BRAIN DEVELOPMENT

Cerebellar Guidelines

from a Correspondent

THE mammalian brain is a structure of such complexity that the discovery of the principles governing its development poses a major challenge to biologists. One particularly productive approach to this problem is that adopted by Sidman and his colleagues at Harvard University. They have been studying, in mice, the effects of single gene mutations on neural structure, concentrating particularly on the cerebellum. This part of the brain is a beautifully ordered neuronal structure which is closely implicated in the fine coordination and control of muscular activity. A mutant animal with an abnormal cerebellum displays characteristic signs of muscular incoordination, low tone in the muscles and frequently a tremor. The various types of mutant have acquired evocative names such as "reeler", "swayer", "staggerer", "weaver" and "nervous".

In a recent report Rakic and Sidman (*Proc. US Nat. Acad. Sci.*, **70**, 241 ; 1973) analyse the cerebellar defect in the mutant weaver. In the homozygous animal there is, by the age of three weeks, an almost complete absence of one cell type—the granule cells. In the adult cerebellum the granule cell lies beneath the layer of Purkinje cells —those large cells whose axons constitute the sole output from the cerebellar cortex. The granule cells receive their input from mossy fibres, one of the two types of afferent fibres to the cerebellum, and send their axons to specialized spines on the dendrites of Purkinje cells. The granule cells are thus an essential link in one of the principal neuronal circuits of the cerebellum and it is not surprising that in their absence gross signs of cerebellar dysfunction are apparent.

What is the cause of the granule cell death in homozygous weaver mutants? Is the demise of the granule cell a primary effect of the defective gene or a secondary phenotypic expression of some more elusive primary genetic effect? During normal development the precursors of the granule cells travel over the surface of the brain to the surface of the cerebellum, where they then undergo massive proliferation. The daughter granule cells then migrate from the cerebellar surface through a dense meshwork of cells and cellular processes to assume their adult position deep in the cerebellum. In homozygous weaver the granule cells die at the cerebellar surface and hence no migration takes place. Rezai and Yoon (*Develop. Biol.*, **29**, 17 ; 1972) demonstrated that in weaver heterozygotes the granule cells proliferate normally but the daughter cells migrate more slowly to their deep position. They suggested that in the homozygote cell death is secondary to a failure of migration rather than the reverse.

Rakic (*J. Comp. Neurol.*, **141**, 283 ; 1971), in an elegant electron microscope study of the developing monkey cerebellum, showed that throughout the entire extent of its difficult transcerebellar passage the migrating granule cell is intimately apposed to the process of a radially orientated glial cell (Bergmann cell). It was suggested that these glial processes act as necessary guidelines for the journey of the developing neurone, and in view of Rakic's discovery (*J. Comp. Neurol.*, **145**, 61 ; 1972) of a similar neurone–glial relationship in the developing cerebral cortex, it seems possible that such glial guidance is a fairly general phenomenon. Rakic and Sidman decided to investigate the relationship between granule cells and Bergmann glial cells in weaver mice to see if some abnormality in this relationship is the cause of the failure of the granule cells to migrate.

Rakic and Sidman found that in homozygous weaver mice the radial processes of the glial cells, although not entirely absent, are very rare. In the heterozygote, which does not display clinical symptoms, Bergmann glial processes are present but abnormal, the distal processes being enlarged, irregular and vacuolated. This reduced effect in the heterozygote is part of the basis for the authors' conclusion that, although neuronal death is the most prominent and clinically relevant phenotypic expression of the weaver mutant, the Bergmann glial abnormality may actually be closer to the primary cellular target of the *wv* genetic locus.

The importance of normal cell migration in brain development is also demonstrated in "reeler" mice where defective migration leads to disordered neural structures. In reeler, however, it is proving more difficult to identify the primary genetic defect (Caviness and Sidman, *J. Comp. Neurol.*, **145**, 85 ; 1972 ; and **147**, 235 ; 1972). In "staggerer", on the other hand, the phenotypic expression of the defect consists of the absence of a specific synaptic relationship, that between the granule cell and the Purkinje cell dendrite. All other cerebellar synaptic relationships are present. Sidman argues that the primary defect, in this case, lies in the Purkinje cell itself.

A potentially very powerful complementary approach to cerebellar development is offered by Altman and Anderson (*J. Comp. Neurol.*, **146**, 355 ; 1972). Controlled X-irradiation at particular post-natal periods can destroy selectively certain neuronal populations

What is the Origin of RD114 Virus?

RD114 VIRUS has attracted much attention recently because it has the characteristics of C-type RNA tumour virus and is released from human tumour cells, albeit human cells that have been passaged *in vitro* and in a foetal cat. The central question, of course, is what is the origin of RD114 virus? Is it a cat virus that infected the human cells during their passage in the kitten, or is it a human virus the replication of which was induced by the passage of the human cells in a kitten?

As has been shown by McAllister and his colleagues, who discovered RD114 virus, and by others, who have helped to characterize it, the antigens and the reverse transcriptase of RD114 virus particles are not closely related to their counterparts in either primate or feline C-type viruses. In an attempt to rule out the possibility that RD114 virus is merely feline leukaemia virus modified by passage in human cells, McAllister *et al.* performed the set of experiments that are reported in *Nature New Biology* next week (March 21).

McAllister *et al.* infected human RD cells, that do not release any virus, with either feline leukaemia virus or the Kirsten strain of murine sarcoma (this latter virus was obtained from rat cells and it grows well in both rats and human cells) and then assayed various properties of the progeny virus particles to see if they had been modified by passage in the human RD cells. McAllister *et al.* also investigated the properties of the infected and transformed RD cells. As far as could be judged from the results of a variety of tests, feline leukaemia virus particles from infected RD cells were identical to feline leukaemia virus particles from cat cells. Likewise the Kirsten murine sarcoma virus was not detectably altered by passage in RD114 cells. This indicates that RD114 virus is distinct from feline leukaemia virus and it is not simply a feline leukaemia virus somehow modified by passage in RD human cells.

McAllister *et al.* hint at the possible origin of RD114 virus. Apparently Todaro and his colleagues have induced from cat cells a virus closely resembling RD114 virus. It may be therefore that RD114 virus is a feline C-type virus quite distinct and unrelated from the already characterized feline sarcoma and leukaemia viruses. As they say, "The cat may be the first species found to have two distinct unrelated C-type viruses" ; this is interesting but is also a great disappointment for anybody who hoped that RD114 virus might be the first human C-type virus to have been isolated.