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CORRELATION OF RADIATION-INDUCED ULTRASTRUCTURAL CHANGES IN MOUSE HEPATOCYTES WITH ALTERATIONS IN PLASMA CONCENTRATION OF PROTEIN-BOUND NEUTRAL HEXOSES

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ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Atomic Support Agency
Bethesda, Maryland

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CORRELATION OF RADIATION-INDUCED ULTRASTRUCTURAL CHANGES IN MOUSE HEPATOCYTES WITH ALTERATIONS IN PLASMA CONCENTRATION OF PROTEIN-BOUND NEUTRAL HEXOSES

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FOREWORD
(Nontechnical summary)

One of the most important of the many functions of the liver is that of combining amino acids, carbohydrates (sugars), and lipids (fats) into complex proteins (biosynthesis). Each stage of these biosynthetic processes is carried out by specific structures within the cell (intracellular organelles). Other structures transfer (secrete) the completed proteins from the intracellular spaces to the blood plasma in which they are transported throughout the body.

In a previous study (AFRRI SR68-4) it was reported that marked differences occurred in the plasma concentrations of protein-bound carbohydrates (PBC) in mice which died after irradiation as compared with animals which survived identical doses.

The present report is a first approach to the explanation of the mechanism of this radiation injury. Thus, the changes demonstrated in the plasma PBC concentration by chemical methods should be referable to abnormalities in the organelles concerned with the biosynthesis and secretion of these complex proteins. Of primary interest, therefore, were the tubules in which the protein portion of the molecules is known to be formed (the rough endoplasmic reticulum), structures which mediate some of the body's utilization of sugars (mitochondria), and the Golgi apparatus, a complex arrangement of tubules which are known to be instrumental in secretory processes.

Mice were subjected to a whole-body dose of 530 rads of mixed gamma-neutron radiation. Irradiated animals, at the point of death, were killed and their livers

rapidly removed and prepared for viewing by the electron microscope. Sections of livers from irradiated survivors and unirradiated mice were similarly prepared and the architecture of the intracellular structures of the groups was compared.

The most dramatic differences in the liver-cell organelles of the irradiated mice as compared with that of unirradiated animals were in the rough endoplasmic reticulum and the Golgi apparatus. In the former, the tubules were greatly distended, suggesting that excessive amounts of material were collected in them. In the same cells, the Golgi apparatus were more numerous and their passages also expanded indicating that the cell was attempting to rid itself of the abnormal volume of accumulated fluid.

The mitochondria, which are normally elongated, were, in the irradiated animals, uniformly spherical. This condition suggested that injury to their limiting membrane had caused them to assume the shape of greatest stability. That they had lost many of their granules indicated that enzyme packets instrumental in the conversion of sugars to energy had been damaged or lost.

These morphological data from electron microscopical observations are in good agreement with the biochemical studies. A cause and effect relationship remains to be established, but it would appear that ionizing radiation may produce damage to intracellular sites of synthesis of complex proteins resulting in abnormal function of the organelles and, in turn, abnormal appearance.

Further, more definitive studies are being designed to resolve the order of occurrence.

ABSTRACT

C3H mice were subjected to a whole-body dose of 530 rads of mixed gamma-neutron radiation delivered at a rate of approximately 20 rads/min. The blood plasma concentration of protein-bound carbohydrates, as neutral hexoses, was estimated daily after irradiation. Ultrastructural architecture of liver tissue taken from irradiated animals in extremis was compared with that of survivors and fed and starved unirradiated controls. Among the radiation-induced differences observed in the hepatocytes were moderate to marked dilatation of the rough endoplasmic reticulum, increased Golgi activity, and rounding of the mitochondria with a decrease in numbers of mitochondrial granules. These alterations, together with other differences noted, were correlated with the increased plasma concentration of protein-bound neutral hexoses uniformly found in animals which succumb to radiation injury.

I. INTRODUCTION

Radiation-induced alterations in the blood plasma concentration of protein-bound carbohydrates (PBC) as neutral hexoses have been studied in C3H mice.[2] In mice which died, the PBC concentration showed a marked increase, while that of the survivors of identical doses changed only slightly or not at all.

Although the detailed mechanism of biosynthesis of the carbohydrate containing plasma proteins has not been defined, it is well established that the liver is the principal site of their formation. The objective of this study was to observe radiation-induced abnormalities in cytoplasmic organelles hypothesized to be instrumental in biosynthesis of complex proteins and to correlate those abnormalities with changes in plasma concentration of glycoproteins.

II. MATERIALS AND METHODS

Young adult male C3H mice,* 6 to 8 weeks of age and weighing between 20 and 24 g were used as experimental animals. They were subjected to a whole-body dose of 530 rads of mixed gamma-neutron radiation from the AFRRI-TRIGA reactor. The dose was delivered at a rate of approximately 20 rads/min. The characteristics of the exposure field and the array for exposure of the mice have been previously described.[2]

Blood samples (60 to 65 μl) were taken prior to irradiation and at daily intervals for 10 days postirradiation by snipping about 1 mm from the tip of the tail. The blood flow was collected with a minimum of expression in capillary tubes which had

* Microbiological Associates, Inc., Bethesda, Maryland

previously been coated with EDTA to prevent clotting. The plasma was recovered by centrifugation and stored in an ultralow temperature freezer (-85°C) until analyzed.

To quantify the protein-bound neutral hexoses, the sulfuric acid-orcinol technique of Weimer and Moshin[10] was scaled down to permit duplicate determinations using only 10 μl of plasma per test. Protein-bound carbohydrates (PBC) were calculated from calibration curves obtained from a series of known equimolar concentrations of galactose and mannose.

Irradiated animals in extremis, 30-day survivors, and starved and fed unirradiated controls were killed by cervical dislocation, and the liver was rapidly removed. The tissues were processed for electron microscopy by washing initially at 4°C in 3.5 percent glutaraldehyde and 0.05 M cacodylate buffer pH 7.2.[5] The tissues were cut in 1 mm cubes and placed in fresh glutaraldehyde fixative overnight. The specimens were then washed in a solution of 0.05 M cacodylate buffer, pH 7.2, and post-fixed in 1 percent osmium tetroxide.[4] Following fixation, the tissues were dehydrated in graded ethanol solutions and embedded in Maraglas.[7] The blocks were cut with a Porter-Blum MT2 ultramicrotome and sections mounted on uncoated grids. After staining with uranyl acetate[6] and lead citrate,[9] the sections were examined in an electron microscope.*

III. RESULTS

The mice which survived the irradiation and the unirradiated controls maintained stable plasma concentrations of protein-bound neutral hexoses throughout the

* Siemens Elmiskop 1A

observation period. Small day-to-day fluctuations were seen, but none was greater than could be attributed to the limits of experimental error in the analytical technique. By contrast, the PBC concentrations in the plasma of the animals which died increased from 1.8 to 2.2 times their preirradiation levels.

The only notable difference in ultrastructural architecture between liver parenchymal cells from fed (Figure 1) and starved (Figure 2) unirradiated mice was the appearance of numerous lipid droplets (L) in the latter. Despite inanition, hepatocytes from irradiated animals did not exhibit this lipid mobilization. No notable

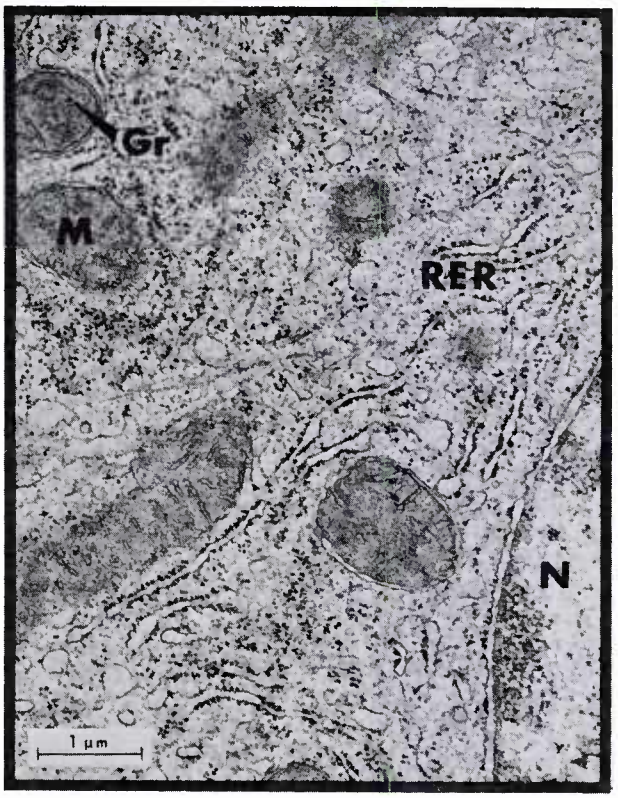

Figure 1. Liver cell of a fed unirradiated control.
Gr = mitochondrial granule
M = mitochondria
RER = rough endoplasmic reticulum
N = nucleus

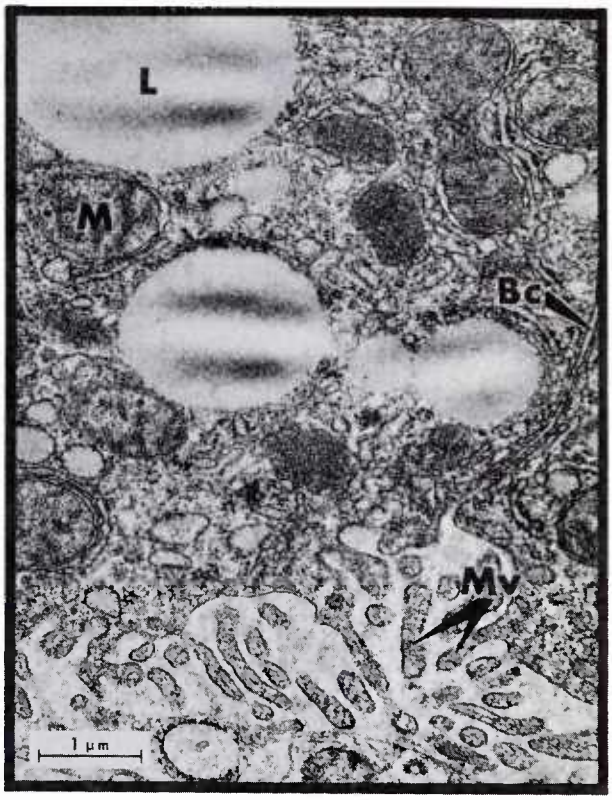

Figure 2. Liver cell of a starved unirradiated control.
L = lipid droplet
M = mitochondria
Bc = bile canaliculus
Mv = microvilli

differences were seen between the hepatocytes of the 30-day survivors and the fed, unirradiated controls. Assessments of radiation-induced alterations in fine structure were therefore made by comparison with specimens from normal, fed unirradiated mice.

The most dramatic changes observed in the cytoplasmic organelles in hepatocytes of irradiated animals were in the rough endoplasmic reticulum (RER) and Golgi apparatus (Go) (Figures 3-7).

In contrast to the uniformity of the cisternae and the regular distribution of ribosomes on the thin single unit membrane of the RER of the normal mice (Figure 1), the irradiated mice exhibited moderate to marked dilatation of this structure. The cisternae of some of the RER of the irradiated animals were greatly distended, forming lakes (La) of sparse filamentous material of low electron density suggesting accumulation of cell products (Figure 3). In some areas the dilated cisternae were separated by narrow cytoplasmic septa. In other areas, cisternal fragmentation occurred forming vesicular images with and without granules very much like the spherical fragments of microsomal fractions seen after cell fractionation. In some instances, the dilation was so extensive that "enwrapping" of the mitochondria by the cisternae occurred (Enr). In many cells the dilation of the RER was associated with a loss of ribosomes (degranulation). These detached granules were seen as clusters of free ribosomes (Fr) in the cytoplasm ground substance. Alterations in the agranular reticulum were not apparent except in the vicinity of the Golgi where a large number of vesicles were present, presumably originating from the smooth endoplasmic reticulum.

There was a marked increase in the Golgi activity in the hepatocytes of the irradiated animals (Figures 3 and 4). The lamellar system was frequently dispersed over a large area. In some cells the Golgi apparatus showed marked enlargement exhibiting a large number of dilated cisternae. The cisternae were allied with vesicles containing concentrated cell products.

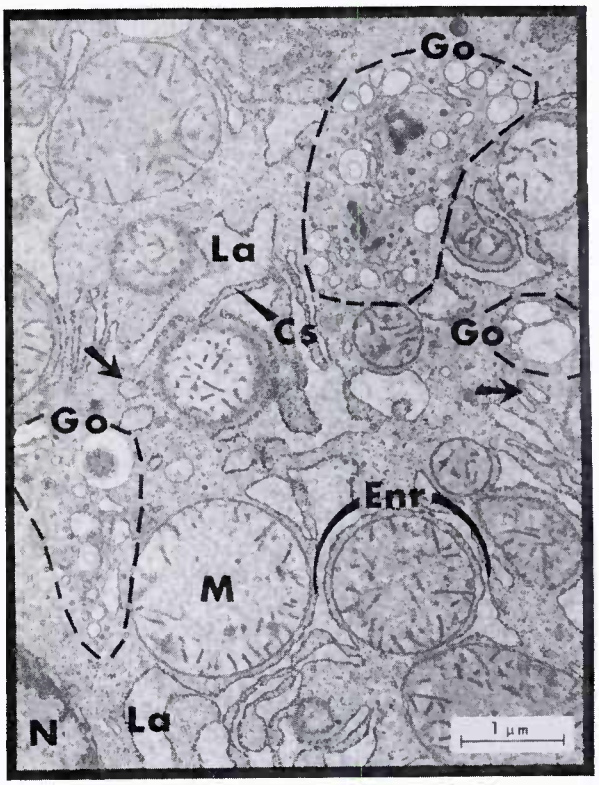

Figure 3. Liver cell of an irradiated animal in extremis.
Go = Golgi apparatus
La = lakes
Cs = cytoplasmic septa
Enr = enwrapping
M = mitochondria
N = nucleus
→ = vesicles

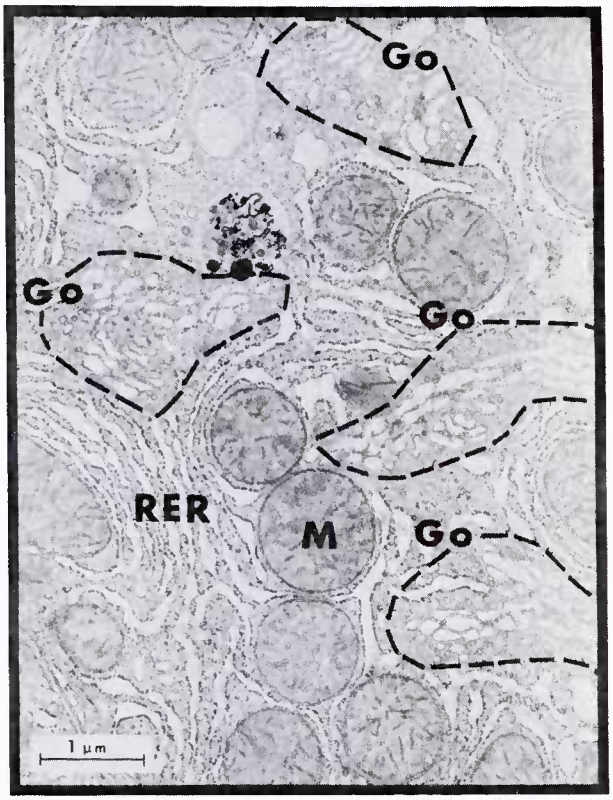

Figure 4. Liver cell of an irradiated animal in extremis.
Go = Golgi apparatus
RER = rough endoplasmic reticulum
M = mitochondria

Vacuoles containing condensation products were present in greater numbers after irradiation and there was indication of polarity in the packets of cisternae which often contained a visible flocculent precipitate (Figure 5, Sp).

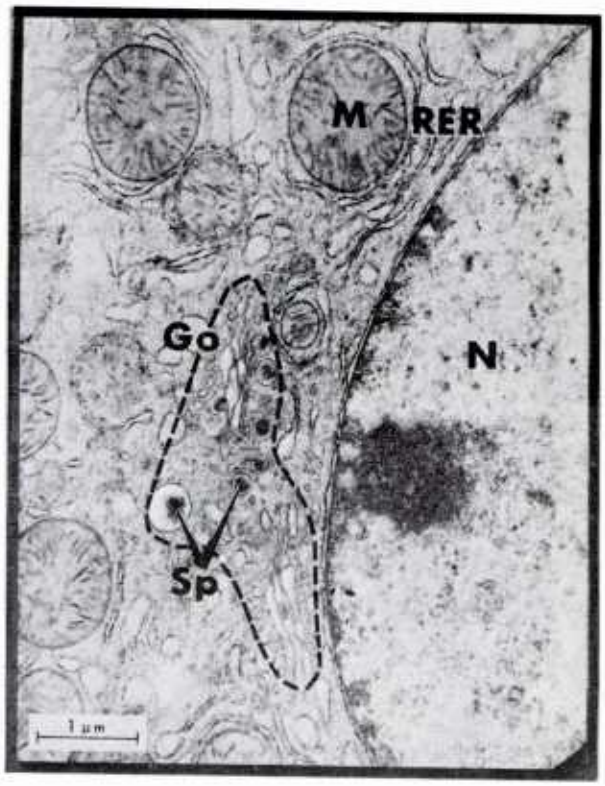

Figure 5. Liver cell of an irradiated animal in extremis.
M = mitochondria
RER = rough endoplasmic reticulum
Go = Golgi apparatus
N = nucleus
Sp = secretory product

The hepatocyte of the unirradiated mice (Figure 1) contained numerous mitochondria (M) which varied in shape according to the angle of cut relative to the longitudinal axis, from near circular to elongated cylinders. Mitochondrial granules (Gr), 20 to 30 nm in diameter, were distributed throughout their matrices. By way of contrast (Figure 6), the hepatic mitochondria in irradiated mice were uniformly circular

or near circular in cross section indicating that they had lost their elongated conformation and had rounded up into spheres. The mitochondrial matrix granules of the irradiated animals were fewer in number than those of the starved and fed unirradiated controls. Indeed, in most of the electron photomicrographs of the irradiated animals there was a decrease in the number of matrix granules. In some instances (Figure 7), there appeared to be either an increase in number or fragmentation of the cristae in the mitochondria. Whether there was an increase or decrease in the number of mitochondria per cell was not ascertained.

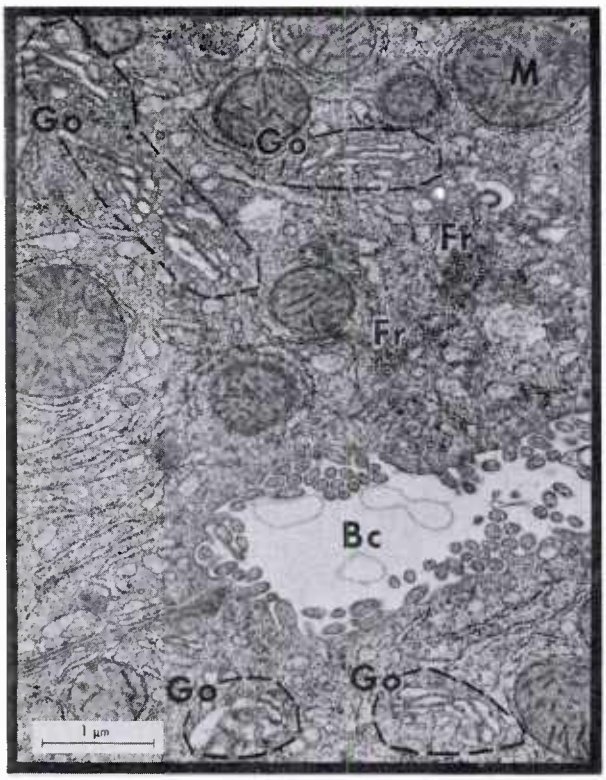

Figure 6. Liver cell of an irradiated animal in extremis.
Go = Golgi apparatus
M = mitochondria
Fr = free ribosome
Bc = bile canaliculus

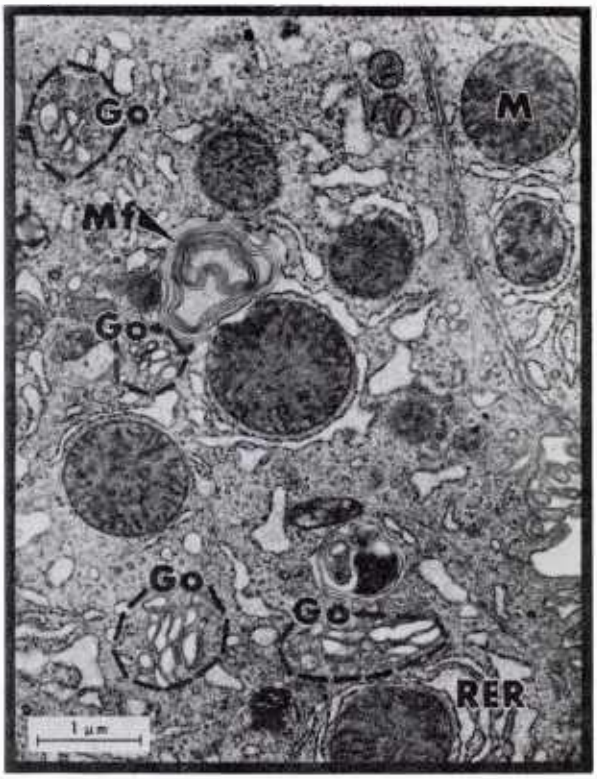

Figure 7. Liver cell of an irradiated animal in extremis.
Go = Golgi apparatus
Mf = myelin-like figure
M = mitochondria
RER = rough endoplasmic reticulum

A sporadic finding (Figure 7) was the occasional formation of myelin-like structures (Mf) in the cytoplasm of irradiated hepatocytes.

The nuclei of irradiated cells did not show regular morphological changes. Slight distension of the nuclear envelope in some cells was seen (Figure 5).

IV. DISCUSSION

Regulation of the concentration of many of the protein constituents of the blood is an important function of normal liver. Radiation interferes with this function by damaging organelles intimately concerned with such metabolic regulation. Whether one assumes that the augmentation of circulating glycoproteins in moribund animals is a result of increased synthesis, decreased catabolism, or both, is not relevant to this discussion. The correlation of ultrastructural changes with alterations in plasma concentrations of protein-bound neutral hexoses as pursued here is operational and does not permit differentiation of specific cause and effect mechanisms. These conditions do not, however, preclude speculation on the overall relationship of radiation-induced damage of certain organelles to abnormal plasma glycoprotein concentrations.

The endoplasmic reticulum and the Golgi apparatus have been implicated in biosynthesis and secretion of complex proteins in cells and appear to be related to each other structurally and functionally. In the present study, these two membranous systems were the most severely altered structures in the hepatocytes of moribund irradiated animals.

The lakes formed by the extreme dilation of the RER has been termed "hydropic degeneration"[8] on the assumption that it reflected an increase in cellular water. That there appears to be an accumulation of fluid in the RER of hepatic cells after

irradiation need not, however, be in itself "degenerative". This accumulation could represent stored secretory product. In addition, the large number of OH^- groups found in all glycoproteins containing a considerable number of sugar residues interact with water molecules of the solvent, probably by H-bond formation, which results not only in increased solubility and a larger effective molecular volume than might be indicated by the molecular weight, but actual entrainment of water.

The marked increase in Golgi activity in the moribund animals' hepatocytes undoubtedly represented a compensatory attempt of the cells to eliminate the excessive amounts of products accumulated in the cisternae of the RER. The fact that the number and complexity of the Golgi apparatus vary directly with the secretory activity of various types and different functional states of cells has established their role in secretion.

It has been suggested that in cells elaborating products rich in complex carbohydrates, such as the hepatocytes in the present study, the synthesis of the oligosaccharide component may take place in the Golgi complex itself and may be combined there with protein synthesized elsewhere in the cell.[3] If this be the case, the condition of the RER and Golgi provides support for the view that damage to regulatory mechanisms leads to excessive production of materials which must be carried to extracellular spaces to prevent further deterioration and death of the cell. In an occasional cell, evidence of necrosis was observed.

The most obvious changes in the mitochondria of the hepatocytes of irradiated mice were the loss of their normal elongated conformation and loss of matrix granules. That they had apparently rounded up into spheres, together with what appeared

to be mild swelling, suggested that damage to their limiting membranes had forced them to take a more stable shape. The loss of matrix granules was probably associated with the cells' change in functional state. The disappearance or decrease in numbers of these granules has been observed in cells after stimulation or secretory activity.[1,8] This condition has also been observed in cells exposed to an anoxic environment and is believed to be associated with a depressed rate of phosphorylation.[8]

The data presented here permit the following conclusions to be drawn. The condition of the cytoplasmic membranes and organelles of the hepatocytes of irradiated mice correlates well with the increased plasma concentration of protein-bound neutral hexoses seen in these animals. The distension of the cisternae of the RER appears to be the result either of an accumulation of excess products synthesized in the RER or excess products synthesized and incorporated in the Golgi which had overflowed and backed up into the channels communicating with the cisternae of the RER. The high amount of Golgi activity is believed to be a reflection of a compensatory response of the cell to eliminate excessive products via their secretory processes.

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C3H mice were subjected to a whole-body dose of 530 rads of mixed gamma-neutron radiation delivered at a rate of approximately 20 rads/min. The blood plasma concentration of protein-bound carbohydrates, as neutral hexoses, was estimated daily after irradiation. Ultrastructural architecture of liver tissue taken from irradiated animals in extremis was compared with that of survivors and fed and starved unirradiated controls. Among the radiation-induced differences observed in the hepatocytes were moderate to marked dilatation of the rough endoplasmic reticulum, increased Golgi activity, and rounding of the mitochondria with a decrease in numbers of mitochondrial granules. These alterations, together with other differences noted, were correlated with the increased plasma concentration of protein-bound neutral hexoses uniformly found in animals which succumb to radiation injury.

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