Neurological disease

Of Mice and Men

from J. B. Martin

SPONTANEOUS autosomal recessive mutations in mice are providing novel neurobiological models for studies of disorders of the central and peripheral nervous systems[1]. The clinical syndromes observed in such mice are given graphic anthropomorphic names: weaver, shiverer, wobbler, totterer, reeler, twitcher, and so on. Such mutants are being carefully investigated in search of clues to the pathogenesis of their disorders, both to gain an understanding of normal development of the brain and to seek hints to the nature of genetic disorders that affect the human central nervous system. Anatomic and biochemical studies of each mutant type have revealed some interesting abnormalities in brain, spinal cord or peripheral nerve. In general, homozygotes are severely affected; heterozygotes less so. Two such mutants have recently been the subject of new biochemical and anatomical investigations. In the shiverer mouse, which fails to synthesize myelin basic protein (MBP) — the most important constituent of the sheath of central nervous system axons — the defect has now been identified as a mutation in the structural gene for the protein[2]. And weaver mice, best known for cerebellar abnormalities, are, in a paper published in this issue of *Nature*, shown for the first time to have a highly selective degenerative disorder of subcortical dopaminergic systems somewhat reminiscent of certain human neurological disorders[4].

The brains of homozygous shiverer mice contain less than one per cent of normal levels of MBP; heterozygotes contain about 50 per cent, indicating a gene dose effect. Demyelination is prominent throughout the CNS and is believed to be a contributory cause of the clinical symptoms.

The recent work by Roach and coworkers[2] is the first successful attempt to relate a structural protein defect to an abnormal gene in mutant mice with neurological syndromes. Working from the known structures of mice and rat MBP, which share close homology[3], the investigators synthesized DNA probes based on the reverse translation of the amino acid sequence of rat MBP. Two cDNA clones encoding MBP were selected and a restriction enzyme fragment from one was completely sequenced. When translated, a portion of this sequence was identical at 126 of 127 positions with the known amino acid sequence for small MBP in the rat. Brains of shiverer mice homozygous for the MBP defect had greatly reduced concentrations of MBP mRNA compared to wild type. With the use of Southern blots for genomic DNA, it was shown that MBP sequences are deleted in shiverer mice. These studies have considerable implications for the investigation of demyelinating diseases in man. Multiple sclerosis, though usually a sporadic not an inherited disorder, has an increased incidence in individuals with certain tissue types (HLA-A3, B7, Dw2) suggesting a genetic propensity for the disorder, at least in some individuals. More important, the fact that rodent (rat and mice) MBP is closely similar in structure to human MBP points to the potential advantage of using such animal models to investigate human afflictions. It is likely that an understanding of the gene transcription and post-translational processing of MBP will increase our understanding of the aberrations of this important protein in the human.

In this issue of *Nature*, Roffler-Tarlov and Graybiel[4] describe an intriguing biochemical and anatomic study of the dopamine abnormality known to occur in the brain of the weaver mutant. Previous studies of this mouse focused on the cerebellum where abnormal migration and death of granule cells were noted[5]. The weaver strain also has a partial deficiency of dopamine in the forebrain[6]. The important contribution of the new report is the demonstration that one dopamine system, the nigrostriatal, is affected, whereas the other, the mesolimbic, is normal. The biochemical deficiency of dopamine in the putamen and caudate is mirrored by an alteration in the specific histofluorescence of the amine-containing neuronal elements. The dorsal striatum, which has a rich innervation from the nigrostriatal tract, shows dopamine depletion, whereas the ventromedial striatum and the nucleus accumbens, innervated by the mesolimbic system, are normal. The authors point to a lack, at the moment, of a similar disorder in humans but make analogies between this genetic disorder and the pattern of cell degeneration in Huntington's disease, an autosomal dominant human disease, recently shown to be associated with a DNA polymorphism on chromosome 4 (see refs 6 and 7). The regional distribution of the cell death that occurs in Huntington's disease is similar. Specifically, the area of the basal ganglia most affected in Huntington's disease is the dorsal lateral region of the caudate and putamen (neostriatum). In contrast, the substriatum, in particular the nucleus accumbens, is relatively spared[8]. The possibility of discovering genetic models of disease with topographic features similar to those present in man is raised by these observations.

The defect in the weaver mouse more closely approximates that of Parkinson's disease, which is usually a sporadic illness, but occasionally occurs as a hereditary or familial disease. The exact nature of the cellular pathology responsible for the dopamine deficiency in the weaver mouse has yet to be defined, and its genetic basis is unknown.

Mutants may also be useful models for exploring new therapeutic approaches. When grafted nerves of twitcher mice, which are defective in the enzyme galactosylceramidase (a model of Krabbe's disease), are transplanted into normal mice, the enzyme defect is corrected after several weeks[9]. Enzyme replacement occurs from adjacent normal tissues pointing to a possible strategy for correcting enzymatic defects. It is likely that future studies of mice mutants will provide additional examples of nature's errors which are applicable to an understanding of human diseases. In search of these, it is evident that defined biochemical changes rather than descriptive anatomic studies will provide the important leads to follow. □

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100 years ago

PROF. J.P. Licherdopol writes from Bucharest, Roumania, that on January 1, at 6.13 a.m., two horizontal shocks of earthquake, from north to south and *vice versâ*, were felt there, and were preceded by a loud noise, as of a distant train coming from the north. The furniture was slightly shaken and crackings were heard. The atmosphere was calm, but charged with a very thick and persistent fog.

A series of ornithological observatories has been established throughout Austria-Hungary at the instance of Crown Prince Rudolf, with a view of paying special attention to the migrations of birds, as well as to their breeding habits. The work done by these stations is satisfactory enough; yet it has been found that a complete insight into the periodical movement of birds cannot be obtained so long as similar stations are not spread over the whole globe. The subject is to form one of the principal topics for discussion at the approaching Ornithological Congress, which will be held under the auspices of the Crown Prince at Vienna on April 16 next and the following days.

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