LOW-LEVEL X-IRRADIATION OF THE BRAIN
DURING DEVELOPMENT: MORPHOLOGICAL,
PHYSIOLOGICAL AND BEHAVIORAL CONSEQUENCES

Progress Report

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1. RESEARCH ACCOMPLISHMENTS

(a) Morphological Effects of Irradiation of the Cerebellum with Different X-ray Schedules

We have recently completed and sent for publication four papers dealing with the morphological development of the cerebellar cortex under normal conditions and following interference with its development with various X-irradiation schedules. In the first of these (entitled "Postnatal development of the cerebellar cortex in the rat: IV. Spatial organization of bipolar cells, parallel fibers and glial palisades) the ontogeny of the spatial organization of some components of the molecular layer was investigated in cerebella sectioned systematically in the sagittal, coronal and horizontal planes. The following observations were made. There is no discernible organization in the distribution of cells of the proliferative zone of the external germinal layer (EGL) but from birth the differentiating bipolar cells of the subproliferative zone are aligned parallel to the surface and to the long axis of the folium. While they are still in or at the base of the EGL, the bipolar cells emit long processes, the future parallel fibers. The next step is the outgrowth of a vertical process which may reach the base of the molecular layer before the granule cell nucleus becomes translocated. The idea that the cell body truly migrates through the molecular layer was not supported by the observations.

Bergmann glia cells are frequently seen in Golgi material in neonates but they are probably less numerous than in older infants and their processes are not as well aligned. It is only gradually that the EGL is perforated by glial endfeet which in older infants are occasionally organized into longitudinal rows. In mature cerebella the parallel fibers are separated by thin and relatively narrow, unstained spaces which are oriented in the longitudinal plane and can be traced from the pial surface to a zone just above the layer of Purkinje cells. It is postulated that these spaces are occupied by glial palisades formed by apposed thin vertical processes to which many Bergmann glia cells contribute. The alignment of these palisades is dependent on the orientation of parallel fibers. When the parallel fibers are reoriented by X-irradiation the glial palisades become correspondingly realigned. These observations indicated that the oriented growth of parallel fibers, which follows the polarization of bipolar cells, determines the spatial organization of the glial framework of the molecular layer. They also suggested, contrary to current views, that the glial palisades mediate functions that are not primarily developmental in nature.

In the three subsequent papers in the series "Experimental reorganization of the cerebellar cortex" the effects of different X-irradiation schedules were assessed. In the first of these (subtitled "V. Effects of early X-irradiation schedules that allow or prevent the acquisition of basket cells") two sets of X-irradiation schedules were used. One set of schedules

allowed the early recovery of the external germinal layer and the differentiation of all the postnatally-forming cell types while the other selectively prevented the acquisition of basket cells. The first schedule did not interfere with the development of normally oriented and arborizing Purkinje cells. The second schedule led to the growth of twisted and entwined stem dendrites even when, in association with the recovered granule cells, parallel fibers were present in the molecular layer together with Purkinje cell spiny branchlets. Evidence was presented that the alignment of Purkinje cell perikarya in a monolayer does not guarantee the normal growth of Purkinje cell stem dendrites which may be dependent on the presence of basket cells. The problem was discussed whether cell differentiation in the cerebellar cortex is governed by a chronological or sequential principle.

In the second paper of this series (subtitled, "VI: Effects of X-irradiation schedules that allow or prevent cell acquisition after basket cells are formed") the area of the cerebellum was X-irradiated with two schedules beginning on day 8 by which time the bulk of basket cells were formed. The shorter schedule of four successive daily doses of 200r between 8-11 days was designed to allow some cell recovery, the longer schedule between 8-15 days was expected to prevent it. Neither of the schedules interfered with the differentiation of basket cells. Purkinje cells remained aligned in a monocellular layer and formed singularly long, upright stem dendrites which were surrounded by the descending collaterals of basket cell axons. This supported the hypothesis that the directed growth of Purkinje cell stem dendrite is promoted by morphogenic interaction with basket cells. The upright stem dendrites had few or no smooth branches where cell recovery was prevented or had few such branches where recovery occurred. It was postulated that the outgrowth of smooth branches is dependent on interaction with stellate cells which form after the acquisition of basket cells. The absence or scarcity of smooth branches did not prevent the formation of spiny branchlets which grew downward to establish synaptic contacts with the spared parallel fibers of granule cells formed before the start of irradiation and, in the group with some granule cell recovery, to a limited extent upward.

In the final paper of this series (subtitled, "VII. Effects of late X-irradiation schedules that interfere with cell acquisition after stellate cells are formed") the area of the cerebellum was irradiated with multiple doses of low-level X-ray beginning on day 12 after the bulk of stellate cells were acquired. The treatment spared basket, stellate and early-forming granule cells but led to a substantial reduction in the total granule cell population and a correlated miniaturization of the cerebellar cortex. Nevertheless most Purkinje cells had normally shaped planar dendritic arbors, with an upward directed stem dendrite, several smooth branches and a multitude of spiny branchlets. The frequent piling up of spiny branchlets near the surface was attributed to the truncation of the bed of parallel fibers by this radiation schedule. In this paper the accumulated results were summarized and evaluated. The hypothesis was offered that while the growth of the Purkinje cell perikaryon is an autonomous process, the oriented perpendicular growth of a single stem dendrite depends

on the presence of basket cell axons, the outgrowth of smooth branches on the presence of stellate cell axons, and the proliferation of spiny branchlets on interaction with parallel fibers. The parallel fibers are responsible for the orthogonal, planar growth of the entire dendritic arbor and a hypothesis is offered about the mechanisms involved.

(b) Behavioral Effects of Irradiation of the Cerebellum
with Different X-ray Schedules

Our efforts in this area continued along two lines: (1) quantitative evaluation of the emergence of motor skills in infant rats and their assessment in normal adults, and (2) examination of the effects of cerebellar X-irradiation during infancy on the development of these skills and the extent of functional compensation produced in adults. A large scale quantitative study (entitled, "Postnatal development of locomotion in the laboratory rat") was recently accepted for publication by Animal Behaviour. In rats aged 1-21 days the emergence of postural and locomotor skills was observed in the open field or examined in experimental situations mostly with homing as a motivation.

When the newborn rat is turned on its back, righting attempts are initiated, but the performance is immature. At first righting is mediated by poorly coordinated rotation, curving and rocking of the trunk with the limbs merely providing passive leverage. Then the head and forelimbs move conjointly with the shoulder region. Not until days 11-12 do the hindlimbs provide coordinated support, and it is only at the beginning of the third week that the paws of the hindlimbs are dorsiflexed and provide immediate support when the animal has righted itself. Righting in midair, which requires a very swift maneuver during free fall, does not appear until days 15-17.

Before the infant rat acquires its quadruped ambulatory skills it displays attempts at locomotion, suggesting that the readiness to move antedates maturation of the ability. Because of the earlier functional maturation of the forelimbs, the ambulatory attempts during the first week lead to pivoting, first to punting then treading, with minimal forward progression. Possibly this type of locomotion is essential during this phase of development as it enables the infant to find the nipples and adjust its head and body during suckling. Observations and quantitative data indicate that pivoting is replaced by crawling during the second week and from days 13-14 walking and running predominate, with associated increase in level of exploratory activity.

Nonambulatory orientation (pivoting) toward the home cage is evident by the middle of the first week, and all animals home successfully by the end of the second week. However, the maturation of balancing skills over narrow bridges, and of balancing and compensating for lateral displacement

on stationary and rotating rods is more protracted. By day 16 all animals were successful in traversing a 3 cm wide bridge to join littermates but on narrower paths falls frequently occurred for several days thereafter. With narrow rods rotating at intermediate speed (48 and 60 RPM) most attempts led to falls up to 25 days of age. The ability to climb up on inclined surfaces with good foothold matured conjointly with walking, but descent on the same surface emerged later. On rods and ropes, ascending skills matured toward the end of the third week, and the ability to descend in the adult manner head downward, which requires support with the hindlimbs while the body is turned around, was only beginning to appear at 18-21 days of age. Maturation of hindlimb coordination was most protracted and with the incentives used in these studies rats 21 days of age or younger could not be induced to jump across gaps.

These studies provided us with normative data about the rather regular sequential appearance of motor skills during the first three weeks of postnatal life. The assessment of the development of motor skills in the irradiated animals is still in progress and is described in the Renewal Request. Results of some pilot studies were described in a chapter contributed to the book, "Plasticity and Recovery of Function in the Central Nervous System" (9).

(c) Morphological Effects of Irradiation of the Hippocampus with Different X-ray Schedules

The morphological consequences of irradiation of the hippocampal region with different schedules were summarized in three papers, the first of which has been published (2) and the second and third are in press (18, 19).

In the first paper the cytogenesis and morphogenesis of the rat hippocampus was examined with the techniques of ^3H -thymidine autoradiography, cell pyknosis produced by low-level X-irradiation, and quantitative histology. The procedure of progressively delayed cumulative labelling was used for autoradiography. Groups of rats were injected with four successive daily doses of ^3H -thymidine during non-overlapping periods ranging from birth to day 19. They were killed at 60 days of age, and the percentage of labelled cells was determined. The pyramidal cells of Ammon's horn and the polymorph cells of the dentate gyrus are not labelled postnatally, confirming earlier conclusions of their prenatal origin. In the dentate gyrus, 85% of the granule cells are formed postnatally, with 45% forming during the first week. The majority of the small cells of the dentate molecular layer and of the Ammonic strata oriens, radiatum, and lacunosum-moleculare are formed during the second week.

As an aid to locating the proliferative compartments of the hippocampus during development and to characterize the time course of both cell differentiation and morphological development, rats ranging in age from gestation

day 17 to postnatal day 103 were killed six hours after one exposure to 200r X-rays, and the pyknotic cells were counted. Cell pyknosis in Ammon's horn reaches a maximal level prenatally and declines rapidly during the early postnatal period. Cell pyknosis in the dentate gyrus reaches its highest level during the second postnatal week and declines gradually with some radio-sensitive cells still present in the adult. Immature granule cells are also at their highest level during the second postnatal week, while mature granule cells gradually accumulate to attain asymptotic levels at around two months of age. The alignment of the pyramidal cells to form the characteristic curvature of Ammon's horn occurs shortly after pyramidal cell cytogenesis is completed. Conversely, the sharp fold in the dentate gyrus is apparent from the day of birth onward, before the completion of granule cytogenesis. Possible mechanisms for the morphological development of the dentate gyrus along with a consideration of the possible migratory route of granule cell precursors was also discussed.

In the second paper (18) the long term consequences of graduated interference with the acquisition of hippocampal neurons and glia during early infancy were examined with quantitative histology and ^3H -thymidine autoradiography. The head region containing the hippocampus was irradiated from day two on with either two (2X), four (4X), six (6X) or eight (8X) doses of 150-200r X-rays. The animals were killed at 30, 60, 90 and 120 days of age. The morphology of the hippocampus was normal in all irradiated groups with the characteristic interlocking folds of the pyramidal and granular layers. While the number of pyramidal cells of Ammon's horn was unaffected, the number of granule cells of the dentate gyrus was progressively and permanently reduced from control levels by the different dosage schedules (2X, 59% reduction; 4X, 77%; 6X, 83%; 8X, 84%). Incidental observations in control animals indicated a 20% increase in granule cells between 30 and 120 days of age in agreement with earlier observations of granule cell labelling after ^3H -thymidine injections in adult rats.

The time of origin of the approximately 15-16% of the granule cells surviving irradiation in the 8X group was determined by injecting either pregnant females (gestation days 19-20) or pups (days 0 and 1) with two successive doses of ^3H -thymidine; the animals were irradiated from day 2 on with eight X-ray doses. The granule cells surviving in the postnatally injected group were all unlabelled and comparable in number to the unlabelled cells in control animals that were given five successive postnatal injections of ^3H -thymidine. This established that the radioresistant complement of granule cells is formed prenatally. In the prenatally injected group, over half the surviving cells were labelled; it was assumed that those not labelled were formed before gestation day 19.

In contrast to the permanent reduction in the number of granule cells, there was partial cellular recovery in the dentate molecular layer and the Ammonic stratum oriens; in the fimbria, recovery in cell number was complete by 60 days. In a supplementary autoradiographic experiment, cell proliferation in the granular layer and in the fimbria was determined at 60

days of age after a single postnatal injection of ^3H -thymidine on either day 15 or day 20 in the control, 2X, 4X and 6X groups. The number of labelled cells in the irradiated groups was always well below control levels in the granular layer, but it was either above or at the same level as controls in the fimbria. Tentative interpretations were offered for the differential long-term effects of variable X-ray schedules on the neuronal and glial populations of the hippocampus.

In the final paper on this topic (19) a comparison was made of the effects of the same irradiation schedules on the hippocampus, cerebellum and olfactory bulb. Beginning on postnatal day 2, either two (2X group), four (4X group) or six (6X group) daily or alternate daily exposures to low-level X-irradiation (150-200r) were used to interfere with the acquisition of granule cells in all these late-developing brain regions. At 60 days of age, the relationship between post-irradiation recovery and permanent granule cell loss was assessed with two quantitative techniques. First, the total number of granule cells was determined to estimate the magnitude of permanent loss. Secondly, the number of labelled granule cells were counted after ^3H -thymidine injection on either day 15 or on day 20 to estimate differential rates of cell proliferation during the recovery period.

Permanent granule cell loss was sustained in all regions by all schedules of irradiation. The time for the most effective exposures varied, being earlier in the hippocampus and olfactory bulb than in the cerebellum. In all regions, both the irradiated groups and the controls showed a decrease in the level of cell proliferation between 15 and 20 days. The number of cells that could be labelled after either the 15 or 20 day injection was below control levels for all groups in the hippocampus, at control levels for all groups in the cerebellum, and either at (2X and 4X) or below (6X) control levels in the olfactory bulb. These results were discussed in the light of the formation time of the granule cells in each region.

(d) Behavioral Effects of Irradiation of the Hippocampus with
Different X-ray Schedules

The assessment of the behavioral consequences of low-level X-irradiation-induced granule cell agenesis was continued and the results were described in two papers (4, 6). The first of these papers showed that the irradiated rats ran faster than controls during extinction of a runway response acquired under a consistent food reward schedule. A training schedule of randomly rewarded and nonrewarded trials increased running speeds to an equal extent in X-irradiated and control groups during extinction. The second and third experiments showed that unlike a reported total inability of hippocampal lesioned rats to pattern their running responses appropriate to a single alternation schedule of reward and nonreward, X-irradiated rats, while

impaired in acquiring response alternation, did pattern and had persistent deficits compared to controls only when the task was made very simple by reducing the number of daily trials to two. The results are discussed in terms of an hypothesized reduction in the aversiveness of nonreward and a consequent reduction in the growth of inhibition in X-irradiated rats. The second paper described results that extended the behavioral similarities previously noted between such hippocampal granule-cell agenesis and conventional hippocampal lesions. Irradiated and control rats were alike in the acquisition of a one-way avoidance response, although there was a trend of greater resistance to extinction in the irradiated group. The irradiated group displayed facilitated acquisition of an escape-from-fear response. When one-way avoidance was preceded by inescapable shock, the irradiated group was superior, suggesting that granule-cell loss, like hippocampal ablation, disrupts a tendency to remain immobile in the presence of stimuli related to inescapable punishment.

These results brought added evidence that granule cell loss produced by X-irradiation leads to behavioral effects that are similar to bilateral ablation of the hippocampus as a whole.

2. SIGNIFICANCE OF RESEARCH

Vulnerability of the Nervous System. It was believed for a long time that the nervous system is a relatively radioresistant part of the body. The demonstration by others and ourselves that cell proliferation remains brisk in many brain regions after birth, dispelled this belief and made it necessary that we re-examine the vulnerability of different brain regions at different periods of pre- and postnatal development. In this context it should be remembered that the proliferative external germinal layer of the cerebellar cortex is present in man up to 20 months of age and that the proliferative subependymal layer of the inferior horn of the lateral ventricle persists into adulthood. The demonstrations that these proliferative sites in animals give rise to nerve cells, and that they can be subtotally destroyed by exposure to a single dose of less than 200r, indicate that certain brain regions remain radiosensitive for some time after birth. Our behavioral tests have shown that postnatal X-irradiation of the cerebellum or hippocampus produces deficits that closely resemble the destruction of these brain structures (even though only the granule cells are directly affected).

Rehabilitation and Regeneration. It has been known for a long time that the deficits produced by trauma to the nervous system tend to subside and may altogether disappear with time. To what extent this is due to dissipation of the initial "shock", to "functional recovery", "neural reorganization" and possibly some degree of morphological "re-wiring" is a matter of speculation. In our studies, and those of others (Ebels, Phemister et. al., Langman) evidence was obtained that the external granular layer of the cerebellar cortex is reconstituted after subtotal destruction, and there is suggestive evidence that its rate of cell production may be actually accelerated. This indicates some degree of functional regulation of cell proliferation but the mechanisms of this regulation remain to be determined. Is the regeneration of the external granular layer facilitated by some form of "physical rehabilitation"? Can it be usefully enhanced by pharmacological or other agents?

Cellular Dissection of Different Brain Regions. In addition to the described practical considerations, our newly developed technique of timed irradiations will make it possible to selectively eliminate some of the neuronal components of selected brain regions. For instance, in the cerebellum, if irradiation is started at birth and continued to prevent regeneration, a cerebellar cortex is produced with all its Purkinje cells present (with input from and output to other brain structures maintained) but without a laminar organization and with all the microneurons absent. If the irradiation is started at 4-5 days, near-normal lamination is produced with subtotal elimination of all the microneurons. If the irradiation is started at 3-4 days and is continued to eliminate the cells that form the basket and early granule cells, but discontinued early to permit regeneration, it will acquire the late forming stellate cells and a large population of the late granule cells. Conversely,

if irradiation is not started until the basket and early granule cells were formed and then it is continued to prevent regeneration, a cortex is formed which has the early-forming microneurons without the late-forming ones. Such an experimental tool for the selective elimination of different cell types has not been hitherto available and it promises to become a powerful tool in neurobiological research.

The Cerebellum as a Model Brain Structure. There are few brain regions that are as well understood, and which are as extensively and intensively being investigated at present as the cerebellum. It is a complex neural structure but experimental work on it is fostered by the circumstance that the cerebellum has a limited number of cell types; a limited number of input lines and only a single output line; a relatively stereotyped, geometrically organized circuitry; and that it controls motor activities which are easier to assess than some other behavioral functions such as perception or learning. It is not unlikely that the cerebellum will be among the first brain structures that neuroscientists will begin to be able to understand in some depth -- an optimism which is supported by the great advances that are now being made in the unraveling of its circuitry with morphological and electrophysiological techniques and its chemistry by the application of microchemical, histochemical and pharmacological techniques. Our effort is directed at obtaining information of how the cerebellar cortex is being assembled during development and what happens if this is disturbed by such agents as X-irradiation. The cerebellum is particularly suited for this task due to the favorable circumstance that it develops mostly postnatally when it has become more accessible for experimental manipulation.

The Hippocampus as a Model Brain Structure. The hippocampus, like the cerebellum, is a laminated structure, components of which develop largely postnatally. There is considerable amount of information about its structural and physiological properties and a wealth of behavioral data. However, unlike the cerebellum, it is involved in an as yet unspeciable series of "mental" functions. It thus represents another model system that may allow the examination of the developmental vulnerability of a brain structure implicated in "higher" brain functions.

3. STUDENTS TRAINED, POSTDOCTORAL AND FACULTY AFFILIATES

(a) Doctorate Granted:

Bayer, S. A. 1974

(b) Masters Degree Granted:

Moore, J. 1974

(c) Graduate Students in Training:

Barnes, D.	Ph.D. Candidate
Bulut, F. G.	Ph.D. Candidate
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Jensen, K.	M.Sc. Candidate
Michaud, N.	M.Sc. Candidate
Moffett, C.	Ph.D. Candidate
Spivack, N.A.	Ph.D. Candidate

(d) Postdoctoral Affiliates:

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(e) Faculty Affiliates:

Bayer, S. A.	Assistant Research Scientist
Pellegrino, L.	Assistant Research Scientist

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5. OTHER FEDERAL SUPPORT

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