1930s First CSHL investigations of electrical properties of nerve cells, under rubric of "biophysics."


1968–1971 As molecular biology tackles gene regulation, some researchers aspire to apply molecular approaches to neurobiology. Seminal CSHL laboratory courses are established by CSHL director James Watson.

1971 The abandoned Animal House is renovated as neurobiology teaching lab and renamed McClintock Laboratory.

Next-Generation NEUROSCIENCE Takes Shape at CSHL
For several years the pieces have been falling into place, one by one. But only in recent months has it been possible to see the broad implication: A new era in neuroscience research is dawning at Cold Spring Harbor Laboratory (CSHL).

The new thrust in neuroscience has some exciting objectives, including the discovery of markers that will permit development of simple diagnostic tests for common neuropsychiatric illnesses such as schizophrenia, autism and bipolar disorder. (See story about Stanley Center, p. 5) Such tests do not presently exist and are urgently needed to bring care at the earliest possible moment to those who manifest preliminary signs and symptoms. Clinical data show that patients often fare better if treated when their illness is in its initial stages.

The emergence of reliable diagnostics is only one aim of a multifaceted effort that will eventually involve nearly 20 distinct laboratories at CSHL and an expansion of neuroscience faculty by some 40 percent, according to Director of Research David L. Spector. New faculty members have begun to arrive on campus, including, this fall, Associate Professor Pavel Osten, Assistant Professor Bo Li and CSHL Fellow Dinu Albeau, and, next spring, Assistant Professor Stephen Shea. [see pictures, pp. 4–5]

As the program expands beyond its current base in the Beckman and Marks Buildings into the impressive Wendt Family Building and Donald Axinn Building for Learning and Cognition — scheduled to open their doors for the first time next summer — CSHL scientists will attempt to trace the process by which the developing brain gives rise to immensely complex neural networks; catalog the full range of human genes implicated in mental illness; and demonstrate with great precision — both in animals and humans — how genetic mutations and a host of related cellular anomalies give rise to disease-specific pathologies.

It is hoped that these investigations will not only make possible the first reliable diagnostics but will also indicate novel paths to more effective treatments and perhaps provide insights about how certain mental illnesses can be halted in their early stages or prevented altogether.

A Fertile Moment

“It’s a very fertile moment for neuroscience, full of new opportunities,” says CSHL President Bruce Stillman. Some of these opportunities are the product of significant progress that CSHL neuroscientists have made over the last decade in bringing together high-resolution imaging and innovative genetic methods to understand mechanisms of learning and memory in flies and rodents. (see timeline, pp. 2–5)

“These methods have by now spread throughout the field and have revolutionized it, permitting researchers to observe the functioning brain in living animals down to the level of individual neurons — quite an astonishing achievement,” Stillman says. In the period just ahead, teams led by Professors Anthony Zador and Yi Zhong, and Assistant Professors Josh Dubnau, Glenn Turner, Adam Kepecs and others will continue using these methods to understand memory and basic cognitive processes in model organisms. As members of the Swartz Center for Computational Neuroscience at CSHL, they will also employ advanced mathematical methods to achieve the larger aim of understanding neural circuits whose activity makes possible complex behaviors.

CSHL neuroscientists want to learn how these circuits are physically configured and assembled — work that Professors Partha Mitra, Josh Huang and others are taking on — but also how the brain as an ensemble of circuits responds to external stimuli and how the processing of these stimuli serves as the basis for decision making. Understanding cognitive processes in the brains of simpler organisms like flies and rodents forms a basis for understanding how the vastly more complex human brain processes information and interprets the surrounding world.

What Goes Wrong in Key Genes

Next-generation neuroscience at CSHL also involves the integration of a wholly independent line of research centering on the human genetics of cognitive dysfunction. This research represents an extension of concepts developed over the last
decade in CSHL's cancer research program, which has generated an impressive body of new knowledge about the linkages between genetic and biological dysfunction.

The laboratories of Professor Michael Wigler and Associate Professor Jonathan Sebat, in collaboration with those of Professors W. Richard McCombie and Gregory Hannon, have already begun to apply advanced genome-scanning techniques to the study of the genetic causes of schizophrenia, bipolar disorder and autism. In the coming years, they and others at CSHL will attempt to specify the total set of human genes that malfunction in these illnesses.

“We've known for decades that there is an important genetic component at work in varying degrees in all of these diseases,” Stillman notes. “But common mental illnesses are highly complex, by which we mean that they are caused not by a single malfunctioning gene, but by multiple genes acting in varying combinations and in the presence of environmental factors. The linkages among these various components have been notoriously difficult to pin down.”

So-called gene-association studies — which show the prevalence of specific genetic mutations in samples of people known to have mental illnesses — have turned up a plethora of "candidate genes." Literally hundreds of such genes have been proposed for schizophrenia alone. Yet costly efforts in labs around the world to perform such identifications, while important, have been inconclusive. CSHL geneticists will try to address what gene-association studies so far have not been able to reveal. How precisely do mutations in a candidate gene such as DISC1 — associated with the emergence of schizophrenia in a subset of patients — perturb brain biology, contributing to an emergent pathology?

An Unexplored Continent

Between dysfunctional genes such as DISC1 and the set of anomalous behaviors that we associate clinically with schizophrenia lies a veritable continent of basic biology. This is the vast and still unfamiliar terrain that CSHL scientists — both genetic researchers and cognitive neuroscientists — are now setting out to explore,
in schizophrenia, bipolar disorder, autism and other neurodevelopmental disorders, with tools and scientific insights not previously available.

The bet is that fundamental knowledge about cognition and behavior in the healthy brain, gleaned in part from work with animal models, will shed new light on what occurs in the human brain, during development and in the adult brain. If the bet pays off, this knowledge will enable neuroscientists to understand with unprecedented specificity how perturbation of genes can lead to complex and devastating behavioral abnormalities.

Consider the brain circuitry engaged when a person tries to focus his or her attention — a basic faculty that is disturbed in different ways in autism and schizophrenia. CSHL scientists including Zador, Osten, Li and Huang will be asking: What are the vital components of such circuits? What happens when a given malfunction occurs in a gene or an encoded protein? Do the discovered genetic anomalies vary in potency, and if so, under what conditions? In parallel with such basic scientific work, innovative studies by Professor Linda Van Aelst and Assistant Professor Hiro Furukawa in intracellular signaling should shed light on the molecular “cascades” specifically implicated in mental illness. What impact do signaling anomalies have on the underlying biology of the brain, and how do these correlate with clinical manifestations of mental illnesses?

Jonathan Sebat calls research that seeks answers to basic questions of this kind “connecting the dots.” Being able to follow the path from aberrant genes to perturbed biology to anomalous behaviors in people with mental illness is a kind of holy grail for neuroscientists. A decade hence, current efforts of CSHL scientists including Zador, Osten, Li and Huang will be paying the dividends that baby steps, if the great enterprise in neuroscience just biological roots of common behaviors, may seem like.

Unambiguous Diagnosis Within a Decade

The great suffering caused by serious neuropsychiatric illnesses such as schizophrenia, autism and bipolar disorder has given rise to a fierce desire among affected families to support research. A generous gift from Marilyn and Jim Simons, whose own family has been touched by autism, provided support for research in Professor Michael Wigler’s lab at CSHL that recently culminated in the discovery, with Jonathan Sebat, of the role of spontaneous DNA mutations in autistic children.

While this work was in progress, Dr. James Watson — who, with his wife Elizabeth, raised a son with schizophrenia and has a nephew with bipolar illness — encouraged Vada and Ted Stanley to support expanded efforts at CSHL to understand the genetic roots of mental illness. After a visit to CSHL, the Stanleys responded almost immediately with a gift of $5 million and, not long after, $25 million more, to launch an Institute for Cognitive Genomics. The institute has grown into a hub of collaborative efforts at CSHL and several partnering institutions including Zucker Hillside-North Shore-LIJ, Johns Hopkins, the NIMH and the University of Edinburgh. The bold first objective: to develop means of unambiguously diagnosing illnesses such as schizophrenia and bipolar disorder within a decade’s time.

Considerable progress already has been made. Under the Stanleys’ first gift, a project led by Sebat called the GEM study of bipolar disorder began almost immediately. GEM is devoted to understanding the genetics of what doctors call early-onset mania, a condition that often leads to severe, full-blown bipolar disorder. Several collaborative projects at the Institute led by CSHL Professor W. Richard McCombie focus on sequencing genes associated with psychiatric illnesses. The first of these is to “deep-sequence” a large gene called DISC1 implicated in schizophrenia. To facilitate other sequencing projects, CSHL Professor Gregory Hannon has honed a highly efficient and low-cost method of selectively targeting highly relevant portions of the genome for sequencing. Hannon is also applying his expertise in small RNAs to research on the brain.

The Stanley Institute for Cognitive Genomics: Unambiguously Diagnosing Illnesses Within a Decade

2007 Wigler and Jonathan Sebat seek to identify genetic changes that cause neuropsychiatric disorders. They demonstrate that spontaneous genetic mutations play a significant role in autism. Wigler proposes “unified theory” of autism’s causation.

2008 Sebat and colleagues demonstrate CNVs are three to four times more prevalent in people with schizophrenia than in healthy people and that these CNVs often impair pathways critical for brain development.