Brain, Genetics, and Behavior

Thirty West Coast medical and basic geneticists met with specialists in various fields of neurobiology at La Jolla, California, 12–13 February, to explore experimental approaches to an understanding of gene action in the central nervous system, in normal and disordered behavior. The workshop-symposium was supported by the National Genetics Foundation and was designed to bring together workers of different backgrounds interested in the genetics of the nervous system.

The complexity of behavioral phenotypes was illustrated in the opening presentation by S. Kety (Harvard Medical School) of ongoing epidemiological studies of schizophrenia in Denmark, where excellent psychiatric and folk registries are available. No anatomical, x-ray, or biochemical markers are known for this disease, so that the diagnosis rests upon clinical judgment, with the risk of numerous biases. Critical studies contrast the incidence of schizophrenia and related disorders in biological and in adoptive families of schizophrenic patients who had been adopted in the first month of life. Adoptive relatives had no increased incidence, while the biological relatives had a significantly increased incidence of schizophrenic illnesses, compared to suitable controls. Several paternal half-sibs were affected, in whom no shared intrauterine environment could be claimed. Nevertheless, nearly all the cases ascertained in relatives were mild. Presumably, what is transmitted genetically is a susceptibility to a schizophrenic personality disorder, which may be brought out by some combination of other genetic or environmental (or both) influences.

Analysis of single-gene mutants has been applied to neurological abnormalities in flies and mice. Y. Hotta (California Institute of Technology) described elegant methods of recognizing *Drosophila* with abnormalities in locomotion, phototaxis, courtship, mating, circadian rhythm, and response to anesthesia or shock. Flies are treated as "molecules" in a type of countercurrent distributor. The relation of phototaxis to activity can be described by an "ideal gas" equation and plotted as a two-dimensional chromatograph. Because flies generate enormous retinal potentials, electroretinograms have distinguished several classes of visual mutants, including a temperature-sensitive phototaxic mutant in which biochemical studies will be possible. X-Linked recessive mutations have been expressed in the XO sectors of gynandromorphs (XX/XO), allowing anatomical correlation of the distribution of X-linked pigment, bristle, and visual markers. After exclusion of abnormalities in the sensory apparatus, certain mutations may prove to lie in the integrative regions of the central nervous system.

M. K. Wolf (Harvard Medical School) presented studies on tissue culture of certain of the many neurological mutants in inbred strains of mice. Normal cerebellar explants form myelinated tracts and cell-cell connections based upon synaptic specificity. "Jimpy" fails to myelinate its axons, while "reeler" forms normal myelinated tracts, but connections between different cell types fail to develop. In "reeler," cerebral and hippocampal cortices also have disordered cell recognition in vivo. "Stagger" and "weaver" lack normal migration of granule cells. These cerebellar cultures permit biochemical and genetic manipulation of selected neurological mutants as models of developmental, "dystrophic," and toxic diseases.

Mixing of cells of two genotypes in vivo by producing allophenic mice offers a complementary approach to analysis of the developmental organization of the brain. B. Mintz (Institute for Cancer Research, Philadelphia) reviewed the techniques of dissociating cleavage stage embryos from two different mouse strains, mixing them in culture, and then implanting them in the uteri of "incubator females." Cell clones of the two genotypes coexist throughout life and can carry markers for specific tissues. The complex interactions of melanoblast and hair follicle and of pigment and neural retina cell populations were presented as models for pattern variability in relationships of physically overlapping and physiologically interacting clonal cell lines in the brain. Suitable histochemical markers for the nervous system are being sought in the mouse, man, and *Drosophila*.

Behavioral tests of allophenic and mutant mice are feasible, with the use of measures applied to inbred strains and to systematically heterogeneous and selectively bred derivative stocks. G. McClearn (University of Colorado) presented strain differences in open-field activity and in ethanol-water preference as evidence for genetic components in these complex behavioral phenotypes. Lifelong drinking histories have been plotted for individual mice, with some BALB/c mice seeming to acquire a "taste" for alcohol. Physiological studies indicate a strain-specific control of alcohol intake set by the amount of ethanol (rather than concentration or volume), and preliminary assays of alcohol and aldehyde dehydrogenases demonstrate strain differences. Defined strains also can be used systematically to assess the effects of environmental variables, such as "gentling" during learning.

A. Motulsky and G. Omenn (University of Washington) discussed biochemical approaches in man. Polygenic traits such as electroencephalographic patterns, intelligence quotient, and temperament could be mediated by a smaller number of genes than is conventionally postulated. Electrophoretic studies of erythrocyte enzymes have shown variants of many enzymes in more than 1 percent of the population, often with small differences in quantitative activity or in susceptibility to drug effects. Extensive screening of glycolytic and other physiologically important enzymes in brain tissue thus far indicates unexpected constraints upon variability; malic enzyme and creatine phosphokinase, on the other hand, have potentially significant variation. Analogous studies of neurotransmitter-related enzymes and their interaction with drugs are being pursued. Several inborn errors of metabolism with specific neurologic or psychiatric manifestations were cited. Lesser deficiency of the same enzymes deficient in these syndromes might contribute to behavioral variation in "normal" individuals. Since some enzymes important in brain metabolism are detectable in plasma, fibroblasts, white blood cells, or platelets, family studies in man may be feasible.

Specialized genetic control mechanisms in the nervous system occur both between cells at synapses and within cells. S. Snyder (Johns Hopkins University) presented studies on a possible transmitter role for histamine in the context of data available for other putative central nervous system trans-

mitter agents. With a sensitive radioassay, histamine was shown in highest concentration in the hypothalamus, was localized to synaptosomes with slightly different density than norepinephrine- or γ-aminobutyric acid–containing nerve terminals, was decreased by inhibition of histidine decarboxylase (turnover half-life only 5 minutes), and was affected by stress. It is clear that such transmitters as acetylcholine and norepinephrine account for only a very small percentage of all the synapses in the central nervous system; therefore, the evaluation of additional potential transmitter substances is an active field. No defined genetic diseases have been associated yet with an abnormality in neurotransmitter metabolism.

R. Rosenberg (University of California, San Diego) presented data on neuronal differentiation in vitro. He used both dissociated normal brain cells from neonatal BALB/c mice and transformed mouse neuroblastoma cells and found that morphologically differentiated neurons appear in culture with characteristic spike potentials upon stimulation and that several neurotransmitter-related enzymes can be detected, though synaptosomes and synaptic transmission have not yet been demonstrated. The effects of serum, of protein synthesis inhibitors, and of the microtubule-protein-binding substance colchicine can be evaluated in culture. Cells seem to become highly differentiated only as they slow their rate of cell division. Acetylcholinesterase activity increases rapidly as neuronal processes appear, while catechol-*O*-methyltransferase and other enzymes do not share the same pattern of regulation. Since there is evidence for both norepinephrine and acetylcholine in these clonal cultures, it will be very interesting to learn whether a single neuron can produce only one or the other of these neurotransmitters when it becomes highly differentiated.

Specialized processes of differentiation in brain may be engrafted upon those common to other tissues, and environmental modification leads to complex behavioral phenotypes, particularly in man. Nevertheless, there was optimism that experimental approaches of the type discussed can unravel some of the mystery of gene action in the nervous system.

G. S. Omenn
A. G. Motulsky
Division of Medical Genetics,
Department of Medicine,
University of Washington, Seattle 98105