

**EFFECTS OF LATE PRENATAL IRRADIATION
ON THE DEVELOPMENT OF THE CEREBELLAR CORTEX
IN THE RAT**

by

TERESA ANNA MARIA RALCEWICZ

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DOCTOR OF PHILOSOPHY

**UNIVERSITY OF MANITOBA
FACULTY OF MEDICINE
DEPARTMENT OF ANATOMY**

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DEDICATION

I thank God for two important people in my life to whom I dedicate this thesis. Throughout the duration of my doctoral thesis they have believed in me, provided support and encouragement, and have always been there for me.

To my mother Antonina,

for "All I am, or hope to be, I owe to my angel Mother"

A. Lincoln.

and

To my brother Henryk,

who has reaffirmed in me that
"Dreams are the touchstones of our character"

H.D. Thoreau

and

"A journey of a thousand miles
must begin with a single step"

Lao-Tzu

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ABSTRACT

The effects of maternal exposure to a single dose of whole body irradiation (0.5 Gy) on gestational days (GD) 17, 18, 19, or 20 on the development of the cerebellum was examined in the offspring of Sprague Dawley rats at 21 and 28 days postnatally. No gross cerebellar anomalies were observed in the irradiated animals. However, rats irradiated on each of GD-17, 18, 19 and 20 showed a significant incidence ($p < 0.05$) of circumscribed cerebellar lesions (CL) distributed in the inner granular layer of the anterior and posterior lobes. These lesions were characterized by a loss of granule cells and atrophied and/or reduced number of Purkinje cells. In 21 day old rats, irradiation on GD-17 resulted in more CL anteriorly (75%) and in the vermis whereas on GD-20, the CL predominated posteriorly (100%) and in the lateral hemispheres. In 28 day old rats, following irradiation on each of GD-17 and GD-20, there was an equal distribution of CL in both the anterior and posterior lobes. However, with irradiation on both GD-17 and GD-20, CL occurred more frequently in the anterior lobe of the lateral hemispheres, whereas in the posterior lobe they predominated in the vermis.

The laterolateral numbers of both granule and Purkinje cells in the pyramis were significantly reduced ($p < 0.001$) from controls in rats irradiated on each of GD- 17, 18, 19 and 20. There was a greater deficit in granule cell

number with irradiation on GD-20 than on GD-17 ($p < 0.05$). Purkinje cells were reduced in number with irradiation on GD-17 and GD-20; however, the decrease did not correspond to the degree of reduction in the number of granule cells. There was a greater reduction of both granule and Purkinje cells in the vermis with irradiation on GD-17, whereas on GD-20, both granule ($p < 0.05$) and Purkinje cells ($p < 0.001$) were more reduced in the lateral hemispheres. The GC/PC ratio was smaller in rats irradiated on GD-20 than on GD-17. The GC/PC ratio between the irradiated animals and the controls were relatively similar.

The results from this study suggest that a direct relationship exists between the proliferation, migration, development, and maturation of granule cells and their induction by Purkinje cells. The findings also support the view that both cell death and the regulation of granule cells by Purkinje cells maximize the effective development and organization of the cerebellum.

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ABBREVIATIONS

GD	Gestational Day
CL	Cerebellar Lesion
PC	Purkinje Cells
GC	Granule Cells
PN	Postnatal
ED	Embryonic Day
PCL	Purkinje Cell Layer
IGL	Inner Granular Layer
ML	Molecular Layer
MC	Medullary Center

1.0 HISTORICAL PERSPECTIVE AND CURRENT INVESTIGATION

The reporting by Roentgen in 1895 to the Wurzburg Physico-Medical Society on a new form of radiation and the discovery of radioactivity by Becquerel in 1896 resulted in the birth of radiobiology. Radiobiology is a branch of science concerned with the action of light, ultraviolet and ionizing radiation on living organisms (Dorlands 1982). It is also characterized by the 4 R's: 1) repair of sublethal damage, 2) repopulation and regrowth of cells, 3) redistribution of cells within the cell cycle, and 4) reoxygenation (Hall 1978m).

After the discovery of X-rays, many of the investigators in radiotherapy who exposed their hands to irradiation for several hours developed radiation induced cancers and died. The one survivor, Hall-Edwards, was the first to record carcinomas as a direct result from exposure to X-rays (Furth & Lorenz 1954). In earlier years, radiation was used to perform therapeutic abortion. The center of the uterus was irradiated with 360 rad no later than the fourteenth week of gestation (Yamazaki 1966, Mayer et. al. 1936). In 90% of the cases, the conceptus aborted spontaneously.

During the late 1910's and throughout the 1920's and 1930's, several investigators reported a variety of fetal abnormalities in rats and rabbits with exposure to prenatal irradiation (Bagg 1922, Murphy & de Renyi 1930, Hanson 1923). The earliest animal work lacked the precise timing of the

stage of development when irradiation was done. In 1935, Job, Leibold, and Fitzmaurice were the first to determine critical periods in development and were able to correlate the defects with the time of irradiation. The discovery of critical periods, prompted other investigators including Kosaka (1927), Warkany and Schraffenberger (1947), Wilson and his co-workers (1951, 1953, 1954) to study the relation between the timing of irradiation and the resultant abnormalities.

In an extensive series of experiments, Russell (1950) defined the critical periods for the induction of malformations by radiation in mice. She correlated the induction of external and gross visceral changes with the precise timing of irradiation during a particular stage of development. Through an extensive series of experiments, Altman, Hicks and each of their co-workers, have used radiation to study the progressive stages of cerebellar neurogenesis in rats from birth to adolescence. They have used radiation as an experimental tool to study radiation induced morphogenetic changes and re-organization of cerebellar constituents following irradiation during specific stages in development (Altman, Altman et. al. 1965-69, 1971-73, 1976-78; Hicks, Hicks et. al. 1950, 1952-58, 1980). Using radiation as an experimental tool, has allowed them to draw inferences about normal patterns of neurological development of the nervous system in mammals based on their studies of the malformation processes.