Meetings

Neurological Mutants of the Mouse

Mutant mice are important research animals for investigation of the nervous system. At a conference, attended by American and European researchers in Bar Harbor, Maine (29 June–1 July 1965), E. L. Green (Jackson Laboratory) announced that 92 neurological mutations now are known in the mouse. D. S. Falconer (Institute of Animal Genetics, Edinburgh) classified these into broad categories—defects of regional development, structural defects of individual cells that fail to make some special product, and functional defects requiring biochemical study. Mammalian geneticists have served neurology by carrying on, almost unaided, the study of these mutants. Neurologists and psychologists in turn might refine the description of phenotypes and elucidate the pathological and physiological disturbances of neural function.

To provide a background for papers on mutants, J. B. Angevine (Harvard) reviewed serial sections and neural circuitry in the brain of the "normal" (C57BL/6J) mouse. Movies were shown to demonstrate clinical syndromes and methods for the clinical examination of mutants (M. M. Dickie, Jackson Laboratory). The need for quantitative parameters was expressed. Grüneberg (University College, London) raised the possibility that docility might have survival value in the laboratory mouse; "feeble-mindedness" could be common among the many inbred strains. Methods for assessing sensory function were surveyed by R. Wimer (Jackson Laboratory). The technical problems are formidable; inbred C3H mice, for example, were raised in large numbers for years before it was recognized that all of them were virtually blind. M. Sidman (Massachusetts General Hospital) presented a behavioral technique that yields reliable auditory threshold data on individual mice and makes sufficiently light demands on motor performance and learning to be useful with neurological mutants.

M. C. Green (Jackson Laboratory) pointed out that more than 90 percent of the known neurological mutants in the mouse occurred spontaneously. A few new ones appear among the 2 million mice produced annually at the Jackson Laboratory. Little systematic effort has been made to increase production of useful mutants by experimental means. Radiation has not been used, and screening for mutants that do not show obvious behavioral or morphological abnormalities has not been done. Green outlined methods for producing congenic lines where mutants and littermate controls are genetically identical except at and near the mutant locus. She also described the use of linked markers to help maintain infertile recessives, recognize heterozygotes, and compare affected animals with littermate controls at the preclinical stages when critical data on disease processes are most likely to be obtained. Among mammals, this degree of genetic control is available almost exclusively in mice.

Most of the known mutant disorders affect the nervous system during its development. E. Taber (Harvard) reviewed normal brain development in serial sagittal sections of 9- to 16-day-old mouse embryos. R. Sidman (Harvard) described the usefulness of radioautography after a pulse label of thymidine-H^3 for tracing the remarkable patterns of cell proliferation and migration in the otherwise inaccessible developing brain of a mammal. Genetic factors and chemical development of the brain in the early postnatal period were discussed by J. Fuller (Jackson Laboratory). The sizes of the brain and body vary markedly and independently between inbred strains, the female brain usually being heavier. Brain size is highly heritable, but behavioral correlates are not known. Chemical development in the mouse brain continues actively until at least 30 days of age. The very complex relationships between behavior and other parameters of development were emphasized by a consideration of the diverse effects of strain and age on susceptibility to audiogenic seizures. The mode of inheritance of complex behavioral traits, alcohol preference for example, may seem deceptively simple unless crosses between enough inbred strains are made to control for polygenic modifiers.

Several specific mutants were presented in detail. P. Karli (Strasbourg) reviewed retinal degeneration (*rd*), characterized by degeneration of partially differentiated photoreceptor cells beginning in the second week after birth. Visual sensitivity is reduced to 10^{-5} of normal, though the spectral sensitivity curve is unaltered. These findings imply the presence of a trace of rhodopsin, possibly located in lamellar material seen with the electron microscope at the surface of retinal pigment epithelial cells, in contact with the residual inner limbs of photoreceptor cells. The possible etiological significance of other metabolic derangements, such as the reduced retinal concentration of lactate dehydrogenase isozyme-5, may become clearer because of the recent development of a congenic stock containing *rd* and control animals distinguishable by a marker gene prior to the onset of histologically recognizable degeneration. S. Hicks (University of Michigan) described quantitative reduction in size of certain cells and tracts in two alleles of ataxia, (*ax*) and (ax^J). Such data are more likely to be reliable when mutant and control mice are comparable in size, as in the case of *ax*. Most mutants, including ax^J, are considerably smaller than their littermate controls. Duchen and Struck (Maudsley Hospital, London) with Falconer (Edinburgh) presented an instance, likely to occur often, of a mutant (wobbly, *wo*) known to geneticists for years but of general interest only since the pathology has been defined. It is a lower motor neuron disorder reminiscent of Werdnig-Hoffman disease of children and may be given the neurologically more appropriate name, neuromuscular paralysis (*np*). A different neuropathy was described by the same authors in dystonia (*dt*). Although the striking alteration in muscle tone and other clinical signs might suggest a disease of basal ganglia, the disorder clearly re-

sults from a disturbance of sensory receptors (for example, spindle apparatus in skeletal muscle), sensory nerve fibers, peripheral nerve trunks, and posterior columns of spinal cord. An allele, dt^1, may also be evidenced by brain disease (Curtis, New Jersey College of Medicine and Dentistry), but this merits further study, ideally when both alleles are available on a common genetic background.

Several mutations affecting the cerebellum have been discovered in recent years. J. D. Martin (Harvard) described leaner, an ataxic and hypertonic mutant with a degenerative disease affecting several cell types in the anterior lobe and nodulus. He also discussed three ataxic, hypotonic mutants, each with a very small cerebellum. In staggerer, cerebellar granule cells form but apparently are not maintained; in weaver, most of these cells degenerate as they proliferate on the external surface of the neonatal cerebellum, so that a granule layer never forms. The third, reeler, was described in more detail by M. Hamburgh (Albert Einstein College of Medicine). The outstanding feature is a disarray of Purkinje and other cells in the cerebellar cortex, of granule and pyramidal cells in the hippocampus, and of isocortical neurons generally. Hamburgh's interpretation that the disease is, at least in part, a disorder of cell migration was confirmed by R. Hayes (Harvard) with radioautography. Neurons proliferating in the ventricular walls at embryonic stages subsequently migrate to abnormal positions in the isocortex. R. S. Dow (Good Samaritan Hospital, Portland) referred to the difficulty of distinguishing failure of formation from degeneration in malformations of the human brain. One wants also to determine whether such hypoplasias are hereditary or result from some intrauterine disturbance, as seems to be the case in familial cerebellar hypoplasia of cats. G. Margolis (Dartmouth) pointed out that rat virus injected into neonatal mammals destroys external granule cells multiplying on the cerebellar surface, and produces a "malformation" similar to that in mutant mice.

M. S. Deol (University College, London) offered a unifying hypothesis about a range of mutations affecting the inner ear and other structures, namely, that a primary disorder in the early embryonic central nervous system interferes with subsequent induction of peripheral structures. Kreisler and dreher, usually classed as inner ear mutants, have antecedent defects in the rhombencephalon and impaired induction of otic vesicle. The abnormal vestibular ganglion and white head spot in dancer mice may result from a neural crest disorder at the level of the fourth rhombomere. Conversely, mutants known to have variable degrees of craniorachischisis were found to have inner ear malformations when, and only when, the disorder of the central nervous system involved the hindbrain. Deol recommended careful examination of the early central nervous system in mutants with spotted fur or malformations of ear, eye, or skeleton.

Mutations were examined biochemically. H. Rauch (University of Massachusetts) reviewed dilute-lethal (d^1) a "phenylketonuric" mouse with low phenylalanine hydroxylase activity in liver. Normal mice have an enzyme inhibitor that diminishes during the third postnatal week, so that enzyme activity rises; d^1 mice retain the inhibitor. The inhibitor, present in brain and other tissues, may alter the pteridine cofactor whose oxidation is coupled with the hydroxylation of phenylalanine. The same cofactor is required in brain for the synthesis of serotonin. G. Jervis (Letchworth Village, New York) compared phenylketonuric humans and d^1 mice. In man one of the phenylalanine hydroxylase enzymes is deficient; blood phenylalanine is increased 10- to 40-fold and metabolites spill over into the urine, whereas levels are only slightly elevated in d^1 mice. Phenylalanine transaminase activity probably is high in affected humans and is low in d^1 mice. S. Appel (University of Pennsylvania) reported that particular amino acids selectively inhibit incorporation of certain other amino acids into protein in a cell-free system prepared from brain, as well as in brain slices. For example, phenylalanine inhibits tyrosine incorporation. Such inhibition of protein synthesis in infancy might disturb neuronal and glial maturation and lead to impaired cellular function associated with mental deficiency.

R. Sidman (Harvard) reported on two mutants (quaking, *qk*, and jimpy, *jp*) with tremors, convulsions, and markedly diminished myelin throughout the central nervous system. Peripheral myelin is normal. By histological and metabolic criteria, *qk* mice fail to make myelin in adequate amount, while *jp* mice also have a myelin-destructive process. Jimpy's sex-linked disease is classified as a sudanophilic leucodystrophy, the first available in a laboratory animal. M. K. Wolf (Harvard) showed that cultures of cerebellum from newborn jimpy mice (identified by means of the linked marker, tabby) fail selectively to myelinate; the cultures do contain normal neuron cell bodies, axons, and synapses. J. Austin (University of Oregon) discussed a human white matter disease, metachromatic leucodystrophy, and emphasized that the accumulation of sulfatide (accounting for the metachromasia) is widespread through the body, is recognizable by urine analysis, and probably is due to the absence of arylsulfatase A.

E. Roberts (City of Hope Hospital, Duarte, California) reviewed the metabolism of gamma aminobutyric acid (GABA), which is an inhibitory neural transmitter in crustacea but has an undefined role in mammalian brain. The mutant mouse spastic (*spa*) is markedly hypertonic and responds clinically to aminooxyacetic acid; this acid raises brain GABA levels. However, whole brain GABA concentrations in *spa* mice are normal, and the rise induced by the drug does not parallel accurately the timing of the clinical response. The mutation probably does not cause GABA deficiency, but may result in some resetting of the steady-state equilibrium between excitation and inhibition of the central nervous system.

Addresses were given by V. McKusick (Johns Hopkins) and R. D. Adams (Massachusetts General Hospital). McKusick compared the current status of the study of inherited neurological diseases in man and mouse. He urged a wider use of genetic analysis to help establish the heterogeneity of many human neurological disorders and gave examples from the spastic diplegia, mucopolysaccharidosis, and deaf-mutism categories. He recommended the pragmatic working postulate that mutations with recessive inheritance are expressed as enzyme deficiencies, while dominant mutations commonly involve altered amino acid sequences in nonenzyme proteins. He also offered a challenge to the mouse geneticists that the human linkage map will come to surpass the mouse's map in completeness; the human X-chromosome now has more known loci than any other metazoan linkage group except for *Drosophila*. Adams stressed the inadequacy of present knowledge of antenatal and perinatal neuropathology. The mutant mice can provide much needed models to aid definition of the responses of

the immature nervous system to disease. He offered a classification of developmental disorders based on two main variables, developmental stage of onset and disease agent. A classification, supported by experimental data, must precede comprehension of mental retardation, epilepsy, and other groups of diseases.

The conference was sponsored by the Jackson Laboratory. In lieu of published proceedings of the conference, a detailed checklist and bibliography of neurological mutants in the mouse will be published by the Harvard University Press, Cambridge, Massachusetts.

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Electronic and Atomic Collisions

When activity in the field of atomic collision physics (along with extranuclear atomic physics generally) went into its decline three decades ago, it was widely felt that the field was completely understood in principle and that a limited number of then impossible experiments and calculations would tie up the entire matter. The 4th international conference on the physics of electronic and atomic collisions, held at Laval University in Quebec, Canada, 2–6 August 1965, disclosed that assessment to be far from adequate.

The "impossible" experiments have disclosed an incredible richness of phenomena in atomic and electronic collision physics, of importance to space, atmospheric, and plasma physics and to gas-phase chemistry; the computer-aided theoretical work has brought to light at least as many new problems as it has solved.

Typical of the new areas is the matter of "resonances" in scattering. As presently used, the term "resonance" refers to observation of energy-dependent structure in electron collision cross sections. This structure appears to be well fitted by the Breit-Wigner resonance formula much used in nuclear physics; moreover, theoretical calculations, especially in e-H scattering, have predicted the observed structure and