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DISCLAIMER

ADAPTATION OF CELL RENEWAL SYSTEMS UNDER CONTINUOUS IRRADIATION[1]

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ABSTRACT

There are adaptive changes in the proliferative characteristics of renewal tissues under the stress of continuous low-dose-rate irradiation which indicate that cell and tissue kinetics will have a considerable effect on the radiation response. Factors that determine the adaptation response involve cellular radiosensitivity, i.e., cell cycle effects, which determine the rate of cell sterilization and death, and compensatory cell proliferation and the capacity for regeneration, i.e., changes in the patterns of cell population kinetics, which determine the rate of cell birth. In rapidly dividing cell renewal systems, there is an effective elimination of damaged cells with almost complete repair of cellular nonlethal damage. In slowly dividing renewal tissues, there is some repair or elimination of cellular radiation damage, and the pattern of cell proliferation during regeneration is relatively little disturbed by prior continuous irradiation. Experimental data on intestinal epithelium, hematopoietic tissues, seminiferous epithelium and regenerating liver are presented. Discussion includes differences in adaptation to continuous low-dose-rate irradiation involving intracellular and extracellular control mechanisms which regulate cellular proliferation and differentiation and, thereby, control cell population levels and physiological function.

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INTRODUCTION

If a dose of radiation is divided into fractions separated by a long enough interval, or intervals, its biological effectiveness may be reduced through the replacement of lethally injured cells. This may occur through regenerative proliferation of irradiated cells that survive or, in the case of partially irradiated tissues, through migration of cells from unirradiated portions of tissue. If the dose is protracted over a long period of time, its lethal effectiveness is decreased even further by cell replacement. The dose rate at which cell replacement can fully counterbalance cell loss varies markedly from one tissue to another depending on the proliferative capacities of cells in the different tissues. Adaptation to protracted low-dose-rate irradiation depends, in large measure, on the proliferative kinetics and capacity of intracellular repair of the cell population. The small intestine of the rat, in which stem cells have a very high capacity of proliferation, is able to tolerate a dose rate of 4 Gy d^{-1} for a limited period of time, owing to its high rate of cell renewal (Qu59b). The testis of the dog can tolerate only one-thousandth as much, a dose rate of about 2-5 mGy d^{-1}, for an indefinite period (Ca68). For most tissues with low rates of cell proliferation, the critical dose rates are not well known (La68; Fa71b).

THE STRUCTURE OF CELL RENEWAL SYSTEMS

Cell renewal systems, e.g., blood-forming tissues, can be structured into classes of cells with specific attributes of form, function and location (Pa63). Normally, a multicomponent compartment of stem cells is self-maintaining while committed to provide differentiated progeny for the proliferating cell population. The proliferative compartment, while undergoing active renewal, is not self-maintaining. It expands and cells leaving the compartment give rise to differentiated forms. These undergo sequential maturation, enter a functional end-cell compartment and eventually

die. Cell population compartment size is maintained and regulated by feedback control mechanisms (Fa71a; Fa71b)(Fig. 1).

All stem cells turn over at some rate because of loss of cells from the renewal tissue. Cell loss may occur at a fast rate, as in the case of extrusion of the intestinal epithelial cells; or by wastage, such as ineffective erythropoiesis; or it may be the result of a relatively slow rate of physiological attrition, as in the liver; or at a varying rate regulated by humoral factors that induce differentiation, such as erythropoietin in erythropoiesis, or estrogens in the uterine endometrium (Pa63; Fa71a; Fa71b).

Cell division occurs in the proliferative compartment; for maintenance, this compartment depends on influx of cells from a stem-cell compartment. Cell proliferation serves primarily to amplify the cell number during transit through the compartment, with eventual cell efflux to a maturation compartment. Cell transit is invariably associated with differentiation and progressive maturation, e.g., in erythropoiesis, from proerythroblast to orthochromatic erythroblast, or in spermatogenesis, the sequentially proliferating series of spermatogonia and the production of primary spermatocytes. It is unidirectional, since there appears to be no evidence of return to less differentiated forms under normal conditions.

Differentiation involves biochemical maturation giving rise to fully-differentiated functional end cells, e.g., erythrocytes or spermatogonia. Functional cell forms have varying life-span durations. It may be a mean value or a statistical average, as in the case of random cell destruction, e.g., in the mouse, erythrocytes live for about 120 d, and granulocytes about 5 d. This is quite different from the life-span of fixed duration of a cell within the proliferative compartment; e.g., the life-span of the dividing duodenal crypt cell in the mouse is about 10 h (Qu59a).

Homeostasis and Adaptation under Continuous Irradiation

In cell renewal systems, homeostatic mechanisms regulating cell prolifera-

tion and differentiation achieve a dynamic balance between cell population size, the rate of cell birth, the rate of cell transfer from proliferating to nonproliferating compartments, and the rate of cell loss, e.g., by differentiation or death. The maintenance of renewal tissues is dependent on the balance between the cell birth rate or immigration of cells into the system, and the cell loss rate by death or emigration out of the system. It is this balance that may be profoundly disturbed by stress and perturbation of various kinds and, particularly, by ionizing radiation. Different renewal tissues display some capacity for adaptation under the stress of continuous irradiation to maintain tissue homeostasis with near-normal levels of cell population and function apparently by recruitment of cells with reserve proliferative potentials (La66; Fa71a; Fa71b). In this regard, the intestinal epithelium, the immunohematopoietic tissues, the seminiferous epithelium and the liver are extremely interesting classes of tissues.

INTESTINAL EPITHELIUM

The epithelium of small intestine is a rapidly proliferating cell renewal system consisting of cells in the crypt of Lieberkuhn and on the villus (Pa63; Qu59a)(Fig. 2). Committed progenitor cells within a stem-cell compartment occur in the base of the crypt (Le76). A proliferative zone occupies the lower two-thirds of the crypt; it is here that cell proliferation occurs in the columnar epithelium. Dividing cells migrate up the crypt, leave the proliferative zone, and undergo biochemical transitions and maturation processes in the upper third. Differentiated functional end cells emerge from the mouth of the crypt onto the villus, lining the intestinal mucosa, and migrate to the tip of the villus, and are lost by physiological attrition. The system is in a steady state of cell renewal; the cell birth rate equals the cell loss rate. The crypt cell cycle times and cell transition times are rapid and narrowly controlled, so that the time required for cell replacement is quite short and of fixed duration -- in the mouse, about 24 h (Qu59a).

Under continuous irradiation, the duodenum of the small intestine appears to be among the less radiosensitive of the rapidly proliferating cell renewal systems. Quastler and his colleagues (Qu59b) demonstrated that at a dose rate of about 4 Gy d^{-1}, the rat small intestine could achieve a steady state of cell population and function in approximately 2 d (Fig 3). The cell cycle parameters and those of cell production were relatively normal when the new steady state was achieved. Recovery was rapid and occurred promptly when the animals were placed in a radiation-free environment after 5 days of exposure, in spite of a total dose of more than 20 Gy.

Cairnie and his colleagues (Ca65; Ca67; Ca69; La66) demonstrated in rats that after exposure to continuous irradiation at about 3.5 Gy d^{-1}, homeostatic mechanisms during regeneration include regulation of cell output from the crypt by shortening the cell cycle time, due primarily to a decrease in the duration of the G_1 phase (Fig. 4), and by cell migration by extension of the proliferative zone above the normal cutoff region in the upper third of the crypt (Ca67; Ca69; La66). The changes were dependent on the dose rate affecting the rate of cell death. Provided the dose rate was not too high, there was return to normal cell cycle time under continuous exposure, but at a lower population level. A speeding-up of the cell cycle is an effective compensatory mechanism for adaptation to increase the birth rate of cells to replace those damaged by irradiation. Increasing the size of the proliferative zone, or maintaining a maximum cell production rate at all times within the proliferative zone, would serve to re-establish or maintain the integrity of the villus by very rapid and efficient repair mechanisms which would be relatively independent of inefficient feedback control from the mature population (Fa71a; Fa71b).

IMMUNOHEMATOPOIETIC TISSUES

In the blood-forming tissues, stem cells give rise to recognizable

populations of proliferating and differentiating cell lines -- the proerythroblast to the polychromatic erythroblast, the myeloblast to the metamyelocyte, the large to the medium lymphocyte, and the megakaryocyte. The maturing elements become nonproliferating functional end forms of the peripheral blood and tissues -- erythrocytes, granulocytes, small lymphocytes, and platelets, respectively (Fa71a; Fa71b)(Fig. 5). Cell proliferation and differentiation are regulated by internal and external control mechanisms which maintain tissue homeostasis. Biochemical events characterize these regulatory mechanisms, e.g., in erythropoiesis, accumulation of hemoglobin, loss of RNA, and mediation through erythropoietin.

Lamerton and his colleagues (La66) demonstrated in rats that the capacity for maintenance of cell population under the stress of continuous irradiation can vary greatly among the hematopoietic tissues in the time taken for establishing of steady states, for regeneration during recovery, and in the dose rates that can be tolerated over extended periods of time. In general, erythropoiesis and myelopoiesis can adapt promptly and can be maintained at reduced levels for prolonged periods of continuous exposure; lymphopoiesis can also adapt, but the system deteriorates under stress. Blackett and his colleagues (Bl68) used transplantation techniques and radioiron to examine erythropoiesis and the response of red cell production and stem-cell proliferation in rats at a dose rate of 0.5 Gy d^{-1} for up to 20 w. Once the steady state of red cell output was reached, normal red cell production could be maintained with a stem cell content of about 10% of normal (Fig. 6). There was a concomitant reduced cell flow rate, by a factor of four, from the stem cell to the proliferative compartments. This was balanced by an increase in cell birth rate in the proliferative compartment, due to an increased proliferative rate and decreased cell cycle time in the erythroblast series, so that extra cell divisions occurred in the proliferative sequence (Ta69) and an increased transit time through the proliferative compartment, which allowed

extra divisions to occur in the long precursor sequence. In spite of the radiosensitivity of the erythroblast series, adaptation was relatively rapid, and compensated for the decreased flow rate from the stem-cell compartment, and for radiation death and damage in the proliferative compartment. There was relatively little effect on the differentiated or mature forms. The thymus could achieve a near-steady state of lymphoid cell population at a dose rate of 0.5 Gy d^{-1} or less by similar mechanisms of compensatory cell proliferation (Fa68c). There was a considerable reserve of proliferative capacity, due, in part, to decreasing the cell generation times in each proliferative compartment, and to bringing-in of a reserve proliferating population. There was a reduction in mean generation time by narrowing of the spread of cell cycle times, thereby effectively increasing the proliferation rates in the recognizable precuror compartment (Fig. 7). There was an increase in size of the proliferative population, in part by an extension of the zone of proliferation, i.e., by recirculation of all lymphoid cells and lymphocyte migration to the thymus from extrathymic pools. Further extension of the proliferative zone occurred by an increased output from the stem-cell compartment (Fa68c; Fa69).

SEMINIFEROUS EPITHELIUM

In the mouse, the seminiferous epithelium consists of self-maintaining progenitor, type A_s spermatogonia, which gives rise to a rapidly proliferating and differentiating sequential series of type A, intermediate, and type B spermatogonia, which, in turn, divide and mature into primary spermatocytes (Oa71a; Oa76)(Fig. 8). Through meiotic division, spermatocytes furnish the spermatids that differentiate into functional spermatozoa. The seminiferous epithelium is a relatively slowly proliferating renewal tissue; the duration of spermatogenesis, or one cycle of the seminiferous epithelium, is about 12 d

in the rat, about 8.5 d in the mouse, and about 1 m in man. The cell cycle times in mouse spermatogonia range about 30 h, and the duration of DNA synthesis, about 10-20 h (Fa72b; Fa72c).

Oakberg (Oa68) found that a dose rate of about 100 mGy d^{-1} or less was near the threshold for recovery processes which permitted maintenance of the mouse spermatogonial population. At about 15 mGy d^{-1} to accumulated doses greater than 3 Gy, spermatogonial cell population reached equilibrium at reduced levels. With dogs, Casarett (Ca68), using brief daily exposures, found no evidence of decrease in sperm production or fertility at about 1 mGy d^{-1}, but progressive decrease at 6 mGy d^{-1}.

Under continuous irradiation at 18 mGy d^{-1} or less, spermatogenesis in the mouse can achieved a near-steady state of cell population consistent with function at 80% of control levels and for at least 15 w by limited mechanisms of compensatory cell proliferation and active recruitment of resting progenitors from within the stem-cell compartment (Fa72a; Hs76). There was some reserve of proliferative capacity maintaining tissue homeostastis due, in part, to a decrease in the cell cycle time of precursor subpopulations in the early type A compartment, to bringing-in of a potentially proliferative dormant stem-cell population and increasing the number of divisions, and to decreasing ineffective spermatogenesis to compensate for cell loss due to radiation damage confined almost entirely to the type A compartment (Fig. 9). Under the stress of continuous exposure there was a delay in the flow of spermatogonia in each proliferative compartment from G_2 into cell division, associated with a decrease in the duration of the S period, and with a shortening of the cell cycle times in the early type A subcompartments. The type A subcompartment was expanded, by extension of the proliferative zone, with a greater number of cycling cells recruited from the stem cell population, and with increased transit time through the compartment (Fig. 8). However, mechanisms of adaptation may be fragile and this tissue

retains only limited capacity to change cell proliferation patterns while still remaining under homeostatic control. Even at dose rates less than 20 mGy d^{-1}, spermatogonia may be very sensitive to radiation death, and the main reason for this low tolerance and failure to adapt to the stress of continuous exposure may very well be the lack of compensatory mechanisms regulating spermatogonial cell reproduction (Fa71c; Fa72b; Hs76; La66).

REGENERATING LIVER

The liver is a conditional cell renewal system that divides very slowly, but has enormous regenerative capacity in response to cell loss due to a demand situation, such as partial hepatectomy. In the rat, following removal of two-thirds of the liver, there is prompt and effective recruitment of hepatocytes from a resting stem-cell population and, following intense proliferative activity, the liver can regenerate to 90% of its normal cell population level within only three to four cell divisions (Fa67; Fa68a).

Following exposure to about 0.5 Gy d^{-1} for long periods, the accumulation of cellular radiation damage was not very significant due to selective removal of damaged cells at division (Fa68b). There was little accumulation of sublethal damage affecting cell proliferation and, thus, the regenerative capacity of the tissue, and the pattern of cell proliferation during regeneration after partial hepatectomy did not appear to be seriously affected. Prior continuous irradiation delayed the appearance of proliferative activity in the parenchymal cell population during regeneration. There was a decrease in the rate of entry of cells into proliferation, a decrease in tne number of cells taking part in the proliferative process, and an increase in the overall duration of proliferation during regeneration. In spite of extensive radiation-induced chromosomal damage, cell proliferation could be initiated and maintained at a reduced rate to restore a considerable proportion of the hepatic deficit within a relatively short time. This occurred primarily through compensatory mechanisms which improve the

regenerative capacity, e.g., by alteration of cell cycle kinetics and decreasing the duration of the parenchymal cell cycle time (Fa68b)(Fig. 10).

A speeding-up of cells through the proliferative compartment compensates for the radiation inhibition of onset of cell proliferation after partial hepatectomy, and for decrease in size of the cell population participating in the regeneration. The prolonged regenerative process after continuous irradiation, by analogy with the increase in transit time through the bone marrow, permits more divisions in the smaller proliferating cell population, indicating that feedback regulatory mechanisms necessary for rapid cell proliferation after partial hepatectomy remain effective for a longer period in the irradiated animal. In spite of accumulation of very large radiation doses under continuous irradiation, there is considerable capacity for adaptation under stress. Homeostatic mechanisms which influence the speed and efficiency of regeneration apparently can operate to reduce deleterious effects and to repair radiation damage, either by intracellular mechanisms or by selective removal of damaged cells at division, while simultaneously effecting compensatory cell proliferation and the recruitemnt of cells from a nonproliferating population into an actively proliferating compartment (Fa68b).

MECHANISMS OF ADAPTATION UNDER CONTINUOUS IRRADIATION

There are changes in the proliferative characteristics of renewal tissues under the stress of continuous irradiation that indicate that mechanisms of adaptation modulate the cell population kinetics and considerably affecting the radiation response (Fa71a; Fa71b; Fa72a). There are two factors that determine response: cellular radiosensitivity, i.e., cell cycle effects, which determines the rate of cell sterilization and death, and compensatory cell proliferation and the capacity for regeneration, i.e., changes in the patterns of cell population kinetics, which determine the rate of cell birth (La66).

In rapidly dividing renewal tissues, e.g., the intestinal epithelium and bone marrow, there appear to be mechanisms for effective elimination of damaged cells with almost complete repair of cellular nonlethal damage. The changes in cell population kinetics during and after irradiation frequently include a shortening of the cell cycle, combined with a lengthening of the transit time of precursors in the proliferative compartment, resulting in increased rate of cell birth. In slowly dividing conditional renewal tissues, such as the liver, there is some repair or elimination of cellular radiation damage during interphase, and the pattern of cell proliferation during regeneration is relatively little disturbed by prior continuous irradiation. Furthermore, the cell cycle time could be important in the radiosensitivity of the precursor cells under continuous irradiation. With a shorter cell cycle, less radiation dose would be accumulated between divisions resulting in a decrease in radiosensitivity if there were an effective selective removal of mutants at division. The cell cycle duration in the stem cell and proliferative compartments would also influence the speed and efficiency of regeneration following radiation injury. It is not known why there are very great differences in cellular response during and after irradiation between the different renewal tissues. However, these differences involve intracellular and extracellular control mechanisms that regulate cellular proliferation and differentiation and thereby control cell population levels and physiological function (Fa71a; Fa71b; La66).

CONCLUSION

The capacity for adaptation of a renewing cell population under the stress of continuous irradiation and the extent to which it can maintain cell population consistent with function are influenced by complex and interrelated factors (Fig. 1). External feedback control mechanisms regulating compartment size are important in the mobilization of cells in the proliferative compartment to increase the cell birth rate in order to compensate for the

increased rate of removal of damaged cells. A precursor population, possibly in the stem-cell compartment, or early precursor cells in the dividing sequence of the proliferative compartment with a continuous removal mechanism for differentiation, may proliferate more effectively to compensate for cell sterilization by increasing the population turnover rate. This can be done by shortening the cell cycle time, increasing the number of divisions in the proliferative sequence, and increasing the transit time within the compartment (La66; Fa71a; Fa71b). This was effective adaptive change in the recognizable precursor cells of the red cell system and was carried out mainly by a speeding-up of the cell-cycle time in the erythroblast compartment, associated with more cell divisions occurring in the precursor sequence. Maintenance of red cell production occurred by increasing the rate of cell proliferation in the stem cell compartment as well, presumably as a result of the action of erythropoietin on the progenitor cells of the recognizable precursor, thereby improving the repopulating ability of the system. The thymus also increased the proliferative rate of the more primitive lymphoid cell to compensate for lymphocyte death under continuous irradiation.

The crypt cells of the small intestine, even though dividing at a very high rate, could adapt to the continuous stress of low-dose-rate radiation as could the seminiferous epithelium, in comparison, a more slowly proliferating cell renewal system. This was done by increasing the rate of cell proliferation in the already dividing population -- by a shortening of the cell cycle time and a lengthening of the transit time of the precursors in the proliferative zone.

These adaptive changes may not be characteristic only of the rapidly proliferating issues, however. Reserve capacity for proliferation and repopulating ability appears characteristic of the very slowly proliferating conditional renewal tissues. The liver can rapidly shorten its cell population turnover time; the removal mechanism is partial

hepatectomy. A speeding-up of the cell cycle with an increased duration of the overall period of cell proliferation during regeneration were the characteristic adaptation responses in this renewing cell population under continuous irradiation (Fa71a; Fa71b).

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FIGURE LEGENDS

Figure 1. Schematic representation of a cell renewal system under continuous irradiation. Upper: unirradiated; Lower: continuous irradiation. S, stem cell compartment; P, proliferative compartment; D, differentiation compartment; F, functional end-cell compartment. (Fa71b)

Figure 2. Intestinal epithelium. Crypt of Lieberkuhn and villus represented as a cell renewal system. (Fa71b)

Figure 3. Intestinal epithelium. Response of crypt of Lieberkuhn in rats under continuous irradiation, 4 Gy d^{-1} for 5 d. Upper: cell number/crypt. Lower: mitotic count/crypt. (Qu59a)

Figure 4. Intestinal epithelium. Percentage labeled mitoses for cells of crypt of Lieberkuhn in mice; the crypt cell populations are segmented according to position from the base. Left: unirradiated. Right: continuous irradiation, 3.5 Gy d^{-1} for 5 days. (Ca65, Ca67)

Figure 5. Schematic representation of erythropoietic tissue as a cell renewal system. S, unrecognized precursor stem cells; U, immediate precursor stem cells; P, proliferation compartment; D, differentiation compartment; Tr, transitional forms in bone marrow; F, functional end cell compartment. The cell population sequence includes proerythroblasts (P) → basophilic erythroblasts (B) → polychromatic erythroblasts (P) → orthochromatic erythroblasts (O) → reticulocytes (R) → erythrocytes (E). (Fa71b)

Figure 6. Erythropoieses. Red cell production in rats under continuous irradiation, 0.5 Gy d^{-1} for 20 wk. RBC $^{(Fe59)}$ activity in blood 5 d after injection; Stem Cells, repopulating ability of bone marrow and spleen cells (Bl67, Bl68).

Figure 7. Lymphopoiesis. Production of TdR-^{3}H-labeled lymphocytes in mouse thymus under continuous irradiation, 0.75 Gy d^{-1} for 14 d. (Fa68)

Figure 8. Schematic representation of mouse seminiferous epithelium as a cell renewal system. Upper: unirradiated control. Lower: continuous irradiation. A_s = type A stem cell; A_1, A_2, A_3, A_4, In, B = type A, intermediate, and B spermatogonia, respectively; RPS = resting primary spermatocytes. (Fa71b)

Figure 9. Seminiferous epithelium. Percentage labeled mitoses for type A, intermediate and type B, spermatogonia in mice. Left: unirradiated Right: continuous irradiation, 0.02 Gy d^{-1} for 15 wk. (Fa71b, Fa72b)

Figure 10. Regnerating liver. Percentage labeled mitoses for parenchymal cells in rats. Upper: unirradiated 20 h after partial hepatectomy. Lower: continuous irradiation for 15 d, 30 h after partial hepatectomy. (Fa68a, Fa68b)

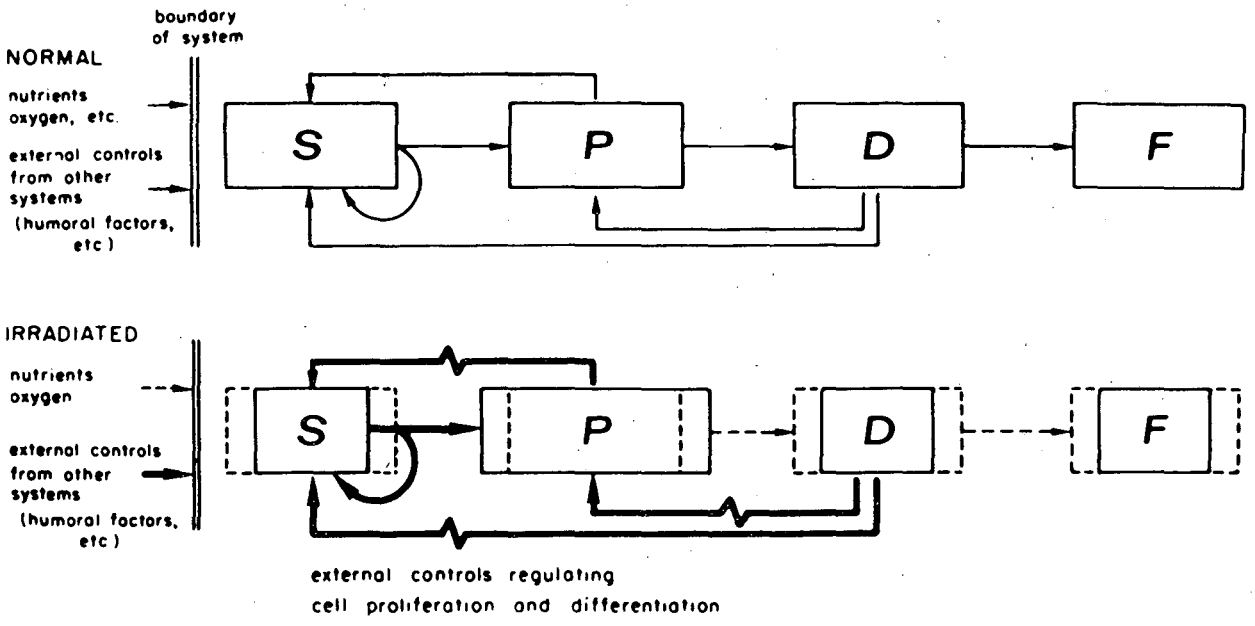

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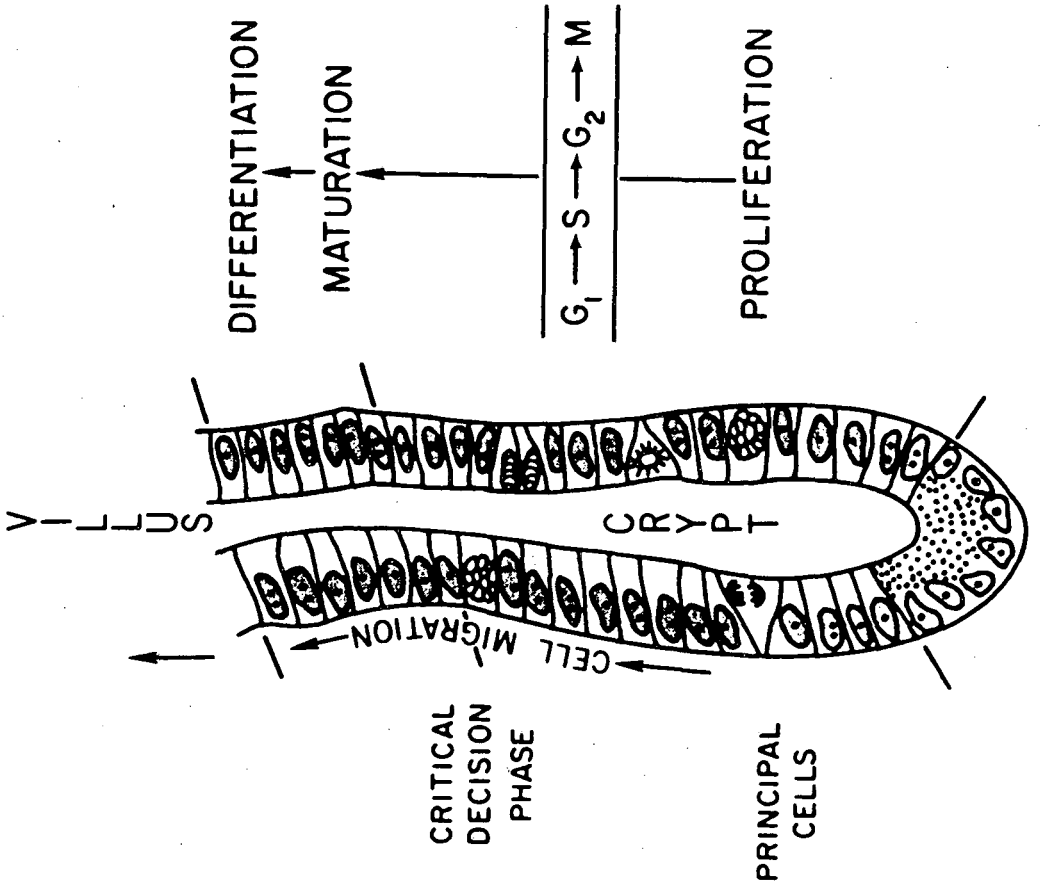
Figure 1



CRYPT OF LIEBERKÜHN

Figure 2

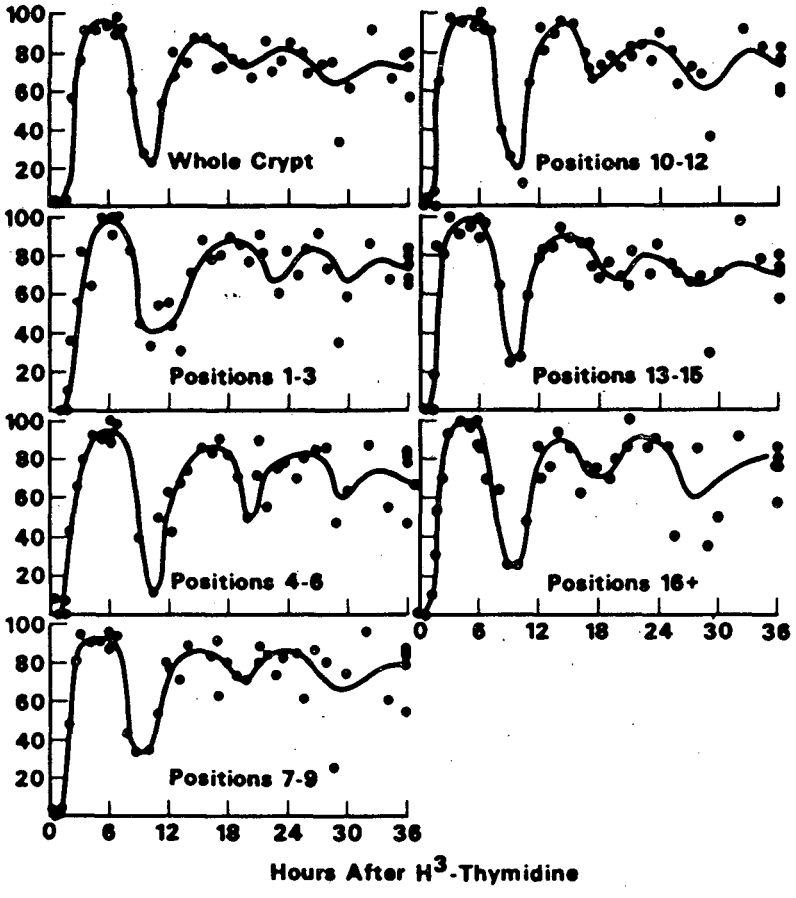


Figure 4a

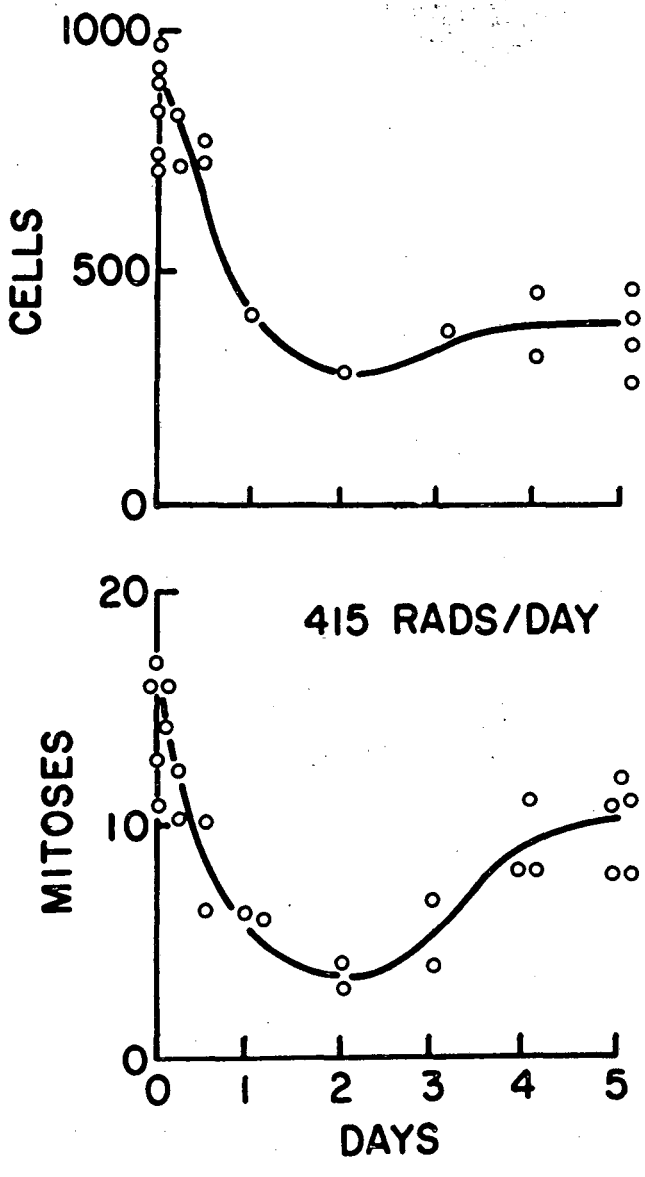


Figure 3

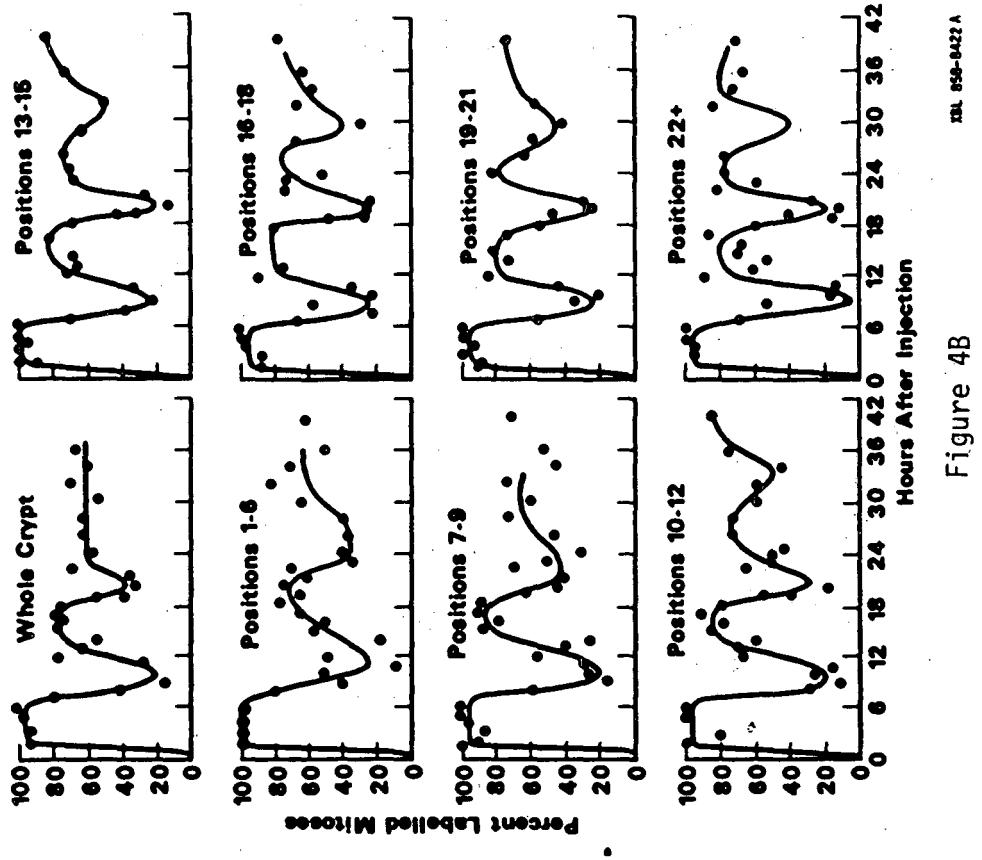


Figure 4B

ERYTHROPOIESIS

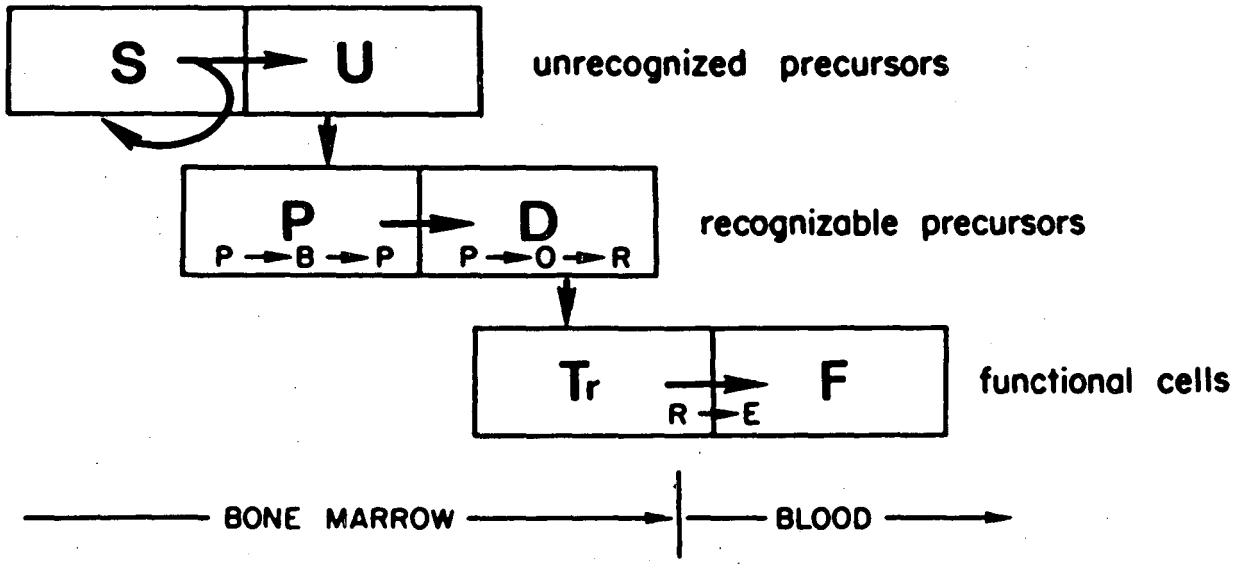


Figure 5

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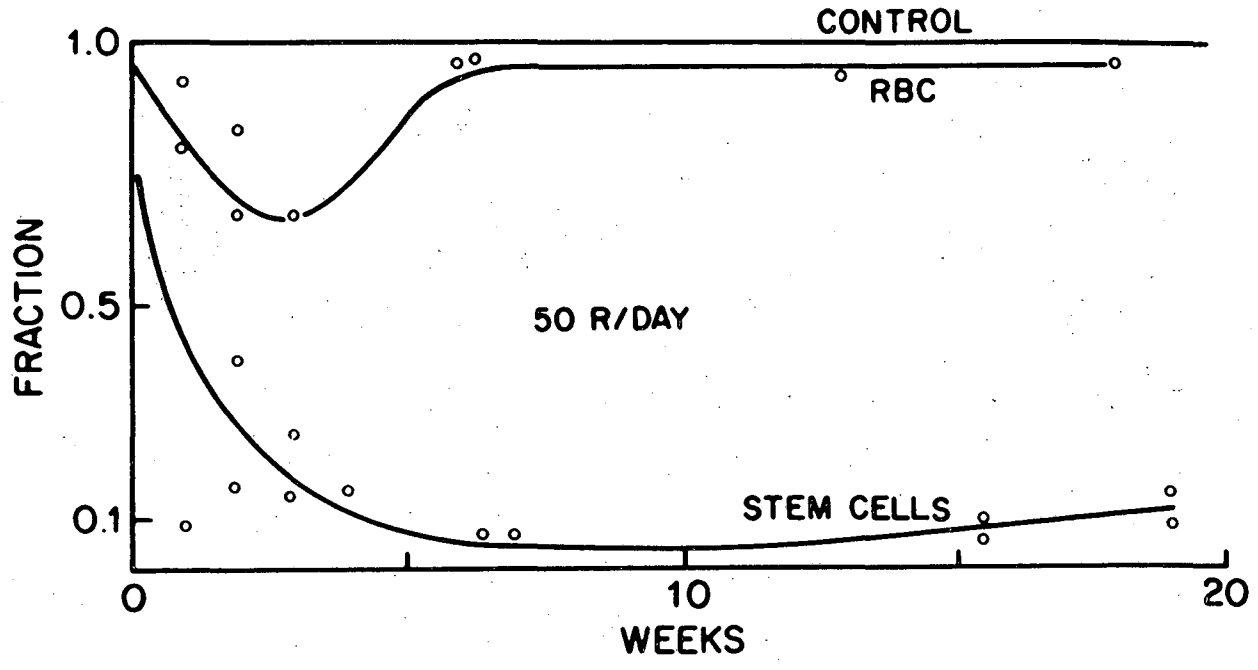

Figure 6

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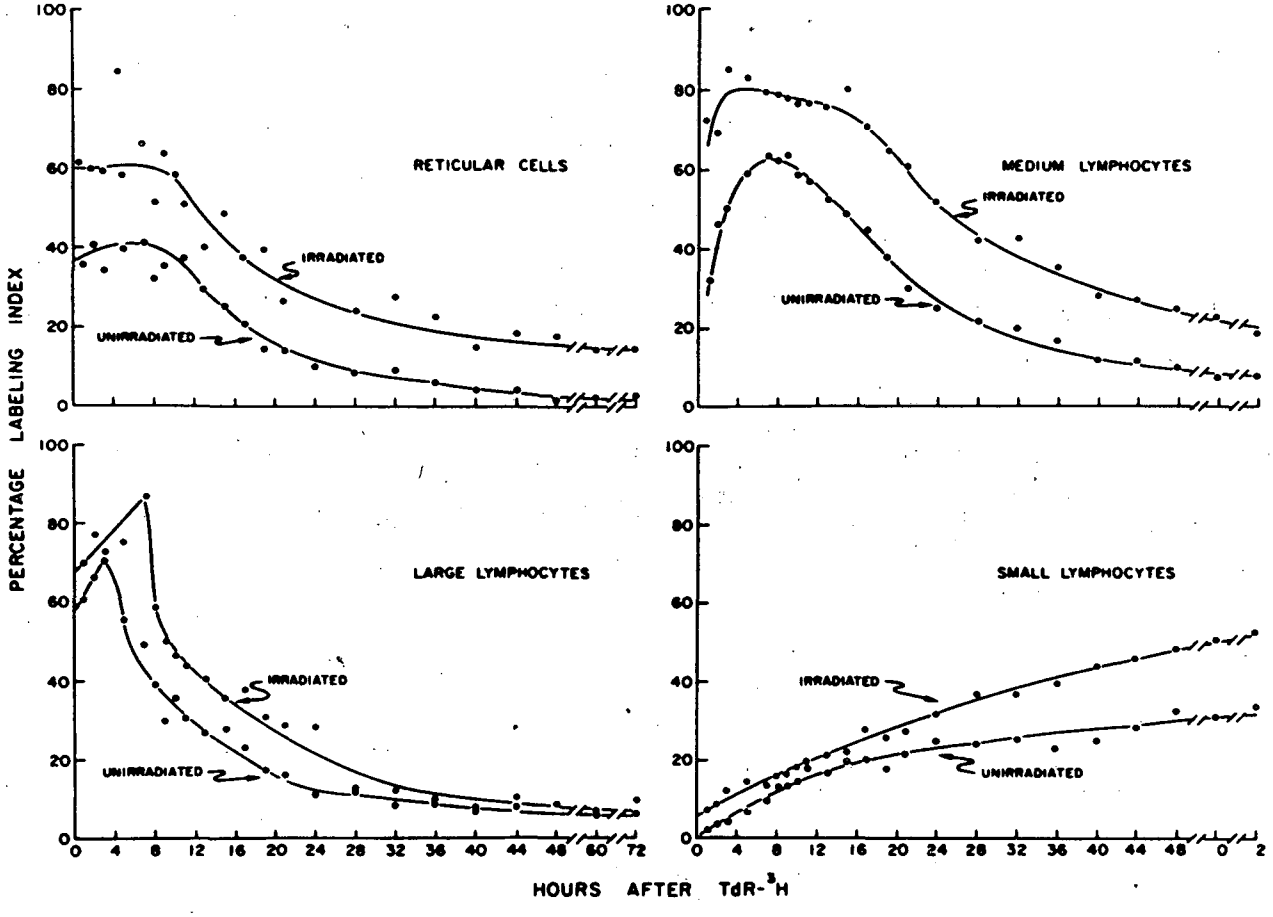


Figure 7

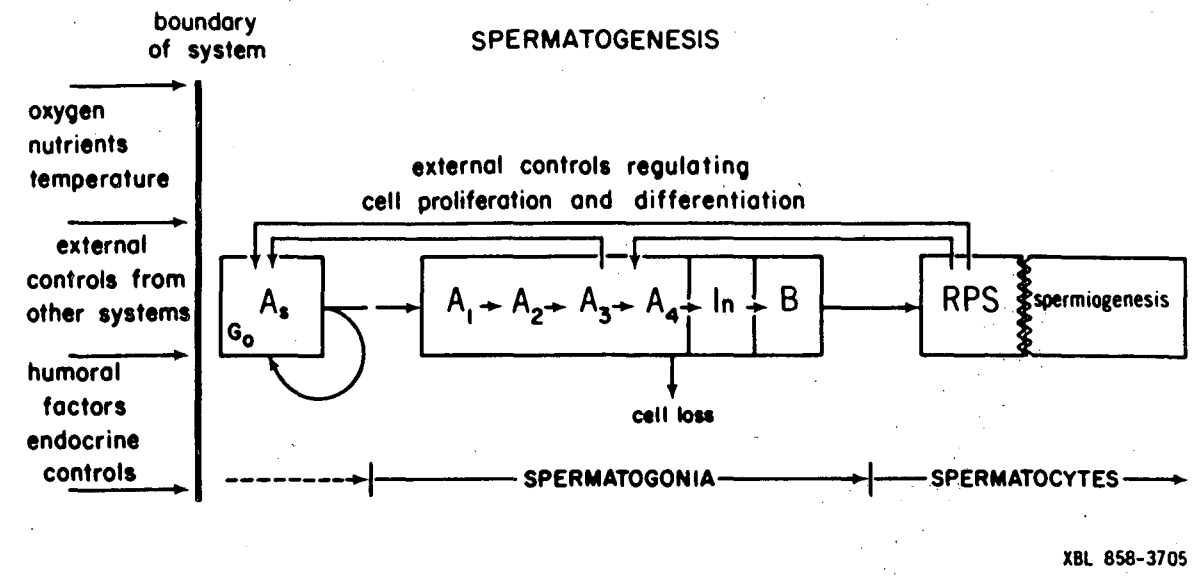


Figure 8a

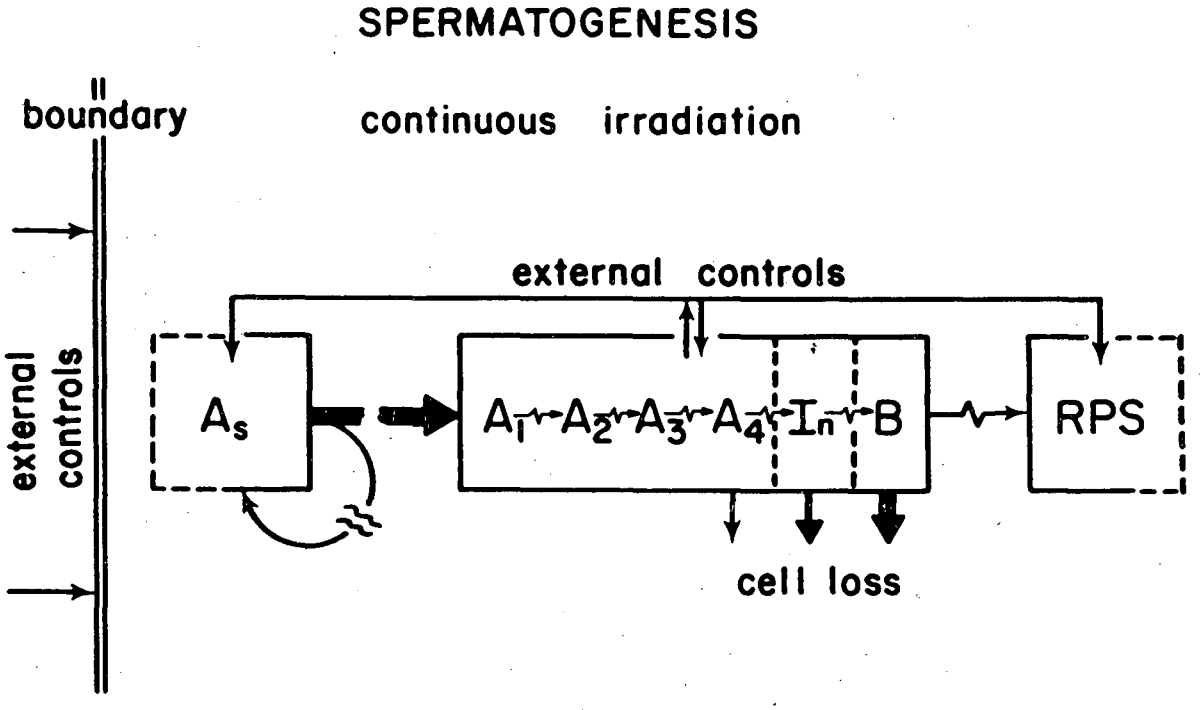
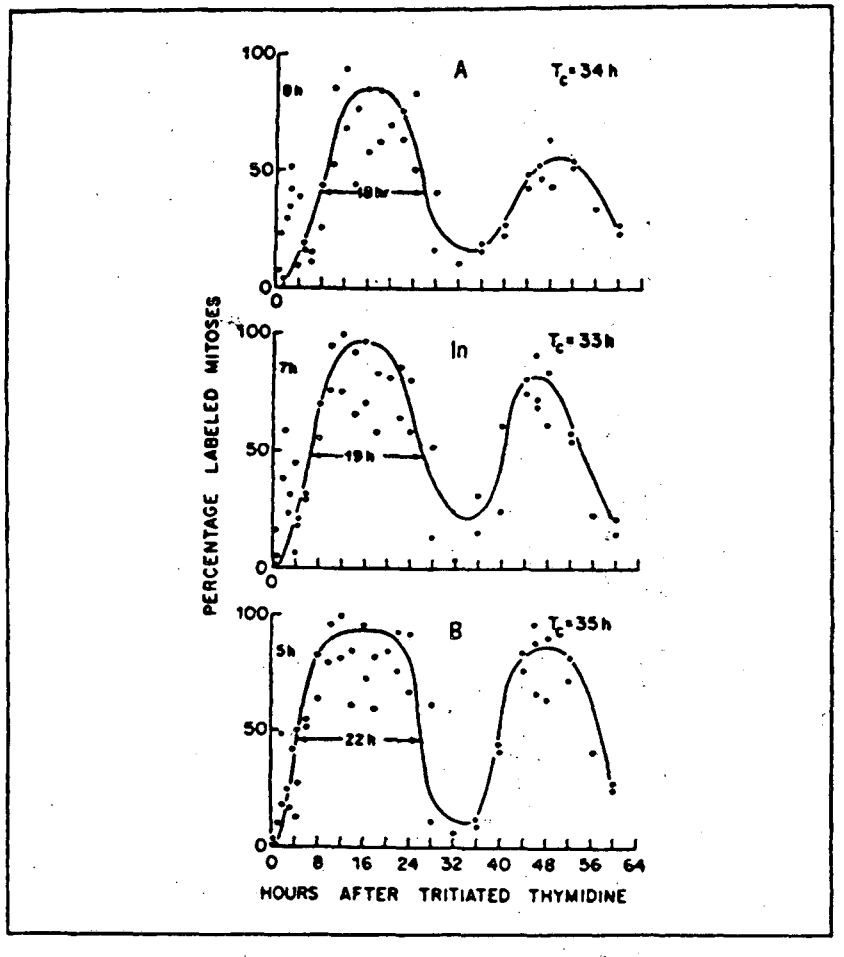


Figure 8b



XBL 858-3352

Figure 9b

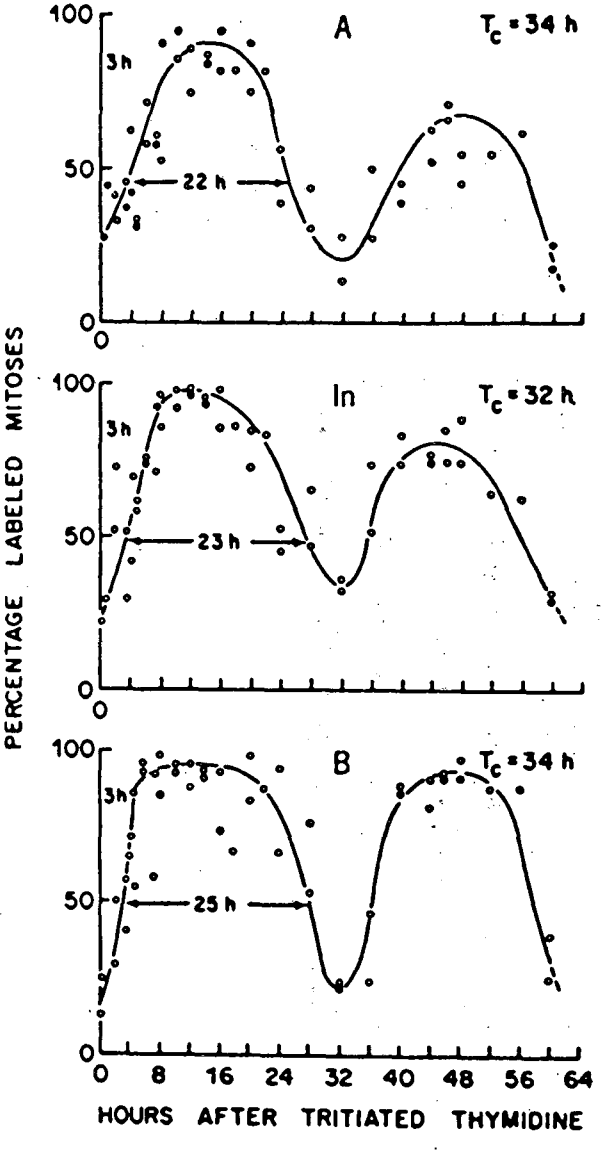


Figure 9a

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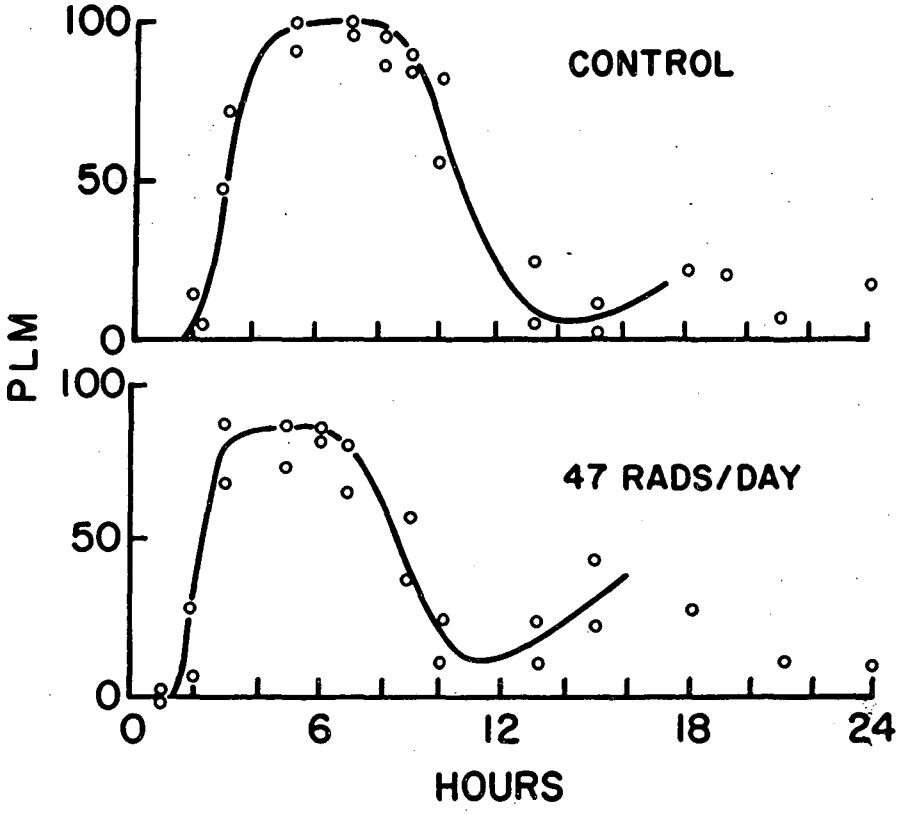

Figure 10

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