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EFFECT OF IONIZING RADIATIONS ON DISTRIBUTION OF PLASMA PROTEIN-BOUND NEUTRAL HEXOSES IN MICE AND DOGS

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

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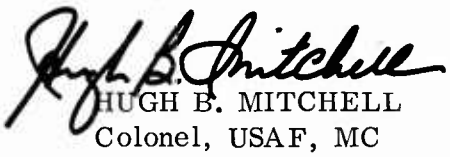
EFFECT OF IONIZING RADIATIONS ON DISTRIBUTION OF PLASMA PROTEIN-BOUND NEUTRAL HEXOSES IN MICE AND DOGS

A. S. EVANS

R. E. GEORGE
Commander, MSC, USN
Chairman
Radiation Biology Department



HUGH B. MITCHELL
Colonel, USAF, MC
Director

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

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FOREWORD
(Nontechnical summary)

Practically all of the proteins in the blood plasma are complex molecules containing carbohydrates (sugars) in addition to amino acids as a part of their primary structure.

In the first report of this series (AFRRI SR68-4), it was suggested that blood plasma concentration levels of protein-bound carbohydrates (PBC) as neutral hexoses (uncharged 6-carbon sugars) may constitute a crude index of radiosensitivity prior to and prognosis after irradiation in otherwise healthy C3H mice.

The presently reported experiments were designed to test whether dogs would exhibit radiation-induced PBC response in plasma similar to that of mice and to identify operationally the specifically affected plasma protein components in both species.

C3H mice and beagles were subjected to single, whole-body exposures of mixed gamma-neutron radiations delivered as a pulse or at a steady-state rate of approximately 20 rads/min. Blood specimens were taken before irradiation and at daily intervals for varying periods, up to 20 days. PBC concentration was determined by chemical analysis.

The affected protein components were identified operationally by sieving through a gel which had a pore size small enough to separate the various proteins roughly by molecular size and at the same time contained groups which accelerated or retarded the molecules according to their electrical charge. The fractions from these columns were then examined by separating the proteins in each by their relative movement in a molecular sieving polyacrylamide gel under the influence of an electrical field.

Further investigations to test the hypothesis that the preirradiation PBC concentration may constitute a crude index to radiosensitivity of the individual were made under specifically designed conditions. The mice and dogs were bled prior to irradiation only. The plasma PBC values of each group were arranged in three sets by a standard statistical procedure: those which were in a zone immediately about the group mean, those below the lower limit of that zone, and those above the upper limit. The hypothesis being tested postulated that the animals with plasma PBC concentrations in the low set would be relatively radioresistant, those in the high set would be relatively radiosensitive, and the set within the limits of the mean value would be undistributed with regard to mortality.

Alterations in plasma concentration of protein-bound carbohydrates followed the same general course in dogs as previously reported for mice. Thus, in the animals which died, the PBC concentration showed a marked increase, while the survivors deviated only slightly from their preirradiation base-line values. The similarity of the radiation-induced plasma PBC response of mice and dogs suggested that this phenomenon may be generally applicable to mammals and not species specific.

A large portion of the increase in PBC in animals near death was accounted for operationally in carbohydrate containing proteins which normally function to help conserve the body's supply of iron.

The findings of these experiments were interpreted to reflect radiation-induced damage to bodily control mechanisms which resulted in excessive circulating concentrations of these proteins. The stability of the plasma PBC concentration maintained

by the survivors suggested that their bodily control mechanisms had sufficient reserve to enable them to maintain balance despite the radiation insult.

The usefulness of the preirradiation PBC concentration as an indicator of radiosusceptibility was confirmed.

The results reported here indicate that changes in plasma concentration of PBC may be developed into a relatively simple, objective prognostic test to supplement clinical observation in cases of radiation injury.

ABSTRACT

Comparison of changes in concentration of protein-bound carbohydrates (PBC) as neutral hexoses in the plasma of C3H mice and beagles as a function of time after exposure to mixed gamma-neutron radiations revealed that the two species react similarly. The animals which died exhibited a marked increase in plasma PBC concentration while the survivors deviated only slightly from their preirradiation values. Analytical acrylamide gel electrophoresis demonstrated that distinctive, progressive postirradiation changes occurred in the plasma of the animals which succumbed. The most striking changes were in the components tentatively identified as transferrin, haptoglobins, and α_2-macroglobulin. Preparative fractionation of plasma of both mice and dogs by combined molecular sieving and ion exchange chromatography revealed that, in the four fractions uniformly obtained, absolute changes in PBC regularly occurred only in the first and third. The protein composition of these fractions and their significance as a prognostic tool in radiation injury are discussed. The suggestion that the preirradiation PBC concentration may constitute a crude index to radiosensitivity was confirmed under conditions specifically designed to test the hypothesis.

I. INTRODUCTION

Evans et al.[4] suggested that plasma concentration levels of protein-bound carbohydrates (PBC) as neutral hexoses may constitute a crude index of radiosensitivity prior to and prognosis after irradiation in otherwise healthy C3H mice. They pointed out, however, that the glycoproteins constitute such a structurally and physiologically diverse agglomeration that analyses which treat them as a single entity cannot be expected to yield clinically applicable criteria.

The presently reported experiments were designed to test whether dogs would exhibit radiation-induced PBC response in plasma similar to that of mice, to identify operationally the specifically affected plasma protein components, and to test the hypothesis that the preirradiation PBC concentration may constitute a crude index to radiosensitivity of the individual.

II. MATERIALS AND METHODS

Two species of animals were utilized in these experiments: young adult male C3H mice, 6-8 weeks of age, weighing between 20 and 24 g, and healthy AKC registrable beagles of both sexes, 2-3 years of age.

Blood specimens were taken before irradiation and at daily intervals for varying periods, up to 20 days. Some of the dogs were utilized in cooperation with other investigators so that doses, dose rates, and intervals of blood sampling were those which would not interfere with the primary experimental design.

All of the animals were exposed to mixed gamma-neutron radiations from the AFRRI-TRIGA reactor. The characteristics of the exposure field and the array for exposure of the mice have been described previously.[4] The dogs were exposed

unilaterally to either pulsed or steady-state doses, the details of the methodology of which have been described.[7] The midline tissue doses (rads) and dose rates (rads/min) received by the animals reported on here are given with the analytical data.

Protein-bound neutral hexoses (as galactose and mannose) were estimated by a modification[4] of the sulfuric acid-orcinol method of Weimer and Moshin.[9]

Combined molecular sieving and ion exchange chromatography were accomplished utilizing a porous polyacrylamide gel with a functional cation exchange group ($\ldots COO^- Na^+$) attached to the gel matrix.* The fractions were eluted from the 0.9 x 12 cm columns by stepwise increases in ionic strength and pH of 0.05 M phosphate (Na^+) buffers as indicated with the experimental data.

It was necessary to pool plasma from similarly reacting mice to obtain sufficient amounts for the columns (0.5 ml). The size of the dogs permitted withdrawal of sufficient blood to allow analyses on individual animals.

The distribution of protein-bound neutral hexoses was determined by precipitation of each of the 0.5 ml collections from the chromatography column with an equal volume of 10 percent aqueous trichloracetic acid. The precipitate was washed with 95 percent ethanol, redissolved in 0.1 N NaOH, and the sulfuric acid-orcinol procedure applied as for whole plasma.[9]

The protein composition of each of the fractions from the chromatography columns was examined by analytical polyacrylamide gel electrophoresis carried out essentially as described by Davis[3] and stained with either Buffalo black or Coomassie blue.[2]

* BioGel, CM-100, Calbiochem, Los Angeles, California

To test the hypothesis that the preirradiation PBC concentration may constitute a crude index to radiosensitivity of the individual, two groups of animals, 18 dogs and 24 mice, were bled prior to irradiation only. The dogs were exposed to a 205-rad pulse ($LD_{44/30}$); the mice to 400 rads at 20 rads/min ($LD_{46/30}$).

The plasma PBC values of each group were arranged in three sets: those which were within the 95 percent confidence interval for the group mean, those below the lower limit of that interval, and those above the upper limit.

III. RESULTS

Alterations in the plasma concentration of protein-bound carbohydrates (PBC) as neutral hexoses followed the same general course in dogs (Figure 1) as previously reported for mice.[4] Thus, in the animals which died, the PBC concentration showed a marked increase while the survivors deviated only slightly from their preirradiation base-line values.

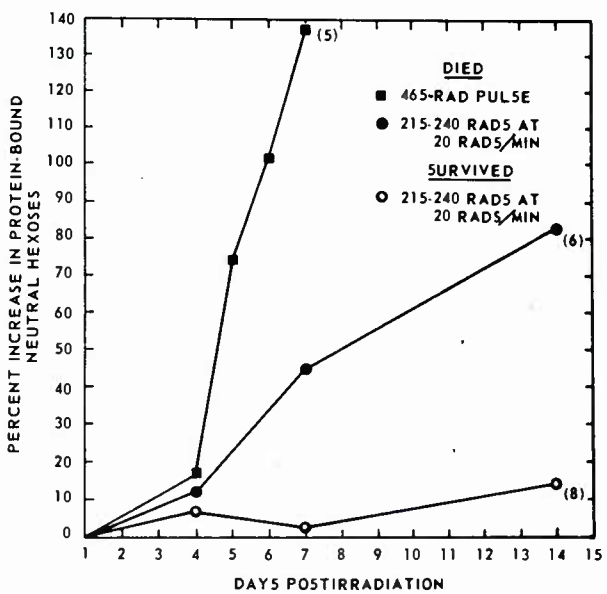

Figure 1. Percent increase in concentration of total neutral hexoses in the plasma of dogs at indicated times after exposure to mixed gamma-neutron radiations. Numbers in parentheses are number of animals represented by each curve.

Hemodilution and hemoconcentration were eliminated as controlling factors in the changes demonstrated by expressing the neutral hexose concentration as milligrams of carbohydrate per 100 mg biuret protein (Figure 2).

Analytical acrylamide gel electrophoresis of plasma of both mice and dogs (Figure 3) revealed that distinctive, progressive postirradiation changes occurred

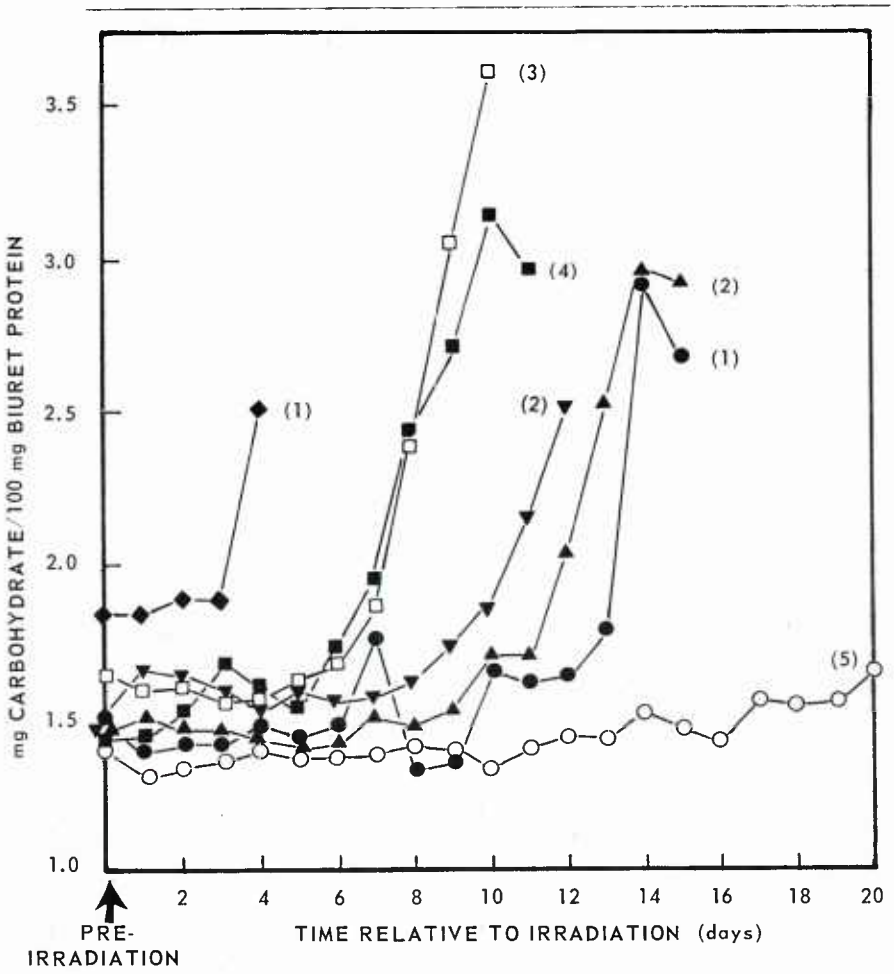

Figure 2. Milligrams protein-bound neutral hexoses per 100 mg protein (biuret) in the plasma of dogs at indicated times relative to exposure to mixed gamma-neutron radiations. The doses were 225 rads: ○ = 30-day survivors; ● = died on 16th day postirradiation; 230 rads: ▼ = died on 12th day; ▲ = died on 15th day; 400 rads: ◆ = died on 4th day; □ = died on 10th day; ■ = died on 11th day. Numbers in parentheses are number of animals represented by each curve.

in the animals which succumbed. The most striking changes appeared in components identified as transferrin, haptoglobin and α_2-macroglobulin.

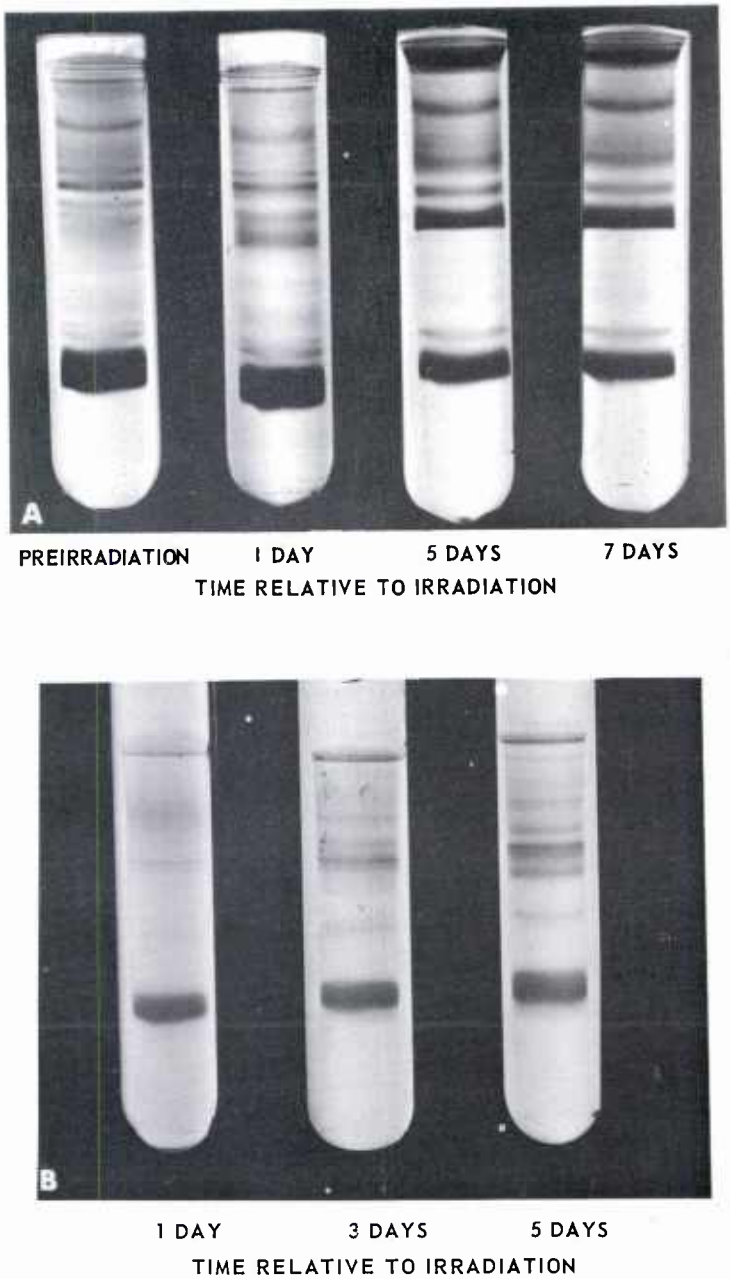

Figure 3. Typical acrylamide gel disc electrophoretic patterns of plasma of a dog (A), and of mice (B), at indicated intervals relative to lethal irradiation with mixed gamma-neutron radiations.

Preparative fractionation of plasma of both dogs and mice by combined molecular sieving and ion exchange chromatography regularly gave four protein fractions as measured by monitoring the column at 280 nm wavelength (Figure 4). A marked

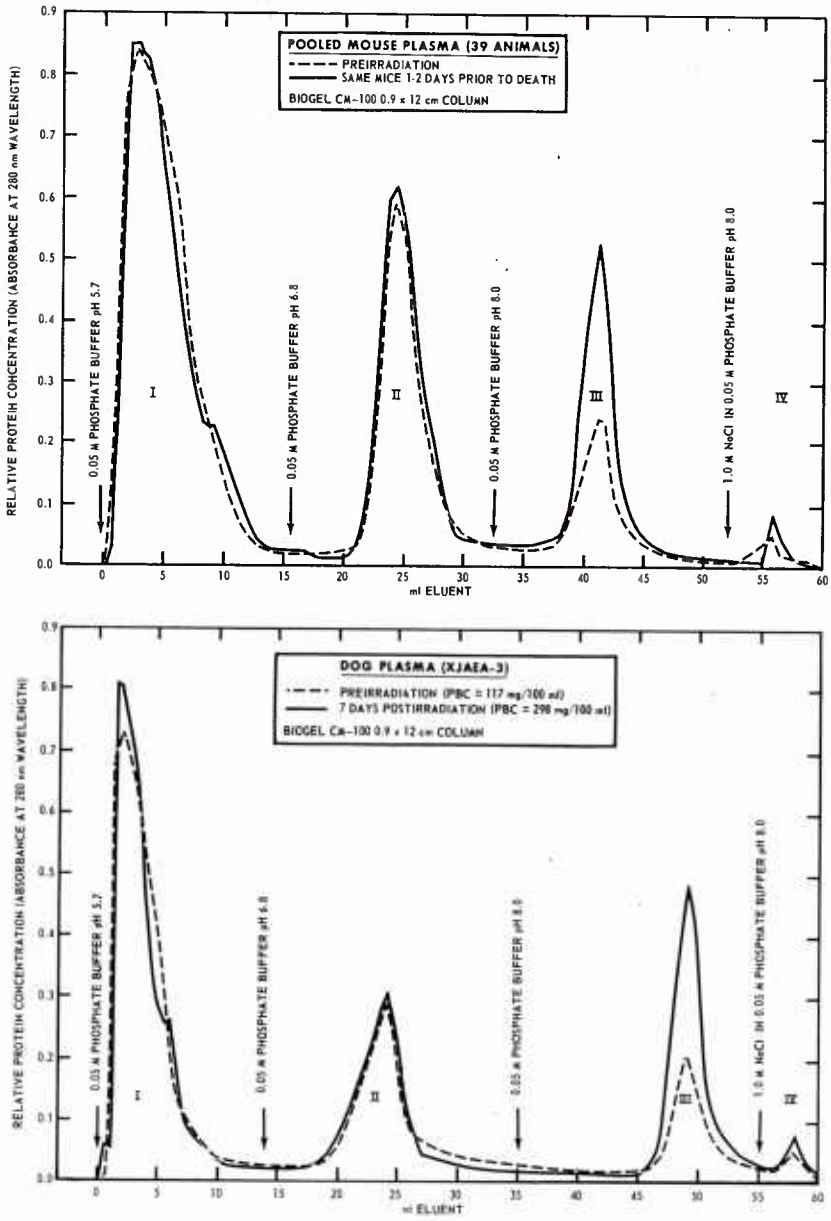

Figure 4. Characteristic protein absorption curve (280 nm) of plasma from mice (upper) and dogs (lower) illustrating the four fractions regularly obtained by combined molecular sieving and ion exchange chromatography. Note marked postirradiation increase in fraction III. Analyses of the four fractions are given in Figure 5.

increase in absorbance at this wavelength was seen in fraction III in all the patterns of moribund animals.

Chemical analyses revealed that all the radiation-induced increases in plasma PBC content were in the first and third fractions (Figure 5).

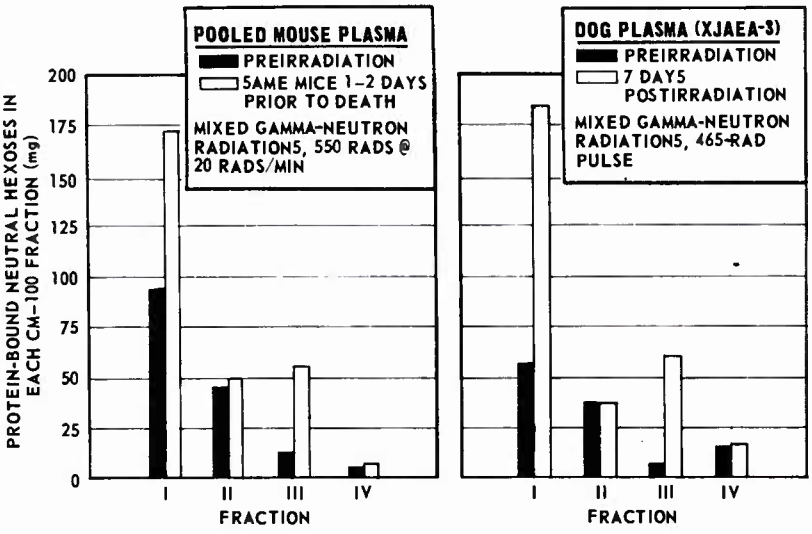

Figure 5. Protein-bound neutral hexoses in fractions from combined molecular sieving and ion exchange chromatography columns. For designation of fraction numbers see Figure 4.

Analytical acrylamide gel disc electrophoresis demonstrated that the increase in PBC regularly found in the first fraction was attributable to the increase in transferrin (compare Figure 6a and 6b). The third fraction in which the absolute PBC content increased up to more than eight times the preirradiation value, contained the haptoglobin complex, β_2-glycoproteins, and the α_2-macroglobulin (Figure 6c and 6d).

Of the 18 dogs on which only preirradiation blood samples were taken, 8 died during the 30-day observation period and 10 survived. The 95 percent confidence interval of the mean of 121.2 mg PBC/100 ml plasma was 112.4 to 130.1. All of the

five animals which had PBC values below the lower limit survived; four of the six which were above the upper limit on the mean died.

In the 24 mice, 11 of which died, the confidence interval of the mean of 159.1 mg PBC/100 ml plasma was 154.3 to 163.8. Eight of the nine mice which had PBC values below the lower limit survived, while eight of the ten above the upper limit died.

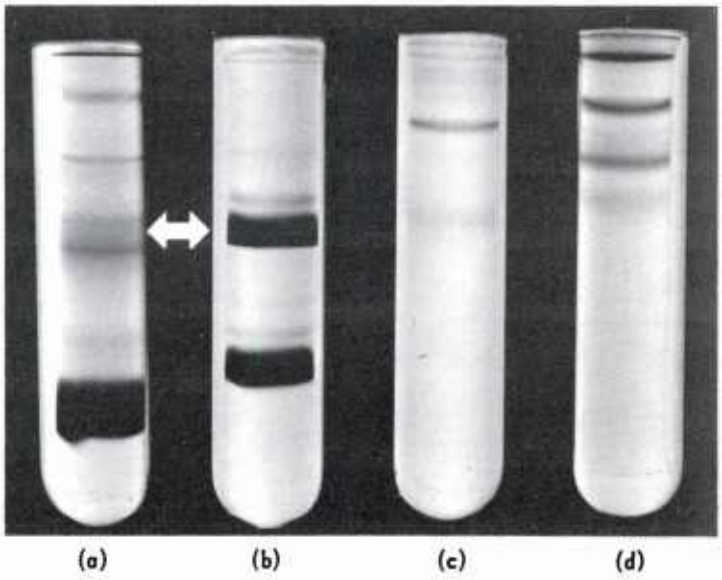

Figure 6. Acrylamide gel disc electrophoretic patterns of material from fractions I and III of Figure 5 (dog): (a) fraction I, preirradiation; (b) fraction I, 7 days postirradiation; (c) fraction III, preirradiation; (d) fraction III, 7 days postirradiation. Note the marked increase in transferrin (⇔).

IV. DISCUSSION

The similarity of the radiation-induced plasma PBC response of mice and dogs as a function of time after exposure suggested that this phenomenon may be generally applicable to mammals and not species specific.

It was apparent that a large portion of the increase in protein-bound neutral hexoses in moribund animals could be accounted for operationally (Figures 3 and 6) in glycoproteins concerned with iron conservation, transferrin and haptoglobin. It is doubtful that the marked increase in these plasma components is totally a response to a biological need for their primary functions, although compensatory attempts to bolster declining erythropoiesis by conserving iron and hemoglobin may have been a factor.

Considering the rapidity of the rise, especially in the animals which died in the first week, it did not appear likely that the elevation in transferrin was as a compensatory defense mechanism.[6] The consistency of this increase compared with the variability in loss of γ-globulins[5] did not support such a hypothesis.

More likely, the findings reported here reflect radiation-induced damage to control mechanisms of biosynthesis and catabolism resulting in excessive circulating concentrations of these proteins. That the surviving animals did not show significant changes lends credence to this hypothesis. Thus, the stability of plasma concentration of protein-bound neutral hexoses maintained by the survivors indicated that their metabolic control mechanisms had sufficient reserve to enable them to maintain physiological balance despite the radiation insult.

The marked rise in the α_2-macroglobulin component in the moribund animals explains the great increase over preirradiation levels in absorbance of the plasma at 280 nm wavelength in fraction III of Figure 4. This protein has been shown[8] to contain over 500 residues per molecule of aromatic amino acids which absorb at or near 280 nm.

The carbohydrate composition of the proteins which have been shown here to account for most if not all of the rise in plasma PBC concentration in moribund animals is similar in the relative amounts of the various classes of sugars they contain. It is expected, therefore, that further analyses should show the neutral hexoses, hexosamines, and sialic acid will remain in direct proportion to one another during the course of radiation sickness. Thus, differentiation of radiation injury from hypertension, myocardial infarction, and liver disorders[1] will be permitted. Experiments are in progress to test this hypothesis.

The results reported here indicate that changes in concentration of circulating protein-bound neutral hexoses may be developed into a relatively simple, objective prognostic test to supplement clinical observation in cases of radiation injury.

The confirmation, under conditions specifically designed to test the thesis that preirradiation levels of protein-bound neutral hexoses permit screening of small groups for extremes in radiosusceptibility offers promise. The general concept has been consistent in this[4] and other[10] laboratories but has been restricted to studies using inbred strains of mice, rats, and dogs. Tests of its applicability to the mongrel human species present obvious difficulties in experimental design.

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Comparison of changes in concentration of protein-bound carbohydrates (PBC) as neutral hexoses in the plasma of C3H mice and beagles as a function of time after exposure to mixed gamma-neutron radiations revealed that the two species react similarly. The animals which died exhibited a marked increase in plasma PBC concentration while the survivors deviated only slightly from their preirradiation values. Analytical acrylamide gel electrophoresis demonstrated that distinctive, progressive postirradiation changes occurred in the plasma of the animals which succumbed. The most striking changes were in the components tentatively identified as transferrin, haptoglobins, and α_2-macroglobulin. Preparative fractionation of plasma of both mice and dogs by combined molecular sieving and ion exchange chromatography revealed that, in the four fractions uniformly obtained, absolute changes in PBC regularly occurred only in the first and third. The protein composition of these fractions and their significance as a prognostic tool in radiation injury are discussed. The suggestion that the preirradiation PBC concentration may constitute a crude index to radiosensitivity was confirmed under conditions specifically designed to test the hypothesis.

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