Use of $^{125}$I- and $^{51}$Cr-Labeled Albumin for the Measurement of Gastrointestinal and Total Albumin Catabolism *

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Abstract. A method for the simultaneous measurement of gastrointestinal protein loss and total albumin turnover entailing the use of a combination of $^{125}$iodine- and $^{51}$chromium-labeled albumin is described. Albumin turnover was calculated by the measurement of albumin-$^{125}$I plasma decay and cumulative urinary excretion, and the results obtained agreed closely with previous studies utilizing albumin-$^{125}$I. Gastrointestinal catabolism was calculated from the rate of fecal excretion of $^{51}$Cr and the specific activity of plasma albumin-$^{51}$Cr, and these data were related to the calculated albumin turnover results. During the period of 6–14 days after administration, the ratio of specific activities of albumin-$^{125}$I and -$^{51}$Cr in plasma and in extravascular spaces or gastric and biliary secretions remained almost identical. Fecal excretion of $^{51}$Cr was also quite stable at this time. In six normal subjects gastrointestinal catabolism accounted for less than 10% of total albumin catabolism. Excessive gastrointestinal protein losses did not contribute to the low serum albumin in three patients with cirrhosis or in two adults with the nephrotic syndrome. Multiple mechanisms leading to hypoalbuminemia were demonstrated in other subjects with a variety of gastrointestinal disorders.

Introduction

An important contribution to understanding albumin metabolism was the recognition that the gastrointestinal tract normally participates in albumin catabolism. Increased intestinal albumin losses can be a major cause of hypoalbuminemia in a variety of disease states as discussed in several recent reviews (2–5). Although enhanced intestestinal losses of protein are solely responsible for the hypoalbuminemia in patients with intestinal lymphangiectasia, it is likely that multiple mechanisms are operative in patients with systemic diseases in which exudative enteropathy occurs. In such patients an increased rate of endogenous albumin catabolism or a decreased synthetic rate may also be important. As therapeutic measures for the alleviation of excessive intestinal protein losses are becoming available, it is necessary to utilize accurate methods for measuring albumin metabolism in individual patients in order to assess the results of such therapy.

Procedures used to study exudative gastroenteropathy have heretofore been qualitative and have detected only gross protein loss. A more accurate measurement of protein catabolism can be achieved through the simultaneous use of two albumin tracers, albumin-$^{125}$I to measure over-all albumin catabolism and albumin-$^{51}$Cr to measure...
gastrointestinal losses. Evidence that the rate of $^{51}$Cr entry into the gut reasonably reflects the rate of albumin exudation is presented. In six subjects without gastrointestinal disease, metabolic studies demonstrated a minor role for the gut in albumin catabolism. In addition to findings in two nephrotics, the results in 13 patients with a variety of gastrointestinal symptoms with and without hypoalbuminemia is reported. In some cases multiple mechanisms causing the low serum albumin are demonstrated.

Methods

Human albumin$^1$ labeled with $^{131}$I was prepared by the method of McFarlane (6) and obtained from Abbott Laboratories, N. Chicago, Ill. These preparations contained 1-2 iodine atoms per molecule of protein. Human albumin$^2$ labeled with $^{51}$Cr according to the method of Waldmann (7) contained 3-4 atoms per molecule of protein. For some studies, a batch of albumin-$^{131}$I was diluted with human albumin and then relabeled with $^{51}$Cr (7 atoms per molecule) in the usual manner (double-labeled albumin). Canine albumin obtained from Pentex, Inc., Kanakee, Ill. was labeled with $^{131}$I and $^{51}$Cr in a similar fashion. All samples of labeled albumin upon receipt (usually within 7 days of manufacture) were further diluted 10-fold with carrier human serum albumin (Cohn fraction V) and were stored at 4°C.

Patient studies

Patients hospitalized at St. Luke's Hospital Center were studied either under close supervision on the general medical ward or in a metabolic ward. Patients with orthopedic disorders without proteinuria or evidence of gastrointestinal or hepatic disease and having normal values for serum proteins by protein electrophoresis were used as "normal" subjects. Lugol solution, five drops three times daily, was given for 2 days before and throughout the duration of the study. The amount of labeled albumin necessary to provide approximately 10 $\mu$g of $^{131}$I and 60-80 $\mu$g of $^{51}$Cr was weighed into a plastic syringe and was injected intravenously. The syringe was rinsed three times with venous blood before withdrawal of the needle. Oxalated blood samples were drawn from the arm not used for the injection at three time periods between 10 and 20 min. Blood samples were collected daily for 4 days and every 2nd day thereafter for the duration of the study (14-18 days). A microhematocrit was immediately obtained on each blood specimen, the remainder was centrifuged, and the plasma was separated and frozen for storage. Insofar as possible, each patient was started on the study in the morning before breakfast and subsequent bloods were drawn at the same time each day while the patient was fasting in order to minimize diurnal variation in plasma volume.

Daily 24-hr urine collections were obtained with a few crystals of thymol added to the collection container. The volume of the specimen was measured to the nearest 5 ml; an aliquot was removed and stored at 4°C for later counting. In some studies the protein in another 5 ml aliquot was precipitated with 10% trichloroacetic acid, and the supernatant was also stored for counting.

All stools for each 24 hr period were collected in 1 quart tared jars. Subsequently, the weight of each stool collection was determined, a known weight of water was added, and the mixture was homogenized. Aliquots were removed and frozen for later counting. In some studies, the stools were collected in tared cans and homogenized by the method of Jover and Gordon (8).

The patients were weighed daily, and the serum proteins were determined at least twice during the course of the study.

Chemical methods

Total proteins were determined by the biuret method (9), and the quantity of albumin was determined both by paper electrophoresis (10) and by Howe sodium sulfate fractionation. Dialysis of labeled albumin preparations and selected specimens of urine, bile, and gastric juice was performed for 3 hr against 25% polyvinylpyrrolidone at 4°C with two changes of the dialysis fluid. The contents of the dialysis bag and an aliquot of the fluids outside the bag were kept for isotope counting. Another aliquot was precipitated and washed with 10% trichloroacetic acid, and the precipitate was redissolved in 80% acetone (11) and counted.

Starch gel electrophoresis was used to determine the specific activity of the protein fractions. Vertical gel electrophoresis was used primarily to compare the electrophoretic bands in several samples simultaneously, and horizontal electrophoresis was used to separate large samples necessary for isotope counting. A borate buffer (pH 8.9) and electrophoretic conditions described by Smithies (12, 13) were employed. Approximately 0.75 ml of serum, or a solution of appropriate lyophilized specimens redissolved in buffer and containing about 10-40 mg of protein was run horizontally at one time with a starch grain support. The position of the protein bands was determined by staining with amido black. Where elution of the proteins from the starch was desired, the starch block was divided according to the protein distribution (12). After being frozen for several hours at $-20^\circ$C and allowed to thaw, the protein and buffer were squeezed out. These samples were adjusted to equal volume by the addition of buffer and analyzed for $^{51}$Cr and $^{131}$I activity in a double channel gamma spectrometer. The protein content of these solutions was determined by the method of Lowry and coworkers (14).

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1 Supplyied by Cutter Laboratories, Berkeley, Calif., as Cohn fraction V heat treated.

2 Labeled albumin preparations obtained through the courtesy of Doctors A. Bruno, H. Maroon, and D. R. K. Murty. Radiopharmaceutical Research Department, E. R. Squibb and Sons, New Brunswick, N. J.
Isotope counting

Radioactivity in all specimens was measured in a Nuclear-Chicago Auto Gamma Spectrometer with a thallium-activated sodium iodide crystal. Fluid specimens, including serum and urine, were 2 or 5 ml in volume while fecal specimens of about 2 g were accurately weighed on a torsion balance. Appropriate standards containing a known dilution of the albumin administered were also analyzed for $^{131}I$ and $^{51}Cr$ activity.

All samples were counted in duplicate for sufficient time to insure 5% reproducibility 95% of the time. In order to correct for radioactive decay during prolonged counting, we included multiple standards for comparison. The gamma spectrometer was found to be very efficient in distinguishing between $^{131}I$ and $^{51}Cr$ when the isotopes were present in the same sample. When estimating $^{51}Cr$, no $^{131}I$ counts were recorded. On the other hand, when $^{131}I$ was counted about 3% of the $^{51}Cr$ counts were also recorded. Corrections for the "spill" of $^{51}Cr$ counts into the $^{131}I$ channel were applied when appropriate. Despite the low energy of $^{131}I$, self-quenching was not a problem. Counting efficiencies were the same for $^{131}I$ in comparable serum, urine, and stool samples.

External counting over the liver, spleen, and precordium was performed with a 2 inch thallium-activated crystal, scintillation probe spectrometer (Nuclear-Chicago DSJ-132B). In order to estimate the rapidity and completeness of fecal excretion of secreted $^{51}Cr$ radioactivity under conditions simulating those in the present studies, we administered 160 mg per day of albumin-$^{51}Cr$ orally in divided doses for a total of 7 days. Over 98% of the isotope fed was recovered in the feces within 2 days of cessation of oral administration, and less than 0.3% appeared in the urine.

Special patient studies

To determine the relative labeling of albumin by the two isotopes in the body and to clarify some aspects of albumin-$^{51}Cr$ metabolism, a number of special studies were performed.

(a) A patient suffering from lymphosarcoma who had a chylous thoracic effusion was given a mixture of albumin-$^{131}I$ and albumin-$^{51}Cr$. The pleural effusion was tapped dry shortly before the study began. On the 18th day after intravenous administration of the labeled albumin, chylous fluid was obtained by thoracentesis. The protein content in this fluid was determined by paper electrophoresis, and the specific activity of the two isotopes was compared with that of serum obtained on the same day.

(b) One patient was given $270 \mu g$ of albumin-$^{51}Cr$. Radioactivity over the liver, spleen, and precordium was monitored at 1, 2, 3, 41, 6, and 24 hr, and daily for 11 days after injection.

(c) One patient having gross albuminuria associated with the nephrotic syndrome was given a mixture of the labeled albumin preparations. Fractions of urine were dialyzed, lyophylized immediately, and stored at $-20°C$ for subsequent starch gel electrophoresis. Samples of sera were taken at the same time for electrophoresis.

(d) Two patients were given a preparation of albumin-$^{131}I$ and $^{51}Cr$ (double-labeled albumin). Approximately 24 $\mu g$ of $^{131}I$ and 72 $\mu g$ of $^{51}Cr$ were administered in these studies. Blood and urine collections were performed as usual.

(e) The excretion of labeled albumin into gastric juice and bile was studied in a 25 kg female mongrel dog with a chronic gastric fistula and a Thomas cannula in the duodenum. After thyroidal blackade with iodine, approximately 100 $\mu g$ of canine albumin-$^{131}I$ was administered intravenously 10 days before study and approximately 250 $\mu g$ of $^{51}Cr$ was administered intravenously 4 days before study. On the day of the experiment, the animal was fasted and placed in a harness.

The fasting gastric juice was discarded and the stomach washed out with a potassium phosphate buffer (pH 8.0). Subsequently, 0.5 ml of acetylcholine in 20 ml of buffer was instilled into the stomach to induce a heavy mucus secretion. We collected the gastric secretion into a chilled container for the next 60 min, using instillation of the phosphate buffer to assist recovery. The gastric juice was frozen immediately on completion of the collection, at which time the pH was still 8.0. After cathe
erization of the bile duct through the Thomas cannula, we collected bile into chilled containers for about 1 hr. When bile flow decreased, a further separate collection was obtained, following secretin stimulation of bile flow.

All specimens of bile and gastric juice were dialyzed in the cold, lyophylized, and stored at $-20°C$ for later starch gel electrophoresis. One portion was also precipitated with 10% trichloroacetic acid; the precipitate was washed and then taken up in 80% acetone and kept for counting. Another portion was dialyzed in the cold, and the contents of the dialysis bag and aliquots of the dialysate were kept for counting.

Blood was taken into heparinized syringes at the beginning of the experiment and centrifuged, and the plasma was frozen for later electrophoresis.

Calculations

Plasma volume, total albumin turnover, and total exchangeable albumin (TEA) were calculated from the $^{131}I$ data by a modification of the methods of Berson, Yalow, Schreiber, and Post (15) and Steinfeld, Davidson, Gordon, and Greene (16).

A summary of these calculations follows.

1. Total counts administered. Weight of labeled albumin (g) injected $\times$ cpm per g.
2. Plasma activity at zero time ($T_o$) was extrapolated from activity in plasma samples collected between 10 and 20 min.
3. Plasma volume (PV) in ml = total counts administered/cpm per ml at $T_o$.
4. Total circulating (intravascular) albumin (TIA) = PV $\times$ plasma albumin concentration (g per 100 ml) $\times$ 1/100.

These studies were performed by courtesy of Dr. Frank Brooks, University of Pennsylvania Hospital, Philadelphia, Pa.
5. Plasma albumin half-life (t1/2): Time in days for 50% reduction in radioactivity determined from linear portion of semilog plot of plasma activity.

6. Fractional degradation rate (per cent) = 0.693 × 100/t1/2.

7. The distribution of albumin between the intravascular and extravascular spaces was determined from the intercept of the linear portion of the semilog plot of plasma activity with the ordinate.

8. Total exchangeable albumin (TEA) = TIA × 100/per cent albumin intravascular.

9. Total daily albumin turnover (g) = fractional degradation rate × TEA.

The portion of the total albumin catabolism occurring in the gastrointestinal tract was estimated from the 51Cr data as follows:

1. Plasma activity at zero time T0 and plasma volume (PV) in ml were calculated as illustrated above for the 131I component.

2. Mean daily 51Cr specific activity (mean SA). The albumin-51Cr plasma activity expressed as a percentage of administered dose was plotted on a semilog scale against time in days. Along the linear portion of the curve the per cent dose remaining intravascularly at the midpoint of each day was estimated.

Mean SA (cpm per g of albumin) = total cpm administered × per cent dose remaining intravenously/TIA × 100.

3. Exogenous albumin turnover. For this calculation a 24 hr delay between the excretion of the albumin-51Cr isotope in the lumen of the gut and its appearance in the fecal collection was assumed unless otherwise indicated by the presence of diarrhea. Thus, the 51Cr activity of each day’s stool was compared with the plasma specific activity of the preceding day. This manner of estimation is valid only after equilibration between the intra- and extravascular spaces has taken place. The period between days 6 through 12 was generally found to be the most satisfactory collection period.

Exogenous albumin turnover (g of albumin per 24 hr) =
total cpm for daily stool/mean SA for preceding day.

4. Endogenous albumin turnover = total daily albumin turnover − exogenous albumin turnover.

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**Fig. 1.** 51Cr-labeled albumin disappearance curve and fecal excretion in a normal subject. Fecal excretion calculated from the specific activity of mean plasma 51Cr activity from the previous day.
**Results**

After a single intravenous injection of albumin-$^{51}$Cr, there was very rapid loss of plasma activity which became linear after 6 days (Fig. 1). Up to 8% of the $^{51}$Cr activity disappeared from the plasma between the 10 and 20 min blood samples. For accurate plasma volume determinations plasma activity was extrapolated to zero time. With this correction, albumin-$^{125}$I and $^{51}$Cr plasma volumes varied by less than 5%. The albumin half-life calculated from the linear portion of the $^{51}$Cr plasma decay curve was 6-8 days, a figure less than half that measured with iodinated albumin.

Within 4 days, more than 85% of the initial $^{51}$Cr plasma activity had escaped from the intravascular space. This was not accounted for by appearance of $^{51}$Cr in the urine or feces. As seen in Fig. 1, the per cent of the administered dose retained in the body showed only a gradual decline throughout the duration of the study which suggested a significant extravascular accumulation of $^{51}$Cr. External monitoring revealed that the concentration of isotope over the liver exceeded that over the precordium within 1 hr and reached a plateau after 24 hr (Fig. 2). Splenic uptake was less rapid and did not exceed precordial values until 6 hr after injection and continued to rise for 48 hr. Thereafter, the radioactivity in both organs increased only slightly for the 11 day duration of the study. Despite the rapid escape of labeled albumin from the intravascular compartment, less than 3% of the $^{51}$Cr activity was dialyzable and greater than 97% was precipitable with TCA before injection. Therefore, little free $^{51}$Cr was present in the material administered. The rapid sequestration of $^{51}$Cr could be explained either by elution from the protein of weakly bound chromium, or by the reticuloendothelial uptake of labeled but denatured protein.

**Special studies**

The distribution of $^{51}$Cr radioactivity among plasma proteins after a single large intravenous dose of albumin-$^{51}$Cr in one patient is illustrated in Fig. 3. In the 15 min sample, the radioactivity was detected throughout the electro-

![Fig. 2. Scintillation probe scanning after $^{51}$Cr-labeled albumin administration in a normal subject.](image-url)
phoretic strip with only 60% being located in the albumin band. Within 24 hr, 84% of activity was detected in the plasma albumin fraction, while the remainder was present in the region of the $\alpha_2$- and $\beta$-globulins. By the 6th and 7th days, over 80% of the activity was consistently detected in the albumin band. The remaining protein bound radioactivity was found to be associated with the $\beta$-globulin fraction. This information, coupled with the very rapid fall-off in plasma activity after injection, suggested elution and clearing of weakly bound $^{51}$Cr. As it is known that heat or radiation denatured albumin-$^{125}$I (17, 18) and in experimental animals albumin-$^{51}$Cr (19) is rapidly deposited in the liver, it is possible that changes induced by the labeling procedure or from the presence of $^{51}$Cr atoms on the albumin molecule might contribute to its altered biologic behavior. Therefore, a batch of albumin-$^{125}$I was subsequently also labeled with $^{51}$Cr by the method of Waldmann (7) and administered intravenously to two subjects. It is evident from Fig. 4 that the plasma decay and renal excretion of $^{125}$I isotope differed markedly from $^{51}$Cr isotope. The initial disappearance rate of plasma $^{125}$I using the double-labeled albumin was more rapid than that for albumin-$^{125}$I not relabeled with $^{51}$Cr. In fact, only 17.5% remained in the plasma after 96 hr compared with over 30% for albumin-$^{125}$I itself. Equilibration occurred after 6-7 days and the half-life of the albumin-$^{125}$I remaining intravascularly was almost normal (13.2 days). Renal excretion of $^{125}$I label was rapid and the slope of $^{125}$I remaining in the body ($-4.055$) differed only slightly from that for plasma decay ($-4.68$). Initial albumin-$^{51}$Cr plasma disappearance was very rapid, and after equilibration the half-life ($t_1 = 6.6$ days) did not differ from that for albumin-$^{51}$Cr alone. Thus, not all the protein was biologically altered, as albumin molecules labeled with $^{125}$I behaved very differently from those labeled with $^{51}$Cr despite the very heavy $^{51}$Cr labeling of the preparation. This would suggest that the conditions of manufacture of the $^{51}$Cr isotope do not necessarily alter the biologic properties of all albumin molecules but rather that the labeling was uneven with some molecules being heavily labeled and as a result greatly denatured.
The preceding results imply that the rapid loss of \(^{51}\text{Cr}\) from the intravascular space is the result of biologic clearing of eluted \(^{51}\text{Cr}\) and denatured labeled protein. Therefore, if the specific activity of the \(^{51}\text{Cr}\) remaining in the plasma is to be used to estimate the exogenous albumin catabolism, the specific activity of albumin-\(^{51}\text{Cr}\) in the intra- and extravascular space should be comparable. A patient with chylous thoracic effusion was given the mixture of albumin-\(^{125}\text{I}\) and \(^{51}\text{Cr}\) shortly after a thoracentesis removed as much fluid as possible. When the radioactivity in the plasma and thoracic effusion was measured 18 days later (Table I) the ratio of albumin specific activity between these isotopes in the intravascular fluid and chyle showed close agreement. Similarly, a patient with the "nephrotic syndrome" excreting in the urine 6–8 g of albumin daily was given the two labeled albumin preparations intravenously. Specimens of urine and serum were separated by starch gel protein electrophoresis on the 4th day after administration. Of the \(^{125}\text{I}\) label, over 97% in the serum and over 91% in urine was detected in the albumin fraction. Of \(^{51}\text{Cr}\), 84.5% and 77% of the label were found in the albumin fraction of serum and urine, respectively. It is apparent from Table II that the relative specific activities of the two labeled albumin fractions in the urine closely paralleled that in the serum.

Also of importance were studies of the distribu-

<table>
<thead>
<tr>
<th>Albumin specific activity</th>
<th>Albumin concn.</th>
<th>(^{125}\text{I})</th>
<th>(^{51}\text{Cr})</th>
<th>(^{125}\text{I})/(^{51}\text{Cr}) ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/100 ml</td>
<td>cpm/g</td>
<td>cpm/g</td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>3.30</td>
<td>2980</td>
<td>725</td>
<td>4.12</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>3.15</td>
<td>3360</td>
<td>780</td>
<td>4.30</td>
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</table>
tion of labeled albumin in intestinal tract secretions. These were performed on the gastric mucus and bile of a dog. On the day of the experiment, over 99% of 125I label and 89.6% of the 51Cr label in the plasma were found in the albumin fraction. Essentially all the remaining chromium label was found in the β-fraction of plasma protein. Of the total activity in bile, 88% of the iodine label was dialyzable and only 7% was precipitated by trichloroacetic acid. In contrast, less than 10% of the chromium label was dialyzable and 90% was similarly precipitable (Table III). Electrophoresis of bile concentrated by dialysis revealed that 94% of 125I and 76% of 51Cr radioactivity was in the albumin fraction. In gastric juice, 99% of the iodine label was not trichloroacetic acid precipitable and was dialyzable, whereas less than 6% of the chromium label was dialyzable. On protein electrophoresis, over 99% of 125I and 92.7% of 51Cr were present in the albumin fraction. Thus, the major portion of 125I activity in both bile and gastric juice was not found in the protein fraction, whereas most 51Cr activity was protein bound and was associated with the albumin band. Analysis of the specific activities of the electro-

TABLE II

<table>
<thead>
<tr>
<th>Nondialyzable protein-bound radioactivity in albumin fraction</th>
<th>Albumin specific activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>125I</td>
</tr>
<tr>
<td>Plasma</td>
<td>97.0</td>
</tr>
<tr>
<td>Urine</td>
<td>91.0</td>
</tr>
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</table>

phoretically separated albumin fractions revealed quite close agreement in the chromium and iodine isotopic labeling in plasma, bile, and gastric juice (Table III). Thus, the chromium label appearing in these fluids closely reflects the excretion of iodine-labeled albumin.

Metabolic studies in normal human subjects

The biological behavior of albumin-125I and of albumin-51Cr is compared in Fig. 5 when these preparations are mixed and injected intravenously. Albumin-125I leaves the intravascular space less rapidly than 51Cr activity and from 10 to 20 min after injection the plasma activity of 125I remains essentially constant. Thus, plasma volumes may be accurately determined from one or two plasma specimens in this time period. After 4 days, over 30% of the initial plasma activity is still detectable in the circulation. The fraction of the administered dose of albumin-125I retained in the body (Fig. 5B) parallels the plasma activity curve (Fig. 5C), which indicated that the iodine isotope is not accumulating in any extravascular site but is being rapidly excreted from the body.

The daily fecal excretion of albumin calculated from 51Cr and 125I data in this subject is shown in the lower part of Fig. 5. During the first 4 days of the study, a small and very variable amount of isotope appears in the stools. Although significant daily variations occur thereafter, a plateau of fecal excretion of 51Cr is evident when 4-day pooled samples on days 5–8 and 9–12 are compared. Therefore, all calculations of the excretion of albumin into the intestinal tract reported here were based on fecal collections between the 5th and 12th days after administration of the albumin preparations. Enteric protein losses calculated from 125I data give consistently lower values than the 51Cr data and were a reflection of variable digestion of “exuded” protein and absorption of secreted and hydrolyzed iodides.

The results of complete studies in six normal subjects using the double isotope technique are presented in Table IV. The biologic behavior of albumin-125I is quite similar to that of albumin-125I, as these data agree with published figures for half-life, total exchangeable albumin, and turnover rate (20–22). Based upon the results of the albumin-51Cr data, less than 10% of daily albumin catab-
oism occurs in the gastrointestinal tract under normal conditions.

Metabolic studies in patients with gastrointestinal symptoms

The levels of serum albumin and the results of the albumin turnover studies are presented in Table V. In no patient was the circulating albumin concentration normal solely because of a contracted intravascular space nor low solely as a result of an expanded circulation.

Patients with a normal serum albumin concentration and no excessive enteric loss. These four subjects were studied because they had gastrointestinal disorders that might have resulted in excessive gastrointestinal protein loss and in whom the serum albumin might have remained within normal limits because of increased albumin synthesis. In fact, the albumin half-life ($t_{1/2}$) was within normal limits ranging from 14.5 to 15.4 days. The fractional catabolic rate and total catabolic rate did not differ significantly from the results in our normal patients and less than 10% of total albumin catabolism occurred in the gastrointestinal tract.

Patients with decreased serum albumin and no excessive enteric loss. The three patients in this group had severe cirrhosis of the liver without ascites. The serum albumin concentration and total exchangeable albumin was low. The prolonged half-life reflected a decreased total catabolic rate. In these patients the quantity of albumin appearing in the gastrointestinal tract was also low, still representing less than 10% of total catabolism.

A patient with normal serum albumin and excessive enteric loss. This patient with abdominal lymphomatosis lost into the gastrointestinal tract 2.6 g of albumin per day which represented 16%
of total daily catabolism. Despite this excessive enteric albumin loss, the plasma half-life was at the lower limits of normal. The fractional catabolic rate of 4.87% per day appears to be within normal limits because of a greatly expanded extravascular space. However, the catabolic rate of the intravascular pool was greatly elevated in this patient. In addition, a high total daily albumin catabolism of 253 mg/kg was measured, and, even after subtracting enteric losses, endogenous catabolism also was increased. In this patient, therefore, there was evidence for increased albumin breakdown both in the gastrointestinal tract and in the body. An increased rate of albumin synthesis compensated for these losses and maintained a normal serum albumin concentration and total exchangeable albumin.

**Patients with decreased serum albumin and excessive enteric loss.** The gastrointestinal losses of albumin in the patients in this group ranged from 13 to 41 mg/kg per day and from 15 to 31% of total albumin catabolism. In addition to excessive enteric losses, calculation of the rate of endogenous catabolism in three of these five patients (patients 9, 11, 12) was below the lower limits of normal. The endogenous catabolism in patient 10 appears to be diminished because of the very low TEA; however, most of the albumin is in the extravascular space so that the fraction of the intravascular albumin catabolized is actually quite high. The prolongation of plasma half-life in patients 9 and 10 was much shorter than might have been expected for the concentration of serum albumin and level of total exchangeable albumin. The hepatic synthetic rate failed to be increased to maintain the albumin concentration. In patients 11 and 12 the albumin half-life was found to be even shorter than in our normal subjects which suggested that albumin synthesis was even less able to compensate for the gastrointestinal losses and endogenous catabolism in order to maintain the total exchangeable albumin pool of 2.3 and 1.75 g/kg, respectively. At the same time, the fractional catabolic rate was greater than normal. In contrast, the patient with amyloidosis was noted to have, in addition to the enhanced enteric loss, a rate of endogenous albumin catabolism which would be expected in a subject with a normal intravascular and total body albumin pool yet with
TABLE V
Albumin turnover of subjects with gastrointestinal symptoms

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Wt</th>
<th>Serum albumin</th>
<th>Plasma volume</th>
<th>t_1</th>
<th>Intra-vascular albumin</th>
<th>Total exchangeable albumin pool</th>
<th>FCR*</th>
<th>Total mg/kg/day</th>
<th>Endogenous mg/kg/day</th>
<th>Exogenous mg/kg/day</th>
<th>Daily turnover in feces</th>
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<tbody>
<tr>
<td>Mean values</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>kg</td>
<td>g/100 ml</td>
<td>ml/kg</td>
<td>days</td>
<td>g/kg</td>
<td>%/day</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A. Normal serum albumin, normal gastrointestinal loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>Postgastrectomy “blind loop”</td>
<td>59.0</td>
<td>3.5</td>
<td>48</td>
<td>14.5</td>
<td>1.68</td>
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<td>4.78</td>
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<td>194</td>
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<td>Chronic pancreatitis steatorrhea</td>
<td>60.0</td>
<td>3.4</td>
<td>45</td>
<td>15.0</td>
<td>1.53</td>
<td>3.84</td>
<td>4.60</td>
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<tr>
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<td>Chronic pancreatitis</td>
<td>52.3</td>
<td>3.6</td>
<td>31</td>
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<td>1.12</td>
<td>3.43</td>
<td>4.50</td>
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<td>151.5</td>
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<td>4</td>
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<td>181.0</td>
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* FCR, fractional catabolic rate.
a serum albumin of only 1.9 g/100 ml. This relatively high rate of endogenous catabolism accompanied by failure to increase albumin synthesis was the major factor producing the extreme hypalbuminemia in this patient.

The relationship between endogenous catabolic rate and the level of total exchangeable albumin is shown in Fig. 6. For this purpose, the results of studies in the patients presented in this report, excluding patients with the nephrotic syndrome (patients 14 and 15) and with abnormally excessive endogenous catabolism (patient 13), were used. The endogenous catabolic rate correlated better with total exchangeable albumin ($r = 0.90$) than with the concentration of serum albumin ($r = 0.80$).

Studies in nephrosis

Several problems in attempting to calculate data in the two patients with the nephrotic syndrome were encountered. Urinary losses of albumin were so rapid that a significant portion of the labeled albumin was excreted before equilibration could occur. The data was recalculated by extrapolating the decay curve of albumin-$^{125}$I retained in the body to time zero and utilizing this figure as the dose administered for the other calculations. In addition, the slope of the decay curve representing per cent of label retained in the body was shallower than that for plasma decay, indicating "sequestration" of labeled albumin at some extravascular location. A nonhomogeneous extravascular albumin pool had been suggested in other experimental studies. In aminonucleoside nephrotic rats, for example, the specific activity of the ascitic fluid albumin was about twice that of the mean extravascular pool (23). In nephrotic children, the average specific activity of extravascular albumin was ten times that of plasma and a 30-fold increase was noted in the edema fluid (24). Despite problems in accurate calculation of albumin turnover in two patients, the quantity of albumin metabolized in the gut was extremely small and well within the range of normal. These results do not agree with those reported using PVP-$^{125}$I (25, 26) in adults and children.

Discussion

There is good evidence that steady-state studies employing albumin labeled with iodine radioisotopes give a reasonably accurate measure of human albumin catabolism (27, 28). Albumin labeled with $^{125}$Iodine was chosen for these studies because it emits a single peak of low energy gamma particles (0.036 Mev) which can be easily measured and distinguished from higher energy gamma sources. The simultaneous use of more than one isotope thus becomes practical. Additional advantages of this isotope are a half-life of 57 days and a reduced dosage of radiation to the body (see Appendix). Because of the weak gamma energies released from disintegration of $^{125}$I, quenching owing to self-absorption may be a problem in the use of $^{125}$I-labeled materials (29). In the present study, the counting efficiency for $^{125}$I was constant in the body fluids and secretions investigated. The trace amounts of potassium iodide used to block thyroidal uptake of iodide did not appear in sufficient concentration in any of these fluids to decrease $^{125}$I counting efficiency.
Although albumin-$^{125}$I has not been extensively used in clinical metabolic studies, our results in normal patients indicate that the preparation gives results identical with albumin-$^{125}$I for a study period of 14–17 days. Since all the studies presented were carried out while the patient remained in a steady state, the rate of total albumin catabolism and rate of albumin synthesis have been equated.

Various techniques have been devised to assess the role of the bowel in albumin turnover. Results are variable and indicate that from 10 to 75% of normal daily albumin catabolism takes place in the gut. One experimental approach compared the rates of body albumin catabolism before and after surgical removal of portions of the gastrointestinal tract. After enterectomy, the reduction in albumin catabolism ranged from 0 to 20% (30–32). Using loops of bowel isolated at surgery, we concluded that the gastrointestinal tract was a major site of albumin catabolism in animals (3, 33–35) and in humans (3). Several major criticisms are raised that apply to all these experimental studies. Collections of intestinal secretions were uniformly obtained within 3 days and usually within 1 day of the intravenous administration of the labeled albumin. The biological “clearing” of poorly labeled or denatured albumin and equilibration between intravascular and extravascular spaces would not have been complete by this time. These authors also based their calculation of intestinal protein losses upon circulating radioactivity at the time of the experiment. Although the observations of Pearson, Veall, and Vetter (36) in nephrotic patients have suggested that total albumin catabolism was related to the concentration of albumin-$^{125}$I within the plasma and thus occurred close to the intravascular space, this conclusion may not apply for albumin that must be excreted in bile and pancreatic secretion or otherwise cross the gastric and intestinal interstitial spaces before entering the gut lumen. This suggestion is supported by the observations in our human studies and those of Wetterfors (3) in dogs that maximal fecal output of radioactivity occurred after equilibration of albumin had occurred. In addition, previous experimental studies were all performed under anesthesia and with a varying degree of trauma to the gut. Anesthesia itself has been shown to influence splanchic blood flow (37), gastrointestinal function (38), and probably permeability. Surgical manipulation and perfusion techniques undoubtedly added to these changes. Increased albumin catabolism has been noted after surgery, and enhanced intestinal losses have been demonstrated (39, 40).

Several isotopic techniques that attempt to evaluate albumin loss into the gastrointestinal tract in normal subjects and patients with increased albumin catabolism have been described. $^{131}$Iodinelabeled albumin is not satisfactory because any proteins entering the gut may be rapidly hydrolyzed by luminal proteolytic enzymes. As the isotope is readily reabsorbed and does not appear in the feces, Jeejeebhoy and Coghill introduced the use of an orally administered ion exchange resin to trap the iodide in the lumen of the gut (41). The recent demonstration that iodide trapping by the resin is variable and that free iodide secreted into the gastrointestinal tract would be readily absorbed by the resin (42–44) has discredited this method.

Polyvinylpyrrolidone labeled with $^{125}$iodine was developed as a qualitative indicator of excessive enteric protein loss (45). This high molecular weight polymer cannot be used for quantitative measurements because it has been found to be unstable in vitro, an unpredictable amount of the labeled iodine may be released in the gut in vivo, and it is not handled physiologically like a protein when injected intravenously. Similar reasoning would apply to the use of $^{59}$Fe-labeled iron dextran (46).

Because of the disadvantages of the iodine label, other isotopes which are neither actively secreted nor absorbed by the gut have been evaluated. $^{64}$Copper-labeled ceruloplasmin has been advocated for quantitative measurements of gastrointestinal protein loss. The results of studies in normal subjects and dogs indicate less than 20% of the daily ceruloplasmin turnover takes place in the gut (47). However, ceruloplasmin metabolism does not mirror albumin metabolism since 70% of this protein is located intravascularly and its half-life is 6.5 days. Although $^{95}$niobium may be firmly bound to albumin and appears to give a reliable index of protein exudation into the gut, it is unsuitable for albumin turnover measurements (48).
Chromium chloride has long been known to label serum proteins readily (49), and Waldmann introduced albumin-\(^{51}\)Cr as a technique to measure increased interstitial protein loss (7). The present studies confirm that albumin-\(^{51}\)Cr cannot be used to measure total albumin catabolism. The rapid accumulation of \(^{51}\)Cr activity in the liver has been demonstrated in experimental animals (19) and is most likely due to the accumulation of eluted \(^{51}\)Cr and uptake of labeled but denatured protein. Although the biological half-life of the "sequestered" albumin-\(^{51}\)Cr was quite long (80–100 days), the calculated radiation dose to the liver, using the assumptions outlined in the Appendix, was 0.6 rad, a figure well within the range of accepted standards of safety.

Based on his studies in the dog, Wetterfors has criticized the use of albumin-\(^{51}\)Cr as a measure of intestinal protein losses (3). The preparation used in his studies was described as "heavily denatured" so that the quality of his material must be seriously questioned. The albumin-\(^{51}\)Cr used in our human studies was chemically and electrophoretically quite satisfactory. Furthermore, in the preparation of this material all albumin molecules cannot have been grossly altered because the biological properties of much of the albumin-\(^{125}\)I remained relatively normal when albumin-\(^{125}\)I was heavily relabeled with \(^{51}\)Cr (double-labeled albumin). With the use of a mixture of albumin-\(^{125}\)I and albumin-\(^{51}\)Cr our studies in a dog clearly showed significant secretion of both isotopes into the stomach and into bile, in contrast to the findings of Wetterfors (3). Of the \(^{125}\)I activity in both secreta, the majority was not protein bound and probably represented secretion of the free iodide. Very little free \(^{51}\)Cr activity was detected, and most of the protein-bound \(^{51}\)Cr activity was present in the electrophoretically separated albumin fraction.

The double isotope method described estimated the gastrointestinal secretion of albumin by measuring the fecal appearance of \(^{51}\)Cr and relating it to the corresponding \(^{51}\)Cr plasma specific activity. The intestinal loss could then be compared with total albumin catabolism concurrently measured with the albumin-\(^{125}\)I tracer. In order to justify such calculations certain criteria had to be fulfilled.

(a) The fecal excretion of \(^{51}\)Cr reflected albumin-\(^{51}\)Cr appearance in the intestine since complete recovery of \(^{51}\)Cr in the feces was achieved within 2 days of cessation of feeding when albumin-\(^{51}\)Cr was fed in daily amounts of 160 mg. In addition, there was no evidence for the excretion of nonprotein-bound \(^{51}\)Cr into the stomach and bile of a dog.

(b) Considerable labeling of plasma proteins other than albumin was detected within 15 min after administration of the labeled material. However, after 6 days over 85% of the plasma activity was in the albumin fraction with the remainder appearing in the region of the \(\beta\)-globulin and most likely attached to transferrin (50). The intravascular distribution of transferrin is similar to that of albumin (53). Since transferrin's molecular weight of less than 86,000 (54) is similar to that of albumin (67,000) the size of "pores" through which protein normally enters the gut should minimally influence the relative transfer rates of these two proteins. Furthermore, with protein-losing enteropathies, loss of protein appears to be a bulk phenomenon independent of molecular size or configuration (55). Therefore, correction in the calculation for the small amount of activity not on albumin was unnecessary as albumin losses were calculated from a ratio of plasma to stool activity.

(c) Although the majority of albumin catabolism occurs in a compartment closely related to the intravascular compartment, this may not hold for albumin that must gain entrance to the intestinal lumen. The mechanism of plasma protein secretion into the gut is unknown, but the source is not the intravascular pool (56) and is most likely interstitial and lymphatic protein. Therefore, the specific plasma activity should closely reflect the specific activity of the albumin isotopes in the extravascular space. Studies of thoracic fluid proteins of a patient with a rapidly accumulating chylous thoracic effusion and of the urine protein in a nephrotic patient confirmed this hypothe-
sis. This indicated that albumin-$^{51}$Cr did not undergo further rapid degradation during its passage into these fluids. Furthermore, the relative specific activity of $^{51}$Cr- and $^{125}$I-labeled albumin separated from canine bile and gastric juice, within the accuracy of these methods, closely reflected plasma activity. Thus, it seemed reasonable to assume that secreted $^{51}$Cr-labeled albumin accurately reflected that proportion of total exchangeable albumin degraded in the gastrointestinal tract.

(d) Previous studies of fecal $^{51}$Cr losses utilized the first 4 days after intravenous administration of the labeled material for estimation of intestinal albumin losses (7). In addition to the extensive labeling of nonalbumin plasma proteins, the present study also showed that fecal $^{51}$Cr excretion was very variable during the first 4 days. Any estimation of fecal albumin losses should await reasonable equilibration of the injected albumin isotope with extravascular albumin spaces (56). Such equilibration usually does not occur for 5–7 days. During this period, biological clearing of the majority of the $^{51}$Cr not associated with albumin also takes place. For these reasons, the estimation of gastrointestinal albumin losses in the present study was made between 6 and 12 days and this correlates well with the maximal appearance of albumin in the feces.

Calculations based on the double isotope technique described in this report indicate that less than 10% of albumin catabolism normally occurs in the gastrointestinal tract. This agrees with very recent observations from other laboratories with different techniques (47, 48, 56, 57). The advantage of the double isotope method described lies in its ability to demonstrate multiple mechanisms responsible for hypoalbuminemia in an individual patient. This is most clearly demonstrated in studies of patients in Group D. In the patient with amyloidosis (patient 13), for example, the calculated endogenous catabolism of albumin (149 mg/kg per day) was within the limits found in normal patients despite a greatly reduced serum albumin concentration and total exchangeable albumin. Although this patient lost 1.6 g of albumin into the gut per day, the major mechanism for the low albumin level undoubtedly was the excess endogenous catabolism. Other patients in this group showed lower levels of endogenous catabolism in conjunction with greater gastrointestinal losses. Thus, the rate of albumin catabolism was accelerated and not compensated by increased albumin synthesis. In contrast, an increase in hepatic synthetic rate sufficient to maintain a normal serum albumin can occur in the face of exaggerated losses. Patient 8 lost 2.6 g of albumin into the gut daily, representing over 16% of total daily albumin catabolism. An increase in the albumin synthetic rate compensated for these losses.

Excessive albumin secretion into the bowel may occur through a denuded mucosa or because of lymphatic abnormalities (58–60). How albumin normally enters the gastrointestinal tract is poorly understood. The mechanisms regulating albumin metabolism are similarly obscure. Most evidence favors a first order process for catabolism of albumin (61, 62) in which the amount catabolized is a fraction of the albumin concentration. The data in Fig. 6 are consistent with this process. Although the most striking reductions in albumin catabolism are seen in analbuminemic subjects (63), an obvious decrease is seen in our cirrhotic patients. Matthews (62) has experimentally shown a similar phenomenon by plasmapheresis in rabbits. In some pathological conditions this normal compensatory mechanism may not be operative. Despite their very low TEA, our data in two nephrotics and a patient with amyloidosis indicated that the endogenous catabolism proceeded at a rate only slightly less than that found in our normal subjects. This has been previously suggested in nephrotics in studies in which intestinal losses of albumin were not measured (24, 64). Factors regulating albumin synthesis are also largely unknown. The genetic information of the liver cell allows control of the composition and the rate of protein production (65), but has no control over its losses. Some feedback mechanism must trigger a compensatory increase in synthetic rate. Although the intracellular concentration of albumin might change in response to decreased extravascular albumin, this possibility has not been investigated. It is possible that the presence of a low molecule weight metabolite of albumin which could readily pass from extracellular to intracellular fluids might stimulate a change in the rate of albumin synthesis (66). An alternative method of regulat-
Ming albumin synthesis could be achieved by altering the number of hepatic parenchymal cells that participate. Such an adaptive mechanism may be operative in the liver of nephrotics. A transfer of free amino acids from muscle to liver has been shown to occur in experimental nephrosis (67), and, in addition, the liver enlarges with a parallel rise in hepatic DNA and RNA (68). Although this suggests that the number of cells synthesizing protein have increased, possible changes in nuclear ploidy populations have not been ruled out.

Successful treatment of some forms of excessive gastrointestinal loss have been described (3). It has been suggested that alterations in dietary fat can reduce the protein losses in intestinal lymphangiectasia (69, 70). The application of the double tracer technique described should provide valuable information about the effectiveness of treatment for exudative enteropathy.

Appendix

Dosimetric method

Locally absorbed dose and gamma ray dose, calculated by the method of Loevinger, Holt, and Hine (71), and mass, using standard criteria (72).

Dose calculations for ¹³¹I-labeled albumin

Assumptions

1. Administered dose is 30 μc.
2. Patient's thyroid is blocked by prior administration of iodide and significant accumulation does not occur in any specific organ. ¹³¹I released is quantitatively excreted in the urine. The critical organ is blood.
3. The ¹³¹I labeled to albumin is distributed between the intravascular and extravascular spaces. The extravascular space, which contained the same albumin concentration as whole blood, is approximately 1.5 times as large as the plasma volume. The hematocrit is 40%.
4. The biological half-life of the ¹³¹I-labeled albumin is 20 days and the physical half-life is 60 days so that the effective half-life is 15 days. Equilibration is assumed to take place immediately, since the dose from the higher concentration in blood before equilibration is small compared to the total dose.

Dose to blood

The blood is irradiated (a) by locally absorbed X-rays and electrons arising from disintegrations within the blood itself, and (b) by photons arising from disintegrations at more distant sites. (a) Locally absorbed dose was calculated using the data of Smith, Harris, and Rohrer (73). They assumed that energy (Eₕ) was deposited within a radius of 1 cm and used this figure (Eₕ = 0.0208 Mev), recognizing that it represents an overestimate of dose to blood.

(b) X- and γ-ray dose. Because of the low energies of ¹³¹I, it is necessary to assume that the ¹³¹I photon energy is totally absorbed in the body. The average dose to the blood from gamma and K X-rays would be approximately the same as the average dose to the total body from these photons. The energy absorbed would be the sum of 27.4 kev × 1.13 (photons per disintegration), 31.1 kev × 0.24 (photons per disintegration), and 35.4 kev × 0.07 (photons per disintegration), or 40.9 kev (70). This value is used in place of Eₕ in the "locally absorbed dose" formula.

Calculations

\[ Dₕ = 73.8 \times (0.0208 \text{ Mev}) \times \frac{30 \mu c}{10,260 \text{ g}} \times (15 \text{ days}) = 0.067 \text{ rad.} \]

\[ Dγ = 73.8 \times (0.0409 \text{ Mev}) \times \frac{30 \mu c}{70,000 \text{ g}} \times (15 \text{ days}) = 0.019 \text{ rad.} \]

Total accumulated dose = 0.086 rad.

Dose calculations for ⁶⁷Cr-labeled albumin

Assumptions

1. Administered dose is 100 μc.
2. Of the ⁶⁷Cr-labeled albumin injected intravenously, 60% accumulates in the liver and is not excreted rapidly. The activity in the liver as a function of time is approximated by a single exponential curve with an intercept of 80 μc and an effective half-life equal to the physical half-life (Tᵢ = Tₑ = 28 days).
3. Of the ⁶⁷Cr, 20% is assumed to be deposited in the spleen. An initial activity of 20 μc and an effective half-life of 28 days are assumed.
4. The geometrical factor \( g \) for the liver is that for a unit density sphere with a volume of 1700 cm³ (radius = 7.4 cm). Thus, \( g = 70 \text{ cm.} \)
5. The geometrical factor for the spleen is that for a unit density sphere with a volume of 150 cm³ (radius = 3.3 cm). Thus, \( g = 31 \text{ cm.} \)
6. The total local energy deposition per disintegration, \( Eₕ \), is 0.0061 Mev, and the specific gamma ray constant is 0.15 röntgens × cm²/mc = hr (73). The conversion factor from röntgens to radi is not significantly different from 1 for this application.

Dose to liver

\[ Dₕ = 73.8 \times (0.0061 \text{ Mev}) \times (60 \mu c / 1700 \text{ g}) \times (28 \text{ days}) = 0.45 \text{ rad.} \]

\[ Dγ = 0.0346 (0.15) (70 \text{ cm}) \times (60 \mu c / 1700 \text{ g}) \times (28 \text{ days}) = 0.36 \text{ rad.} \]

Total dose to liver = 0.81 rad.

Dose to spleen

\[ Dₕ = 73.8 \times (0.0061 \text{ Mev}) \times (20 \mu c / 150 \text{ g}) \times (28 \text{ days}) = 1.7 \text{ rad.} \]

\[ Dγ = 0.0346 (0.15) (31 \text{ cm}) \times (20 \mu c / 150 \text{ g}) \times (28 \text{ days}) = 0.6 \text{ rad.} \]

Total dose to spleen = 2.3 rads.
Dose to blood

The blood dose is estimated to be of the order of 0.05 rad.

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