complex orchestrates the performance of displays used in social communication. Moreover, one obtains pieces of evidence from experimental and clinical findings that the R-complex provides an intelligence for linking together the requisite behavior of the daily master routine, as well as those of subroutines.

The Limbic System: Summary of Earlier and Continuing Research

It cannot be overemphasized that "psychomotor epilepsy" provides the best evidence (and the only self-descriptive, subjective evidence) that limbic structures are basically involved in the generation and expression of emotional feelings. I will therefore introduce this summary with a brief classification of emotional feelings referred to as *affects,* as opposed to their outward expression for which Descartes' word *emotion* is appropriate. At Yale, just as at the MGH, I continued to see patients with psychomotor epilepsy or who were candidates for electro-encephalographic diagnosis. This background, together with my reading of numerous case histories, led me to develop a workable classification of the affects, described in four chapters on the phenomenology of psychomotor epilepsy in *The Triune Brain in Evolution* (MacLean, 1990, Chapters 22–25).

It is the element of subjective awareness that distinguishes psychological from other functions of the brain, the most common of which are sensations, perceptions, drives, emotional feelings, and thoughts. Under usual conditions, sensations and perceptions depend on the immediate excitation of receptors. Through different processes of mentation, however, drives, emotional feelings, and thoughts may recur and persist after the inciting incidents. Subjectively, the affects may be characterized as either agreeable or disagreeable. By definition, there are no neutral affects. The affects can be divided into three kinds—basic, specific, and general. The so-called basic affects are associated with basic bodily needs such as thirst for water, hunger for food, the need to expel, and so on. The specific affects are feelings associated with specific sensory systems and thereby also include the cultural affects. The general affects correspond to what we usually describe as emotional feelings, and are so named because they may be activated by things, situations, or individuals. There are six main kinds of general affects characterized, respectively, by feelings of desire, anger, fear, dejection, joy, and affection. During the aura at the beginning of a limbic epileptic storm, a patient's mind may light up with typical feelings that, in one case or another, cover the entire range of basic, specific, and general affects.

Functions of the Three Main Limbic Subdivisions. Based on a review of experimental and clinical findings, including the growing amount of information from anatomical, electrophysiological, and neurochemical studies, I had suggested that the limbic system could, operationally speaking, be divided into three main subdivisions, all of which derived information in terms of affective feelings that guide behavior required for self-preservation and the preservation of the species. Phylogenetically, the two oldest divisions include limbic cortical areas reciprocally connected with two telencephalic nuclei, the amygdala and the septal nuclei, which are closely associated with the olfactory apparatus. Experimental and clinical findings have revealed that cortical and subcortical structures most closely associated with the amygdala are involved in experience and behavior, and are primarily concerned with self-preservation as it relates to feeding, the search for food, and the fighting and defense that may be required in obtaining food. The septal division, on the contrary, appears to promote survival of the species as evidenced by its involvement in primal sexual functions and manifestations conducive to sociability, courtship, and reproduction.

The newest subdivision, of which there is no clear counterpart in the reptilian brain, and which culminates in the human brain, is referred to as the thalamocingulate division because of the preponderance of its cingulate cortical connections with the anterior and midline thalamic nuclei. In contrast to the two just-mentioned divisions, some workers would argue that it has nothing to do with emotional behavior. Recent experimental findings point to the unlikelihood of such a negative statement. In the evolutionary transition from therapsids to mammals, three forms of behavior appear to have developed that most clearly distinguish mammals from other vertebrates. This cardinal family related triad comprises: (1) nursing, conjoined with maternal care; (2) audiovocal communication for maintaining mother–offspring contact; and (3) play behavior.

Nursing and Maternal Care. The important role of the cingulate cortex in maternal behavior, including nest-building, nursing, and pup retrieval, has been known since the important publication on this subject by Stamm in 1954. His findings in rats were subsequently confirmed and extended by Slotnick, who also showed the importance of cingulate function in paternal behavior (MacLean, 1990, pp. 388–395). With Michael Murphy, who had developed an extensive ethogram on feral hamsters, we observed similar maternal deficits in another type of experiment involving cingulate ablations in neonatal hamsters which had grown to maturity.

Audiovocal Communication. In my studies of the functions of pallidotegmental pathways, I noted that squirrel monkeys with certain lesions developed abnormal kinds of vocalization and, occasionally, did not vocalize at all. I discussed this with John Newman, of the Child Health Laboratory of Comparative Ethology, who was particularly interested in the vocalization of primates, and the separation cry in particular. The separation cry possibly ranks as the most basic mammalian vocalization. A preliminary analysis of the spectrograms of monkeys that had been operated on showed harmonic evidence of the infantile nature of the cry or other abnormalities. We then undertook a study to attempt to narrow down the tegmental structures involved in such changes (MacLean, 1990, pp. 402–403). After that, the next step was to test the effects of ablating parts of the medial frontal cortex containing the anterior cingulate cortex because of the long-known importance of the latter in primate vocalization. We found that ablation of a strip of pregenual cingulate cortex with its continuation in the subcallosal cingulate cortex resulted in an enduring elimination of the spontaneous production of the separation cry (MacLean, 1990, pp. 403–410).

Play Behavior. Our observations on the developmental behavior of neonatal hamsters deprived of the entire neocortex revealed that they matured normally and acquired all forms of hamster-typical behavior. What was surprising and of great interest was that, if in addition the cingulate cortex had been destroyed in either males or females, they failed to develop playful behavior expected around the 13th day, or at any time thereafter.

Significance of the Family-Related Behavioral Triad

Here it is enough to say that there are numerous situations that, for both people and mammals generally, make separation painful. In this respect it is of interest that the part of the cingulate cortex involved in the production of the separation cry receives some of its innervation from thalamic nuclei involved in the perception of pain (MacLean, 1990, p. 541). Of further relevance is the high content of opioid receptors in the cingulate cortex, and that morphine, in all varieties of mammals to which it has been given, eliminates the separation cry. I have suggested that the origin of the cry is perhaps evolutionarily traceable to the times of beginning nursing and the fatal consequences that would ensue if the young were separated from a nursing mother.

In speaking of play, I have noted that few people, even experts in animal behavior, seem to be aware that mammals are the only vertebrates that engage in indisputable play. In this regard, I have suggested that play may have originated as a means of promoting harmony in the nest and, later, sociability and muscle-building for the strategies of survival. There is no need here to elaborate on all the ways that play enters into the imaginative and creative aspects of the arts, literature, and science.

These considerations of separation and crying also bring up the question of the neural substrate of laughing and crying which have long remained a mystery. The results of the foregoing studies suggest that it would be worthwhile to review cases of psychomotor epilepsy in which there were manifestations of either or both laughing and crying. The findings are too extensive to be reviewed here, as are the many implications. In one sentence, the location of irritable foci involve nuclei and cortical structures along the course of Papez's circuit that suggest opportunity for reciprocal innervation of laughing and crying.

An interesting question arises here about the specific nature of tearing in human beings. It is said that all mammals are subject to tearing when exposed to irritating conditions such as smoke. However, it is claimed that human beings are the only creatures in which tearing is induced by emotional feelings. Human beings are also the only creatures to discover the use of fire for a variety of purposes such as cooking food, making tools, and the like. Evidence of the hominid use of fire can be found as early as 1.4 million years ago. Briefly, I have suggested that the tearing associated with grief may have been conditioned by the irritation of smoke when burning the remains of loved ones (MacLean, 1990, pp. 556–558). The tears of laughter, on the contrary, might have been conditioned by amusing forms of communication occurring during cooking or relaxation around a fire or in a cave (MacLean, 1990, p. 558).

The Meaning of Life in Regard to the Limits of Knowledge

Sense of Being (Ontology) and Memory

On the basis of introspection alone, one might infer that sense of self and reality depends on an integration of internally and externally derived experience. Whereas the neocortex receives most of its information from the outside world via the visual, auditory, and somatic pathways, the limbic system not only is closely tuned to the internal environment, but also, as previously emphasized in our experimental studies, receives information from all the exteroceptive senses. Hence, it could be argued that a sense of self depends on an integration of limbic and neocortical systems.

Such a concept would seem to be borne out by manifestations of psychomotor epilepsy. Following the aura, patients may engage in automatisms that range in individual cases from simple to very complex forms of behavior for which they have absolutely no memory. The complex automatisms can involve skilled, cognitive functions, as illustrated by a physician who correctly diagnosed and treated a patient, and an obstetrician who performed a breech delivery. At autopsy, a former physician (Hughlings

Jackson's famous Case Z) was found to have a small cyst involving the region of junction of the amygdala and hippocampus (MacLean, 1990, pp. 563–564). As noted earlier, limbic seizures tend to spread within and be confined to structures of the limbic system. Evidence exists that the onset of the automatism coincides with a bilateral spread to limbic structures necessary for a sense of self-identity. Without a sense of self, there is, so to speak, no place to deposit a memory of ongoing experience (anterograde amnesia). The same argument could be made in cases of anterograde amnesia associated with destructive lesions of the hippocampus and certain other limbic structures.

The Matter of Belief

Finally, it is of profound epistemic significance in regard to human belief that the symptomatology of psychomotor epilepsy suggests that the limbic cortex generates free-floating, affective feelings conveying a sense of what is real, true, and important. The same applies to feelings of discoveries (eureka-type feelings) that would compare to the nonepileptic, "this is it" revelation, such as what Kepler experienced upon his wrongful conception of "the five perfectly fitting solids" (MacLean, 1990, p. 578).

There is evidence that limbic cortical structures by themselves are incapable of verbal communication. On the other hand, evidence just reviewed suggests that without a cofunctioning limbic system, the neocortex lacks not only the requisite neural substrate for a sense of self, of reality, and the memory of ongoing experience, but also a feeling of conviction as to what is true or false. It would therefore seem that we are left in an intellectually shaky position. It is one thing to have an illiterate brain for judging the authenticity of food or a mate, but where do we stand if we must depend on this same mind for belief in our ideas, concepts, and theories? (MacLean, 1990, p. 453).

Even with a normally functioning brain, the neocortex is incapable of dealing with one problem that brings us right up to the limits of knowledge. This is because the logical functions that we attribute to the neocortex are such that no logical system of any complexity can be cleared of contradiction. This situation, as proved arithmetically by Gödel, is owing to the axiomatic need of self-reference. As Bronowski commented, self-reference "creates an endless regress, an infinite hall of mirrors of self-reflection" (MacLean, 1990, p. 571). To this might be added that, because the subjective brain is solely reliant on the derivation of immaterial information, it could never establish an immutable yardstick of its own; it must forever deal with a nondimensional space and a nondimensional time for which it establishes its own arbitrary standards of measurement.

One might hope that further developments in quantum mechanics clarifying the interplay of the wave and quantum might lead to some further surety of knowledge. But here again the viscoelastic properties of the brain make its calculations so incommensurably slow and crude as to make many of the questions of quantum physics incomprehensible. Nevertheless, it adds intellectual interest to deal with such questions. For example, in a recent paper of mine dealing with the brain and the derivation of subjective experience, it gave appetite to my thinking by raising the question of the role of certain proteins and their being affected by resonance at the molecular, submolecular, and atomic levels (MacLean, 1997).

The Meaning of Life

The Four Horsemen of the Apocalypse (conquest, war, famine, and death) have always been with us, but since the onrush of worldwide communication, they have never seemed to be riding in so many places at once. Psychic anguish, starvation, horrendous kinds of killing, and war keep appearing everywhere. To this must be added the untold suffering of countless animals as, for example, the tons of fish dragged up on deck every day to die a slow, suffocating death. These are thoughts to temper anyone's attempt to understand the meaning of life. And I must admit, in the last few years it has tempered my once lively curiosity about the meaning of life. In discussion now with people about this question, my phrasing has acquired a negative slant. Why, I ask, with all the suffering in this world—human suffering, animal suffering—would anyone want to create life, and perpetuate life, here or elsewhere in the Universe?

When, as usual, there are no persuasive answers, I call attention to what has been for me a comforting observation. The development of the prefrontal cortex in human beings has been shown to be involved in anticipation and planning, as well as with empathic and altruistic feelings. The prefrontal cortex is closely tied in with the limbic cingulate cortex which, as noted above, has been found in animals to be involved in parental behavior, the separation cry, and play. As I have suggested elsewhere, the evolution of prefrontal connections with the limbic "parental" cortex would make it possible for a concern for the future welfare of the immediate family to generalize to other members of the species, a psychological development that amounts to an evolution from a sense of responsibility to what we call conscience. What does it tell us about the meaning of life when we can now say that for the first time in the known history of biology, we are witnessing the evolution of human beings with a concern not only for the suffering and dying of their own kind, but also for the suffering and dying of all living things?

Acknowledgments

In 1993, I decided to satisfy my desire to return primarily to the study of the human brain. Most needed, I thought, was a three-dimensional picture

of the cortical and subcortical neural circuitry with which the viscoelastic brain derives its own species of algorithms (i.e., solutions) accounting for everything we do. Such reasoning led me to ask to be assigned to the NIMH Neuroscience Center at St. Elizabeths, where I hoped a start could be made for a multipurpose national brain facility for perfecting the methods by which we study the anatomical and chemical connectivity of the brain. Unfortunately, the introduction of the marvelous technique of brain imaging has led to the wrongful impression that it will replace classical methods. However, if we rely mainly on imaging techniques, we shall be a little like those in Plato's cave trying to obtain information from changing light and shadows. At the proposed facility on the beautiful St. Elizabeths campus overlooking nearby Washington, one could foresee the formation of a museum-quality collection of brains with excellent histories that would be representative of diverse human diseases and of different genetic stock.

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Selected Bibliography

Bernstein J. *Quantum profiles.* Princeton, NJ: Princeton University Press, 1991.

Broca P. Anatomie comparée des circonvolutions cérébrales. Le grand lobe limbique et la scissure limbique dans la série des mammifères. *Rev Anthropol* 1878;1: 385–498.

Gergen JA, MacLean PD. *A stereotaxic atlas of the squirrel monkey's brain (Saimiri sciureus).* Washington, DC: U.S. Government Printing Office, 1962. [PHS Publication 933]

Greenberg N, MacLean PD, eds. *The behavior and neurology of lizards.* Washington, DC: U.S. Government Printing Office, 1978. [DHEW Publication (ADM) 77–491]

Hotton III N, MacLean PD, Roth JJ, Roth EC, eds. *The ecology and biology of mammal-like reptiles.* Washington, DC: Smithsonian Institution Press, 1986.

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

MacLean PD. Some psychiatric implications of physiological studies on the frontotemporal portion of limbic system (visceral brain). *Electroencephalogr Clin Neurophysiol* 1952;4:407–418.

MacLean PD. The triune brain, emotion, and scientific bias. In: FO Schmitt, ed. *The neurosciences: Second study program.* New York: The Rockefeller University Press, 1970;336–349.

MacLean PD. A triune concept of the brain and behavior. Lecture I: Man's Reptilian and Limbic Inheritance; Lecture II: Man's limbic brain and the psychoses; Lecture III: New trends in man's evolution. In: Boag T, Campbell D, eds. *The hincks memorial lectures.* Toronto: University of Toronto Press, 1973;6–66.

MacLean PD. On the evolution of three mentalities. *Man Envir Sys* 1975;5:213–224.

MacLean PD. Effects of lesions of globus pallidus on species-typical display behavior of squirrel monkeys. *Brain Res* 1978;149:175–196.

MacLean PD. Triune brain. In: Adelman G, ed. *Encyclopedia of neuroscience.* Cambridge, MA: Birkhauser Boston, 1987;1235–1237.

MacLean PD, ed. *The triune brain in evolution: Role in paleocerebral functions.* New York: Plenum, 1990.

MacLean PD. Neofrontocerebellar evolution in regard to computation and prediction: Some fractal aspects of microgenesis. In: Hanlon RE, ed. *Cognitive microgenesis: A neuropsychological perspective.* New York: Springer-Verlag, 1991;3–31.

MacLean PD. Limbic system. In: Beaumont JG, Kenealy PA, Rogers JC, eds. *The Blackwell dictionary of neuropsychology.* Oxford: Basil Blackwell, 1996.

MacLean PD. Women: A more balanced brain? *Zygon J Religion Sci* 1996;31: 421–439.

MacLean PD. The brain and subjective experience: Question of multilevel role of resonance. In: Vandervert L, ed. Nonlinear dynamics (including chaos) and quantum theory (perspectives on consciousness) in psychology. *J Mind Behav* 1997;18:247–268.

MacLean PD, Arellano AP. Basal lead studies in epileptic automatisms. *Electroencephalogr Clin Neurophysiol* 1950;2:1–16.

Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiat* 1937;38: 725–743.

Ramón y Cajal S. *Charlas de Café,* ninth edition. Madrid, Spain: Espasa-Calpe, SA, 1966.

Vandervert LR. Systems thinking and a proposal for a neurological positivism. *Sys Res* 1988;5:313–321.

Wiener N. *Cybernetics, or control and communication in the animal and the machine.* New York: Wiley, 1948.