Age Differences in the Cellular Response to Cerebral Lesions in the Dog and Mouse

Introduction. Functional regeneration of the nervous system of young animals has not been a consistent finding (RAMON Y CAJAL[1], BARNARD and CARPENTER[2], and WINDLE et al.[3]). The cellular response following ablation of certain areas of the cerebrum of the young dog (ZOLENKOVA and MIRTOVA[4]) was characterized by macroscopic 'regeneration' of the ablated area. Description of the histology of these lesions was, however, inadequate and the question of neuronal regeneration was posed but not investigated further. KASTRIKIN[5] studied effects of mechanical injury to the cerebrum of adult rats; no total restoration of brain tissue occurred in these adults, in which a glio-fibrotic cicatrix formed.

Materials and methods. Thirty C57/Bl6 mice (5 days old) and 10 beagles (8 new-born and 2 adults) were operated on aseptically under general anesthesia. Following craniotomy a core of cerebrum was removed from the parieto-occipital region of each subject by trochar and cannula (16–18 mg tissue removed from mouse, 25–35 mg from 4 new-born and 45–55 mg from 1 adult dog). The other 5 dogs were given 'stirred' lesions (no tissue removed: tissue disrupted with silver probe, size of lesion being same diameter as extirpated lesions).

Two and four weeks postoperatively, three mice (total six) were anesthetized with ether and perfused intracardially with acrolein. The brains were then removed and, following fixation, were prepared for serial section and histologic staining with H. & E., Holmes' silver nitrate, cresol violet and Luxol fast blue. The remaining mice were euthanatized four weeks postoperatively and examined macroscopically.

All dogs were euthanatized four weeks postoperatively with intravenous pentobarbitone; the brain was removed following intracardiac perfusion with heparin saline and formalin and the lesioned area dissected for histologic staining with H. & E., Holmes' silver nitrate, Thionin and Ora's myelin stain.

The cellular reaction to mechanical injury in the neonate mouse was dependent upon the integrity of the original lesion. If collapse of the adjacent cortical edges of the lesion occurred, healing took place and macroscopically no scar was visible, although the cerebral hemisphere was smaller in size than the opposite unoperated hemisphere. In approximately 50% of the subjects, collapse did not occur and a large meningeal adhesion developed, preventing cortical repair (Figure 1).

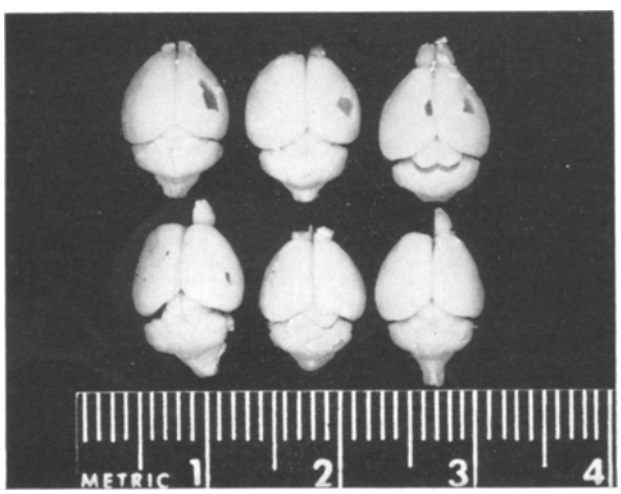
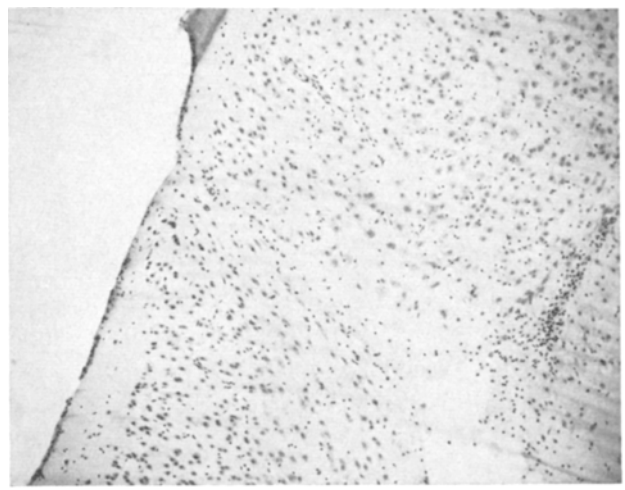


Fig. 1. Brains of 32-day-old mice showing variations in cortical reorganization 28 days post-operative. Note smaller cerebral lobe where healing has occurred.



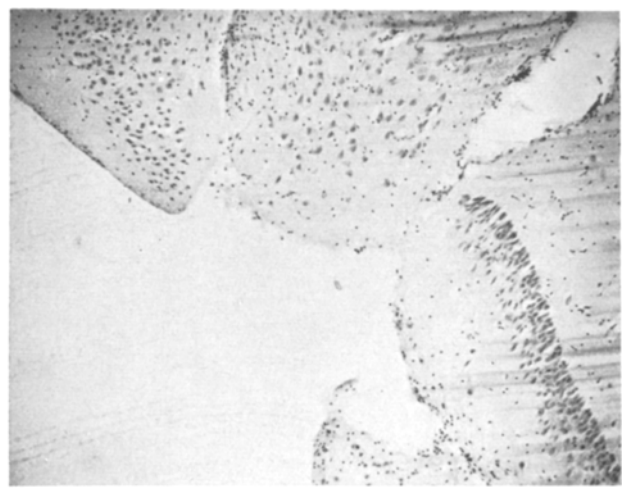


Fig. 2. Mouse cortex 4 weeks post-operative. Complete (a) and partial (b) apposition of lesion. Note paucity of glial reaction (H. & E. × 200).

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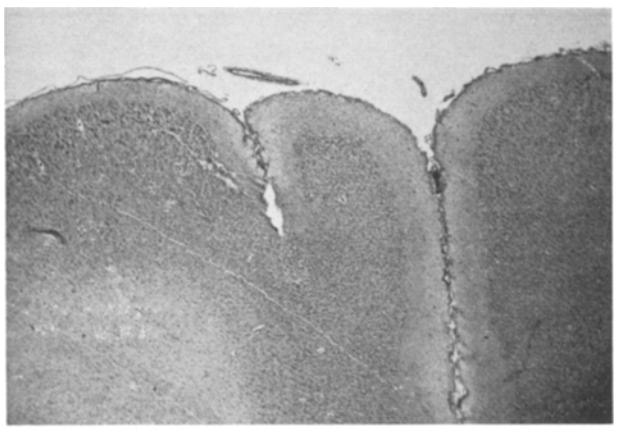
Histologic examination of neonate dog and mouse revealed a marked lack of cellular, vascular and meningeal reaction to the mechanical injury at the site of apposition of the edges of the lesion (Figure 2). In mice examined two weeks postoperatively, there were more microglia than in subjects examined four weeks postoperatively. Endothelial cells forming capillaries were present, but the lesion in all cases characteristically lacked macroglial proliferation; few dividing astrocytes were found. Compared with similar lesions in adult mice (stab wounds) (from the collection of Dr. R. L. SIDMAN[6]) astrocytosis was minimal. Normal neurons in reduced numbers were present at the site of the lesion but no mitotic figures were evident.

A meningeal plug formed in adult dogs and macroglial reaction was intense with capillary endothelial vacularization of the region, lymphocytic reaction from the meninges and microglia as engorged macrophages (gitter cells) were present (Figure 3). In the stirred adult lesion the meningeal and vascular reactions were less pronounced and the macroglial and macrophage proliferation around the isolated cortical fragment more intense with neuronal chromatolysis and degeneration in the center of the lesion. In the new-born these neurons, although reduced in size, stained normally, resembling CAJAL's[1] neuronal preservation phenomenon. Macrophage and macroglial proliferation was minimal, and re-orientation of the cellular elements occurred so that the normal appearance of corticocellular layering was seen. In one new-born, a focus of proliferating cells resembling an ependymoma was found; these were most probably translocated ependymal cells drawn outwards by the cannula during the operation.

The intense cellular proliferation following injury in the adult and the necessity of removing large quantities of lipids following myelin degeneration (SPATZ[7], PENFIELD[8]) is contrasted by the lack of myelinization of the cerebral cortex in the new-born dog (HARMAN[9]) and mouse (KOBAYASHI et al.[10]), and consequently fewer degenerative elements are present. Mitosis and migration of neurons occur postnatally (ANGEVINE and SIDMAN[11], ALLEN[12], and BUCHHOLTZ[13]), and some neuroblasts may effect a form of replacement of degenerating neurons. Cellular reorganization is facilitated by the normal growth and development of uninjured neurons through the wound area and paucity of glial and macrophage reaction (CHAMBERS[14], CLARK[15], and BRODAL[16]). We conclude that the neonatal cerebrum of non-precocial mammals has superior healing abilities, characterized by cellular reorganization with minimal gliosis[17].



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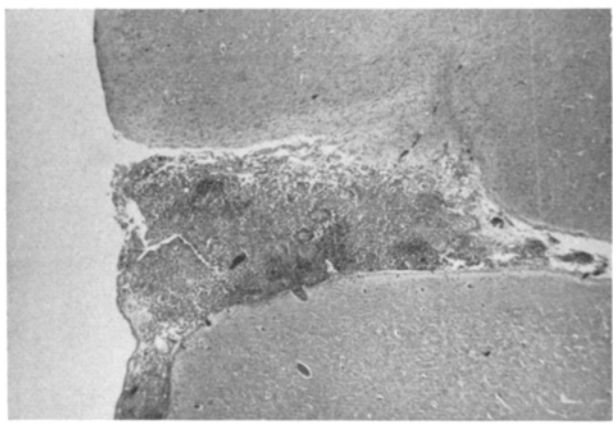

b

Fig. 3. Cortical lesions (extirpated) in neonate dog (a) and adult (b). Note lack of cellular reaction in (a) showing reorganization of cortical layers.

Zusammenfassung. Die zelluläre Reaktion an traumatischen, mechanisch gesetzten Läsionen in der Gehirnrinde wurde an neugeborenen und erwachsenen Hunden sowie an Mäusen untersucht. Die Heilung der Läsionen in Neugeborenen war so, dass das Gehirngewebe makroskopisch normal aussah; histologisch waren die durchtrennten Elemente durch die Heilungsprozesse unter minimaler glialer Reaktion wieder gut reorganisiert.

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