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Cortical anomalies in brains of New Zealand mice: A neuropathologic model of dyslexia?

(autoimmunity/cortical anomaly)

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ABSTRACT **Cortical anomalies have been reported in the brains of dyslexic individuals. In addition, dyslexic and left-handed individuals have a higher than expected rate of some immune-related diseases. The possible association between immune and cerebrocortical pathology was investigated in the immune-defective New Zealand Black mouse and its hybrid with the New Zealand White mouse. Structural anomalies similar to those present in the dyslexic brain were seen in the brains of these mice.**

Every brain from a dyslexic individual studied in detail at postmortem has shown forebrain abnormalities consisting of ectopic collections of neurons and distortions (dysplasias) of cortical architecture (1–5). In the four brains studied in our laboratory, the abnormalities involved primarily perisylvian association cortices and were more frequent in the left hemisphere. The abnormalities probably reflect developmental alterations occurring on or before the 24th gestational week (when neuronal migration has, by and large, ended in humans) because lesions acquired after that period do not produce similar alterations (6–8). In addition, analogous malformations can be produced experimentally in animals by interventions (i.e., freezing lesions) that precede the end of neuronal migration to the cerebral cortex (9). Neuronal ectopias and cortical dysplasias similar to those seen in the dyslexic brains are only found in 10% of allegedly normal brains (showing a predilection for the frontal lobes and, slightly, for the right hemisphere) (10, 11). The distribution of the lesions in the dyslexic appears to be unique. Therefore, this consistent finding in the brains of dyslexic individuals suggests a meaningful association between the structural anomalies and developmental dyslexia.

Geschwind and Behan (12, 13) have reported an association between left-handedness and learning disability and a group of diseases involving the immune system. Dyslexia was found to be 10 times more frequent among strongly left-handed than among strongly right-handed subjects, and it occurred more commonly in families of left-handed individuals. Conditions implicating defective immune function (predominantly gut and thyroid disorders) also were significantly more frequent in left-handers and their relatives. An increased incidence of migraine, allergies, attention deficit disorders, and skeletal anomalies were also seen and, more recently, a soluble ribonuclear protein known as Ro antigen, which is present in high concentrations in cardiac and brain tissue, was seen in some mothers of dyslexics (19). These associations may offer useful clues to the etiology of the cerebral anomalies in dyslexia.

To address the question of whether a relationship between immune pathology and abnormal brain development exists, we examined the brains of New Zealand Black mice (NZB/BlNJ) and their F_1 crosses with New Zealand White mice (NZBWF1/J), strains that spontaneously develop autoimmune disease. The NZB mouse develops hemolytic anemia and the F_1 hybrid develops severe renal disease. Both strains are considered models of human systemic lupus erythematosus (14, 15).

Table 1. Numbers of New Zealand and control mice with cerebral anomalies

	Anomalies		Total	
	Male	Female	Male	Female
NZB/BlNJ	6	3	23	21
NZBWF1/J	0	1	6	6
CFW	0	0	29	30

METHODS

We examined 56 brains from 30- to 90-day-old New Zealand mice: 44 NZB/BlNJ and 12 NZBWF1/J mice. For control comparisons, we studied 59 brains of the Swiss–Webster (CFW) outbred mouse strain, which does not have a history of immune dysfunction. Each group was evenly divided between males and females. After transcardial perfusion with 10% formalin, the brains were embedded in celloidin. They were then coronally sectioned at 30 μm, and every 10th section was stained for nerve-cell bodies with cresylecht-violett. Comparisons between control and experimental mice were made with a compound microscope. The cytoarchitecture of the cerebral cortex was examined, and the presence of any abnormalities was noted.

RESULTS

Ten of the 56 New Zealand mice had clearcut anomalies in the cerebral cortex, whereas no CFW mouse had any cerebral anomalies ($\chi^2 = 9.40$; $df = 1$; $P = 0.002$; see Table 1). Nine (6 males and 3 females) of the NZB/BlNJ and one female NZBWF1/J mouse had ectopias. The anomalies were unilateral in the New Zealand mice, except for one NZB/BlNJ male in which bilateral ectopias were seen. Of the unilateral ectopias, two were in the right hemisphere and three were in the left hemisphere of male New Zealand mice. In female New Zealand mice, four ectopias were in the right hemisphere and none were located in the left hemisphere.

The anomalies consisted of ectopic collections of neurons in layer I with underlying distortion of layers II–IV (Fig. 1). The ectopic neurons stretched from layer II through layer I up to the pial surface. The dysplastic cortex, which was often

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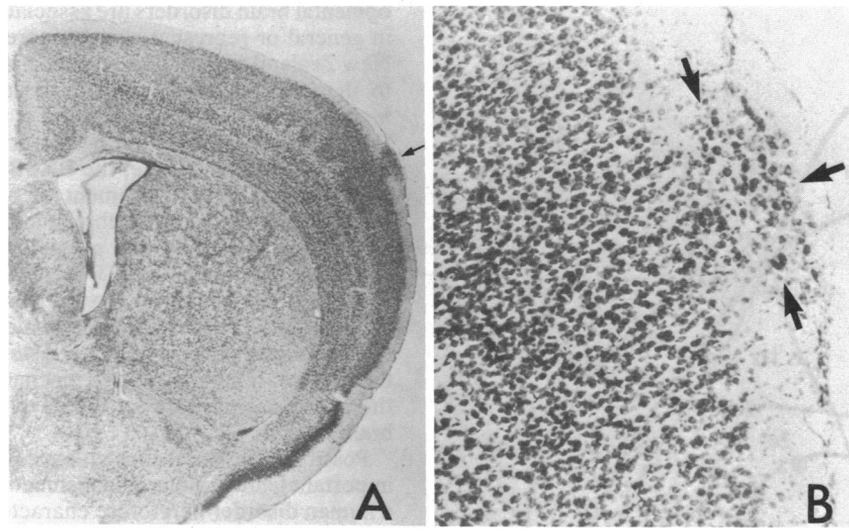

FIG. 1. Ectopic collection of neurons (arrows) in layer I of the cerebral cortex of the New Zealand mouse under low power (*A*) and higher (*B*) magnification. There is architectonic distortion in the subadjacent cortex.

found in close proximity to the ectopic nests of neurons, consisted of laminar distortion, cell-free areas, and disoriented neurons (Fig. 2). Occasionally, abnormal blood vessels were present within the dysplastic cortex. In general, the ectopias were small in width and were present only in somatosensory and motor cortices (Fig. 3).

DISCUSSION

This study revealed that the immune-defective New Zealand mouse can show disordered development of the cerebral cortex. The impairment consists of ectopic collections of cells and architectonic dysplasia. Thus, the NZB mouse can

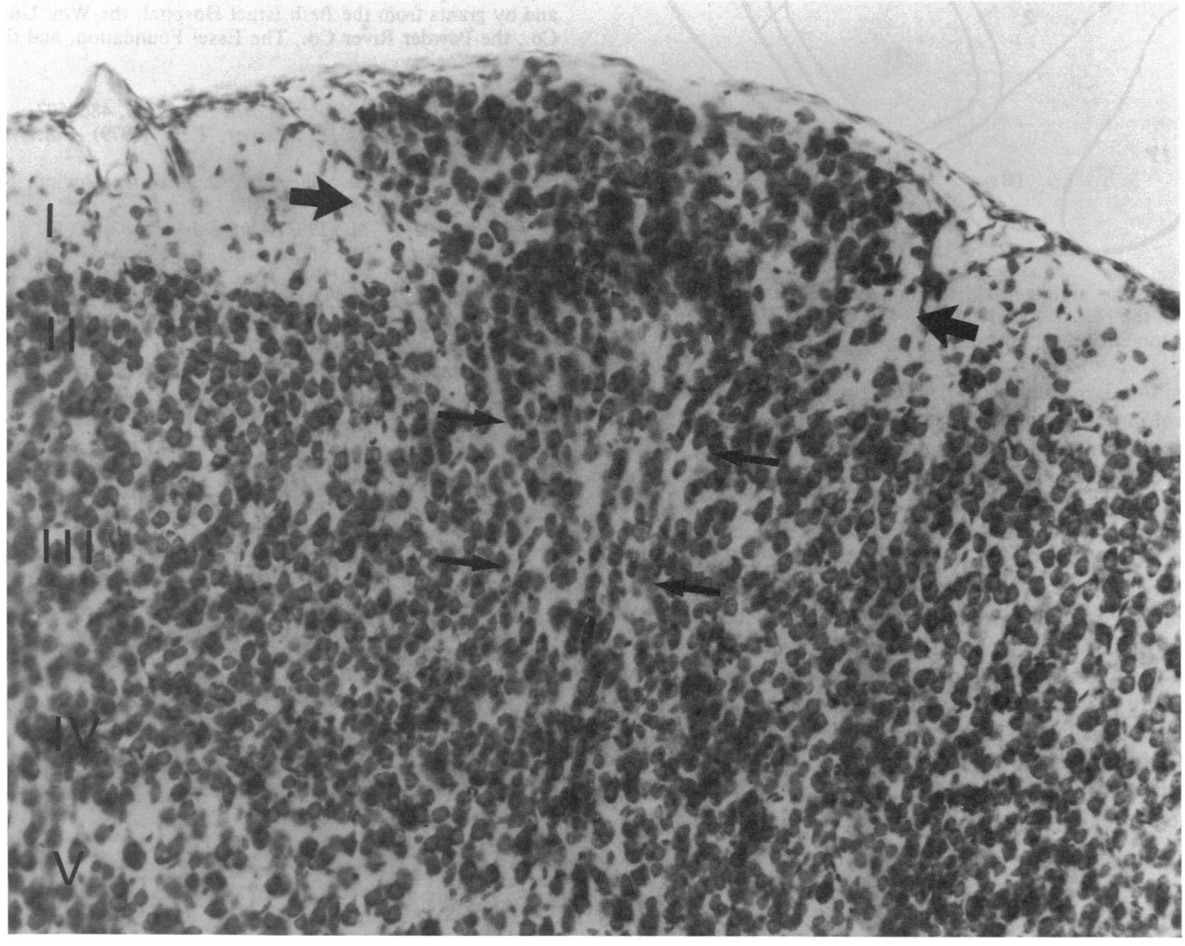

FIG. 2. High magnification photomicrograph of an ectopic collection of neurons (thick arrows) and underlying dysplastic cortex (thin arrows) extending from layer II through layer IV in the New Zealand mouse brain.

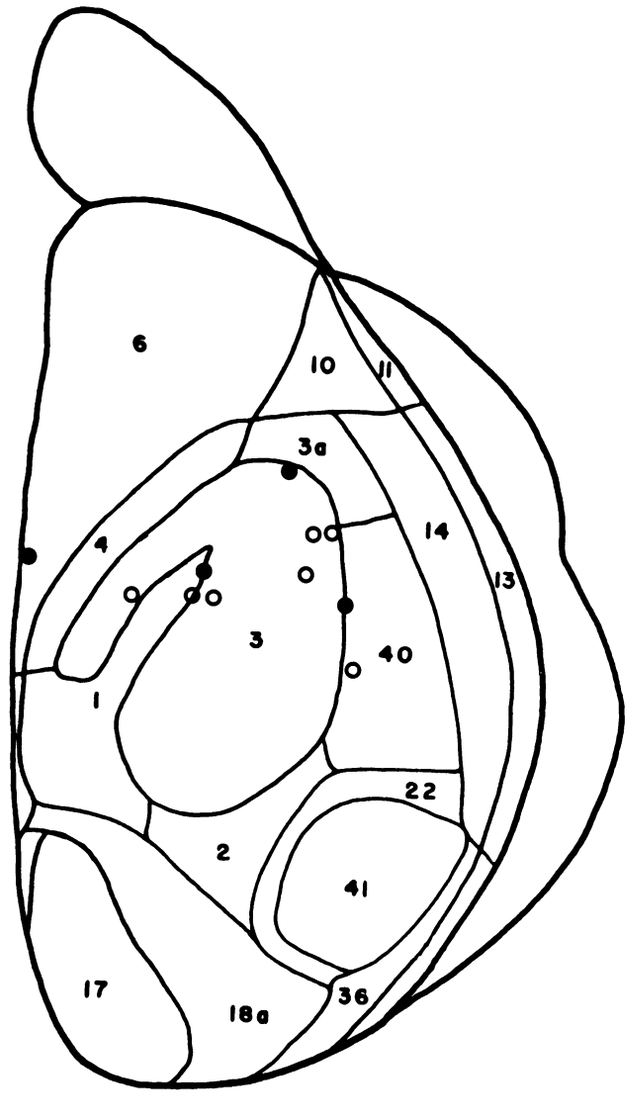

FIG. 3. The architectonic location of ectopias on the lateral surface of the New Zealand mouse brain. ○, Right side; ●, left side. Architectonic parcellation from Caviness (16).

be considered, in general, as a model for spontaneous cortical maldevelopment. Moreover, it may be useful as a model for the cortical abnormalities seen in the dyslexic brain, where similar anatomical changes and disease associations are seen. In both the dyslexic brains and affected mice, the lesions affect the upper cortical layers, thus supporting the notion of an event occurring late in corticogenesis. In both the dyslexic and New Zealand mouse brains, the lesions are predominantly unilateral and involve primary and association cortices. The ambilaterality of the mouse anomalies may reflect the fact that the animals were selected randomly and not for their failure in a specific behavior. In contrast, the dyslexic brains were selected based on their left hemisphere (linguistic) deficits.

The study of additional strains of mice that develop immune pathology is needed to ascertain whether the developmental brain disorders are associated with immune defects in general or represent only an unrelated peculiarity of the New Zealand mouse. This question is of particular relevance to the issue of developmental dyslexia, in which a single immune defect has not been and is not likely to be found. Preliminary work from our laboratory indicates that another immune-defective mouse, the BXSB, shows similar cortical alterations. The establishment of an association between immune pathology and cerebral malformation is important as a first step toward testing possible etiological factors. For instance, Geschwind and Behan (12) postulated that the abnormalities in the dyslexic brain may result from an abnormal effect of testosterone, which is also known to alter the development of the immune system through its actions on the thymus. Similarly, shared mechanisms may play a role in the New Zealand mice for the development of immune and brain defects.

Possible behavioral consequences of the brain changes, an important feature in the establishment of an animal model for a human disorder heretofore characterized mainly in behavioral terms, can be examined thoroughly in the New Zealand mice. Behavioral deficits have been reported in NZB mice. Nandy *et al.* (17) found that only 1 NZB mouse of 33 could learn a conditioned avoidance response after 70 trials, whereas 33 of 55 C57BL/6 control mice acquired the response in 30 trials or less. NZB mice also are initially less active in the open field (18). The exact relationship between the behavioral abnormalities and the brain anomalies awaits further study.

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1. Drake, W. E. (1968) *J. Learn. Disabil.* **1,** 486–502.
2. Galaburda, A. M. & Kemper, T. L. (1979) *Ann. Neurol.* **6,** 94–100.
3. Galaburda, A. M., Sherman, G. F. & Geschwind, N. (1983) *Soc. Neurosci. Abstr.* **9,** 940.
4. Galaburda, A. M. (1983) *Ann. Dyslexia* **33,** 41–53.
5. Galaburda, A. M., Sherman, G. F., Rosen, G. D., Aboitiz, F. & Geschwind, N. (1985) *Ann. Neurol.* **18,** 222–233.
6. Poliakov, G. I. (1937) *Early and Intermediate Ontogenesis of the Human Cerebral Cortex* (Brain Institute, Academy of Medical Sciences, Moscow).
7. Sidman, R. L. & Rakic, P. (1973) *Brain Res.* **62,** 1–35.
8. Chatel, M. (1976) *J. Hirnforsch.* **17,** 189–212.
9. Dvorak, K., Feit, J. & Jurankova, Z. (1978) *Acta Neuropathol.* **44,** 121–129.
10. Jacob, H. (1940) *Z. Gesamte Neurol. Psychiatr.* **170,** 68–84.
11. Morel, F. & Wildi, E. (1952) *Rev. Neurol.* **87,** 251–270.
12. Geschwind, N. & Behan, P. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 5097–5100.
13. Geschwind, N. & Behan, P. (1984) in *Biological Foundations of Cerebral Dominance*, eds. Geschwind, N. & Galaburda, A. M. (Harvard Univ. Press, Cambridge, MA).
14. Howie, J. B. & Helyer, B. J. (1968) *Adv. Immunol.* **9,** 215–266.
15. Talal, N. & Steinberg, A. D. (1974) *Curr. Top. Microbiol. Immunol.* **64,** 79–104.
16. Caviness, V. S. (1975) *J. Comp. Neurol.* **164,** 247–264.
17. Nandy, K., Lal, H., Bennett, M. & Bennett, D. (1983) *Life Sci.* **33,** 1499–1503.
18. Spencer, D. G. & Lal, H. (1983) *Soc. Neurosci. Abstr.* **9,** 96.
19. Behan, W. M. H., Behan, P. O. & Geschwind, N., *Dev. Med. Child Neurol.*, in press.