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EFFETS OF TOTAL BODY IRRADIATION
UPON LIPOPROTEIN METABOLISM*

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Berkeley, California

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and the Atomic Energy Commission.
A visible lipemia in the serum of rabbits 24 hours after total body x-irradiation was noted by Rosenthal (1) in this laboratory. It was observed in that study that most of the animals in which the post-irradiation lipemia was marked die within a 30 day period after exposure to radiation. The underlying mechanism responsible for this post-radiation lipemia was unexplained. Further, the opalescence observed in these radiation experiments was not characterized as to the actual physico-chemical entities in the serum responsible for its appearance. The observation that the opalescence appears to be a highly unfavorable prognostic sign with respect to survival following irradiation has prompted us to investigate the evidently vital lipid metabolic derangement which has been produced as a result of irradiation.

Recent ultracentrifugal investigations of Gofman and associates (2, 3, 4) have provided a method for the intimate study in the native state of a "spectrum" of lipoproteins. Serum opalescence may be due to the presence of one or more of the lipoproteins characterizable in the ultracentrifuge. In fact, opalescence itself may be a highly deceptive guide in the evaluation of lipoprotein alterations that may occur. This is the result of the fact that trivial concentrations of very high molecular weight lipoproteins or lipids can give rise to intense light scattering (and hence opalescence), whereas very high concentrations of much lower molecular weight lipoproteins may give rise to much less light scattering. With the ultracentrifugal technique this potential source of confusion is eliminated since one is able to determine which classes of lipoproteins have been altered as a result of radiation, and the actual quantitative extent of alteration in lipoprotein concentration may be measured directly. As will be detailed below, the ultracentrifugal method of lipoprotein study has led to the uncovering of important
prognostic alterations in a class of serum lipoproteins that would not have been
detected by opalescence alone.

ULTRACENTRIFUGAL CHARACTERIZATION OF SERUM LIPOPROTEINS IN THE RABBIT.

By the procedures outlined in the section on "Methods", it is possible
to characterize quantitatively serum lipoprotein transport in a single animal and
to follow changes in this transport. From our own and other studies in this
laboratory it appears that the normal rabbit shows lipoproteins characterized by
flotation rates in the range $S_f 5-15^*$ at concentrations ranging up to 120 mg.%. In
some normal rabbits one may find in addition low concentrations of several of
the lipoprotein species in the range of $S_f 15-20$. In general higher $S_f$ rates of
the lipoproteins are associated with higher molecular weights and lower molecular
densities.

Several experimental procedures are now known to alter both the concen-
trations of lipoproteins in rabbit serum and the distribution of lipoproteins
among the various $S_f$ classes. For example, cholesterol feeding in the rabbit re-
sults first in an alteration of concentration of lipoproteins in the $S_f 8-12$ region
followed by progressive elevation in concentration of lipoproteins of successively
higher $S_f$ classes. In carbon tetrachloride intoxication of the rabbit(5), many
of the members of the high $S_f$ classes of lipoproteins appear in high concentration
on normal diets. From these and other observations a concept has developed of the
probable interrelationship of the various lipoprotein classes. This interrelation-
ship may be described in terms of the diagram below.

* One $S_f$ unit represents a flotation rate of $1 \times 10^{-13}$ cm/sec/dyne/gm. in a sodium
chloride solution of density 1.063 gm/cc at 26° C.
It appears that lipids of dietary and/or endogenous sources enter into this serum lipoprotein transport pathway somewhere in the higher \( S_f \) classes (\( S_f 100 - S_f 40,000 \)). The direction of metabolism then seems to be that of actual successive transformation into lipoproteins of lower \( S_f \) classes. Evidence supporting this transformation sequence has been obtained in this irradiation study. (See below.)

In general the actual lipoprotein level observed in any \( S_f \) class is the resultant steady state balance between influx into this class and removal from this class. Under normal conditions very low levels of lipoproteins above \( S_f 12 \) are observed. This is still consistent with lipid metabolism going through the transformation sequence described above, except that conversion rates of the higher \( S_f \) classes are high enough to prevent the build-up of appreciable concentrations of the high \( S_f \) lipoproteins. One might anticipate the appearance of elevated concentrations of the high \( S_f \) lipoproteins by either of two mechanisms:

(a) A decrease in the utilization rate of a particular \( S_f \) class of lipoproteins, or

(b) an excessive influx of lipid into a particular \( S_f \) class of lipoproteins.
In a particular case of disturbance of serum lipoprotein pattern, an evaluation of which mechanism is operative would be valuable in understanding the underlying physiologic defect.

METHODS

For the irradiation studies a total of 49 adult New Zealand White rabbits were used. The average weight was 3 kg. The number of animals of each sex was approximately equal.

Each animal received total body irradiation from a 220 KV x-ray beam filtered through 0.5 mm Cu. At the target distance used, 60 cm, the machine delivered 40 r/min. to the center of the animal. The dose was measured in a paraffin phantom using a portable Victoreen r-meter. The doses given ranged from 800 to 900 r.

Lipoprotein concentrations were determined in the following manner: The lipoproteins were separated as a group from the other large molecules of the serum by preparative ultracentrifugation as follows: The serum, with its density raised to 1.063 gm/cc by the addition of NaCl, was spun at 30,000 RPM for 12 hours. Under these conditions all the lipoproteins of density less than 1.063 float to the top of the tube and can be pipetted off in the top fraction. This separation results in a concentration of the lipoproteins. The top fraction so obtained is then run in an analytic ultracentrifuge at 52,640 RPM; where a series of pictures is taken of the moving lipoprotein boundaries. From these pictures the flotation rate (Sf rate) and concentration of the component lipoproteins can be determined (Fig.2). Our analysis included lipoproteins characterized by flotation rates of 5 to 400 Sf units.
RESULTS AND DISCUSSION

Lipoproteins of the $S_f$ 5-400 group show a general increase after total body irradiation (Table 1). Illustrative ultracentrifugal patterns of the serum are given in Figure 2. In general, it may be said that the changes fall into three classes. In some animals the increase in any class is very small (Fig. 2A); in others there is a large increase in the $S_f$ 30-400, (Fig. 2B) and in the third group there is an increase in the $S_f$ 5-30 group of lipoproteins (Fig. 2C).

Figure 3 shows an analysis of the serial changes in the various lipoprotein components with time for one rabbit. A period of 8 to 12 hours elapsed before any change occurred. This was found to be true for all animals. At about 12 hours there is a sharp increase in the $S_f$ 100-400 class which reaches a maximum at 30 hours and falls back toward normal at 3 days. The $S_f$ 30-100 class builds up as the $S_f$ 100-400 falls, reaching a maximum at 45 hours.

As the $S_f$ 30-100 class of lipoproteins falls the $S_f$ 5-15 class increases, reaching a maximum at three days. The observed sequence of post-irradiation events is consistent with the transformation scheme outlined in Figure 1. The character of these changes is similar for all animals showing initially a large increase in concentration of lipoproteins of the high $S_f$ classes. Not all animals first showed the lipoprotein increase in the $S_f$ 30-400 group. In some cases the initial change was an increase in the $S_f$ 5-30 lipoproteins. It may well be that in this latter group the lipids were actually introduced in the $S_f$ 30-400 class or higher, but that rapid transformations down to the $S_f$ 5-30 class prevented an appreciable build-up in $S_f$ 30-400 concentration. In either case, the total lipoprotein level reached a maximum at 30 hours. Forty of 49 irradiated rabbits survived at least 12 hours. It is this group of 40 in which lipoprotein changes were assessed.
A series of histograms is given in Figure 4, plotting mg.% of lipoproteins vs. the number of rabbits having a given lipoprotein value both at the outset and at 30 hours. A shift of distribution is seen after irradiation for each Sf class and for the total Sf 5-400 range. In each case the mean of the distribution is increased after irradiation.

These figures illustrate the correlation of death with lipoprotein level. In the pre-irradiation graphs there is a random distribution of the animals which subsequently died. Therefore, apparently the lipoprotein levels prior to irradiation have no appreciable correlation with the radiosensitivity of the animal. In the 30 hour graphs, however, it is seen that there is an excellent correlation between high lipoprotein levels and subsequent death. Since the animals show high levels in general in either the high (Sf 30-400) or low (Sf 5-30) lipoprotein groups, the correlation for total lipoprotein values is better than with any single lipoprotein group.

A $\chi^2$ analysis is given in Figure 5. Before irradiation the $\chi^2$ is approximately 0, whereas measuring the lipoprotein values at 30 hours and correlating these values with the subsequent death of the animal gives a $\chi^2$ of 22.0. Thus the probability that these two variables, lipoprotein levels and death, are related is extremely high. There are four exceptions to the test. Three animals lived with very high total lipoprotein values (Nos. 19, 32 and 46). One animal died with a low value (No. 60)*. All of these exceptions were males. There is some suggestion that males are more susceptible to this lipoprotein increase after irradiation. The $\chi^2$ of 4.8 for sex vs. lipoprotein increase indicates a possible relationship between these two variables. There is no indication that the time

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* This animal, No. 60, lived 3 weeks, 8 days longer than any other animal which died.
of death is a function of lipoprotein level.

A high concentration of $S_f$ 30-400 lipoproteins is associated with serum opalescence (Table I). However, the $S_f$ 5-30 group of lipoproteins may be high enough to produce a significantly high level of total lipoproteins and the serum will remain clear. Compare, for example, Rabbit No. 91, showing no change in opalescence after irradiation, with Rabbit No. 30 which showed a moderate increase. The lipoprotein values for these rabbits are approximately equal, but in Rabbit No. 91 the increase was manifest in the $S_f$ 5-30 group whereas Rabbit No. 30 showed an increase in the $S_f$ 30-400 group. Thus, increases in the $S_f$ 5-30 group which are correlated with death are not detectable by means of serum opalescence.

Since the metabolic defect in lipoprotein metabolism after irradiation is so closely associated with death, it is of interest to study any agent capable of influencing lipoprotein metabolism. The importance of heparin in producing lipoprotein transformations has been reported by Graham, et al. (6). Figure 6 shows the effect of a single heparin injection on the abnormal lipoprotein pattern produced by radiation. In terms of the transformation concept discussed above, it appears that heparin accelerates the progressive conversion of the lower density molecules into those of higher density. This graph (Figure 6) may be compared with Figure 3. The sequence of events following the appearance of the high $S_f$ rate component is similar in that there is a fall of the very low-density molecules accompanied by an increase in the higher density components. However, after the injection of heparin this process is greatly accelerated. Without heparin, it required 3 days for the fast component to drop to an approximately normal level; with the injection of 10 milligrams of heparin this change occurred in 15 minutes.

In view of the observed reduction by heparin of lipoproteins of $S_f$ 12 and above, the possibility is suggested that the post-irradiation levels of
lipoproteins could be accounted for by an ahoparinemia. Several heparin precipitants (Toluidine blue, Protamine sulfate, and Quinine) were injected into normal rabbits to test this hypothesis. A pronounced elevation in the levels of lipoproteins above $S_f$ 12 was found at 30 hours. A typical pattern is shown in Figure 2D.

It is very unlikely that these three chemical substances are causing the effect on lipoprotein metabolism by any other mechanism than that they have a very strong affinity for heparin, and in the doses administered probably bind all available heparin for many hours. Under these circumstances, changes occur in the serum lipoproteins identical with the severe post-irradiation changes. This strongly suggests that the irradiation effects on serum lipoproteins come about through the unavailability of heparin.

The mechanism of the heparin control of blood lipoproteins is being studied currently by others in this laboratory (Graham, Nichols, Lindgren, Pierce and Ruben). It is certain that heparin initiates the release of another substance in the blood stream. This substance may contain heparin and as it has not identified chemically it is convenient to refer to it as the "active factor". The active factor causes some lipoprotein transformations from higher $S_f$ to lower $S_f$ in vitro. It is always present in detectable amounts in the blood following intravenous administration of heparin and at the same time as the acceleration of transformation of lipoproteins from higher classes to lower $S_f$ classes in vivo. The active factor is formed in appreciable quantities by very small injections of heparin. Current methods of detection can identify the active factor generated by less than 100 micrograms of heparin per kilo of body weight. No active factor circulates in so-far-detectable quantities in the normal rabbit or apparently in the post-irradiation rabbit up to the third day. At this time it appears that the active factor is being generated and this most probably represents the release of unusual quantities of free heparin.
This phase is being investigated for possible relationship to the severity of irradiation damage on the theory that following lethal levels of irradiation heparin becomes unavailable for the control of normal lipoprotein transformations. The lack of available heparin causes a piling up of lipoproteins in the blood stream in molecules that are blocked from metabolic conversion to lower Sf molecules. These transformations can still occur in these animals if small quantities of heparin are injected into the animal. It is not yet explained why the site of greatest inhibition of transformation should be at somewhat different Sf levels in different animals.
SUMMARY

1. There is an excellent correlation between high level of total lipoprotein 30 hours after irradiation and subsequent death of the animal.

2. A serum opalescence is associated with low density lipoprotein only, not with total lipoprotein level.

3. Changes in the lipoprotein levels after irradiation are consistent with the theory of conversion of low density lipoprotein to higher density components.

4. The injection of heparin after irradiation hastens the return of lipoprotein levels to normal values.

5. The injection of toluidine blue, protamine sulfate or quinine produces changes in the lipoprotein pattern similar to those shown after irradiation.
REFERENCES


Table I shows a summary of the lipoprotein changes for each rabbit used. Areas from the ultracentrifuge patterns have been converted into milligrams percent by means of an appropriate proportionality factor. Animals classified as "lived" have lived at least 30 days after irradiation. Deaths occurring beyond that period are not considered attributable to radiation damage. A group of 9 animals shown at the end of the table died within 1 to 3 hours post-irradiation. They were therefore not included in this study. The last column gives a purely subjective estimation of the degree of opalescence in the serum before ultracentrifugation. It is based on a 1 to 10 scale.

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Animals classified as "lived" have lived at least 30 days after irradiation. Deaths occurring beyond that period are not considered attributable to radiation damage. A group of 9 animals shown at the end of the table died within 1 to 3 hours post-irradiation. They were therefore not included in this study. The last column gives a purely subjective estimation of the degree of opalescence in the serum before ultracentrifugation. It is based on a 1 to 10 scale.
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### TABLE I
(conc.)

**Animals dying in less than 12 hours post irradiation**

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<tr>
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<td>900r</td>
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<tr>
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<td>900r</td>
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<td></td>
<td>2 hr</td>
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</table>
FIGURE 2

Lipoprotein patterns before and after radiation. From left to right successive frames are at 0, 6, 12, 22, 30 and 38 minutes after the rotor has reached 52,640 RPM. A flotation rate scale for each frame is drawn at the top of the figure. The smooth curves drawn in above the patterns represent the position of the top of the pattern when no lipoprotein is present. The area bounded by the reference curve, the top of the pattern and any two vertical lines is proportional to the concentration of the lipoproteins characterized by this $S_f$ range. To measure the $S_f$ 5-400 lipoproteins considered in this paper, areas were measured in four frames and added together.

A. Rabbit #74, shows very little increase of total lipoprotein 30 hours post-irradiation.

B. Rabbit #50 shows an increase of total lipoprotein due to a large increase of the $S_f$ 30-400 class.

C. Rabbit #92. Here the lipoprotein increase is found mainly in the $S_f$ 5-30 component.

D. Lipoprotein changes due to single injection of 10 mg. of toluidine blue. Note similarity to post-irradiation changes. (Figure 2B above)
FIGURE 3

Serial lipoprotein changes with time for a single animal. (Rabbit #32)
Fig. 3
FIGURE 4

Distribution of lipoprotein concentrations before and after irradiation in 40 rabbits. Each square represents one animal.
Fig. 4
LIPOPROTEIN Sf 5-15

PRE IRRADIATION

30 HOURS POST IRRADIATION

Fig. 4
Fig. 4
FIGURE 5
ASSOCIATION TABLES

A. Association of lipoprotein levels with death.

Pre-irradiation Lipoprotein mg.%. 30 hrs. post-irradiation Lipoprotein mg.%.  

<table>
<thead>
<tr>
<th></th>
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<th>Died</th>
<th></th>
<th>Lived</th>
<th>Died</th>
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</thead>
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<tr>
<td>&lt; 73</td>
<td>11</td>
<td>9</td>
<td>&lt; 350</td>
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\[ x^2 = 0 \]
\[ p \geq 1 \]

B. Correlation of sex with lipoprotein level 30 hours after irradiation.

<table>
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<tr>
<th></th>
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<td>&lt; 350</td>
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<tr>
<td></td>
<td>19</td>
<td>21</td>
<td></td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

\[ x^2 = 4.8 \]
\[ p = .03 \]

In each case the dividing line was arbitrarily chosen to give the best correlation. The 350 mg. dividing line is shown graphically by an arrow in Figure 4.
FIGURE 6

Effect of a single injection of heparin on post-irradiation lipoprotein changes for one animal.
SERUM LIPOPROTEIN, Mg. %

TIME AFTER IRRADIATION, HOURS

10 Mg. HEPARIN

Sf 30-400

Sf 5-15

MU 2729

Fig. 6