STUDIES ON ALBUMIN SYNTHESIS: THE EFFECTS OF DEXTRAN AND CORTISONE ON ALBUMIN METABOLISM IN RABBITS STUDIED WITH ALBUMIN-\textsuperscript{131}I \*  

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Following plasmapheresis, the depressed serum albumin concentration rapidly returns to normal (1) indicating alterations either in albumin synthesis or degradation. Both dextran administration (2-6) and elevation of serum globulin levels produced by means of hyperimmunization (7, 8) are associated with hypoaosmotic regulatory mechanism has been suggested as responsible for the reciprocal changes in serum proteins observed after hyperimmunization (7, 9). If such a mechanism does exert control over the concentration of serum albumin, alterations of albumin metabolism either in the rate of synthesis or in the rate of degradation might be expected when osmotically active molecules other than albumin are added to the circulation. The present study represents an attempt to define, more specifically than heretofore reported, the changes in albumin metabolism resulting from such a procedure. Dextran was administered to rabbits to depress albumin concentration. After the development of hypoaosmoticemia, the rates of albumin synthesis and degradation were studied and compared with control values. Cortisone acetate was then given to increase the rate of albumin degradation (10), and the rates of albumin synthesis were remeasured.  

METHODS  

Female rabbits were used in all studies. Animals were kept in metabolism cages and fed a standard rabbit diet. Lugol's solution was added to the drinking water daily.  

The distribution and metabolism of albumin were studied by means of 1\textsuperscript{31}I-labeled rabbit serum albumin. Assays of 1\textsuperscript{31}I in plasma, stool and urine were made for a control period of 10 to 14 days following intravenous administration of albumin-1\textsuperscript{31}I. Following the control period, 1.0 to 1.5 g of dextran (Laros, lot H., average molecular weight 188,000) dissolved in 20 ml 0.9 per cent saline was injected i.v., once daily in 10 animals. After 15 to 30 days, the animals received a second injection of albumin-1\textsuperscript{31}I while the daily dextran infusions were continued, and observations were continued for another 12 to 18 days. Six of the 10 animals were then started on cortisone acetate (3 mg per kg per day, s.c.) and dextran infusions were continued for another 9 to 14 days. At the end of this period a third injection of albumin-1\textsuperscript{31}I was made to remeasure albumin synthesis, degradation and pool size. In two other rabbits, cortisone and dextran were administered simultaneously from the beginning of the study for a period of 15 days. Two other animals were infused with 20 ml of 0.9 per cent saline for 15 and 24 days. Two of the animals receiving dextran alone were studied again with albumin-1\textsuperscript{31}I 6 and 8 weeks after the termination of the original studies to determine whether the prolonged dextran infusions had had any lasting effects on albumin synthesis. During periods of cortisone administration rabbits received 0.25 g streptomycin and 75,000 U procaine penicillin intramuscularly every other day and 5 to 8 mEq potassium chloride in the water daily, of which the animals consumed 2 to 3 mEq per day. Injections of albumin-1\textsuperscript{31}I were made into an ear vein. Five- to eight-tenths ml heparinized venous blood was obtained from the opposite ear 6 and 10 minutes after injection, at daily intervals for 1 week, and every second or third day thereafter. Blood samples taken for assay were obtained just prior to the daily injections of dextran.  

Rabbit albumin was separated from whole serum as previously described (10) and occasional lots of rabbit albumin preparation, no. 7305,\* were employed after re-

\* This material was presented in part at the meeting of the Eastern Section of the American Federation for Clinical Research on December 10, 1959. This investigation was supported in part by Grant no. A-2489 from the United States Public Health Service.  

\* Repeated injections of albumin-1\textsuperscript{31}I were made at such time intervals and dose levels that the residual activity from previous injections was negligible and did not affect the subsequent calculations.  

\* Purchased from Pentex Inc., Kankakee, Illinois.
purification. The 1\textsuperscript{st}-labeling procedure has been described previously (11). All lots of albumin-1\textsuperscript{35}S were tested in normal control animals to insure against the use of a lot that contained any significant amounts of denatured labeled protein (10).

Dextran solutions were prepared by dissolving 120 g in 1,500 ml of normal saline and filtered through a bacterial filter. Plasma dextran concentrations were determined by the method of Roe (12). Urine was tested for protein by precipitation with cold 20 per cent trichloroacetic acid.

Plasma, urine and stool samples were assayed for radioactivity in a well-type scintillation counter with a sensitivity of 9.7 \times 10^{4} cpm per \mu c 1\textsuperscript{35}S above a background of 170 cpm. Total plasma protein was determined by a micro-Kjeldahl method. Concentration of plasma albumin was determined by boundary electrophoresis with a Kern microelectrophoresis apparatus. In this method, 0.2 ml serum or plasma was diluted to 0.8 ml with Michaelis-veronal buffer at pH 8.6 and the solution was dialyzed against the buffer for 30 minutes prior to electrophoresis for 40 minutes at 80 v. The presence of dextran did not interfere with the determination, since the albumin fraction remained constant at dextran concentrations ranging from 0.1 to 2.0 g per 100 ml. Dextran itself resulted in a clearly differentiated interference pattern at the initial boundary (Figure 1).

Plasma volume was determined from the space of distribution of albumin-1\textsuperscript{35}S at 6 and 10 minutes after injection. Total exchangeable albumin and the extravascular: intravascular distribution of albumin were determined as previously described (11). The rate of albumin metabolism during the control period was determined from

\begin{center}
\begin{table}
\caption{Albumin distribution *}
\label{tab:1}
\begin{tabular}{lcccccccccccc}
\hline
 & & & & & & & & & & & & \\
\hline
\hline
Weight & kg & 4.08 & 4.08 & 36.8 & 28.5 & 27.9 & 34.8 & 74.5 & 105.8 & 37.4 & 33.0 \\
 & & 3.63 & 3.86 & 38.6 & 25.8 & 37.8 & 47.2 & 94.5 & 126.5 & 40.1 & 37.4 \\
 & & 5.45 & 5.45 & 33.6 & 24.5 & 34.5 & 45.0 & 86.6 & 112.5 & 39.8 & 40.1 \\
 & & 6.66 & 6.37 & 39.0 & 32.7 & 29.1 & 35.2 & 70.4 & 90.0 & 41.4 & 39.2 \\
 & & 5.05 & 5.91 & 5.23 & 37.8 & 27.0 & 29.2 & 30.9 & 53.8 & 57.9 & 77.8 & 109.0 \\
 & & 5.08 & 4.66 & 4.32 & 37.8 & 23.8 & 18.3 & 38.0 & 41.4 & 82.5 & 100.5 & 119.0 \\
 & & 4.78 & 4.34 & 4.20 & 35.6 & 23.2 & 18.4 & 29.7 & 40.4 & 66.6 & 77.8 & 126.6 \\
 & & 5.33 & 5.00 & 4.78 & 42.3 & 29.6 & 23.0 & 24.6 & 35.2 & 69.1 & 108.2 & 137.5 \\
 & & 3.87 & 4.34 & 4.10 & 43.0 & 33.0 & 25.8 & 33.6 & 36.8 & 58.5 & 93.4 & 98.0 & 132.0 \\
 & & 4.54 & 4.34 & 4.66 & 32.0 & 25.2 & 18.5 & 35.5 & 42.8 & 59.6 & 100.0 & 122.0 & 165.0 & 36.2 \\
 & & 5.94 & 5.54 & 39.8 & 26.4 & 28.3 & 53.0 & 76.4 & 114.2 & 37.3 & 46.4 \\
 & & 5.24 & 5.13 & 36.3 & 23.6 & 33.2 & 60.5 & 86.5 & 133.8 & 38.4 & 45.2 \\
\hline
Mean value & 4.86 & 4.90 & 4.75 & 37.7 & 27.3 & 22.8 & 31.9 & 39.3 & 62.7 & 84.0 & 111.8 & 143.7 & 38.2 & 35.3 & 43.3 \\
 & ±SE & 0.9 & 1.1 & 1.5 & 1.2 & 1.6 & 3.7 & 3.1 & 3.8 & 8.8 & 0.5 & 1.0 \\
 & p Value & <0.001 & <0.001 & <0.001 & <0.001 & <0.001 & <0.001 & <0.001 & <0.001 \\
 & & Per cent change & \(N - D) / N\) & -27.6 & +23.2 & +33.1 & -7.6 \\
 & & Per cent change & \(D = (D+C) / D\) & -16.5 & +59.5 & +28.5 & +22.7 \\
\hline
\end{tabular}
\end{table}
\end{center}

* TEAS = total exchangeable albumin space. N = control study. D = dextran study. D+C = dextran and cortisone study. SE = standard error of the mean. All \(p\) values are based on comparisons between the control (N) and experiment values (D and D+C). † Rabbit 18 was studied while it received saline injections between the control and dextran study. The experimental periods, however, are compared with the initial control values.
the product of the clearance of plasma-$^{131}$I and the plasma albumin concentration. This technique has been described in detail in previous reports (10, 13, 14). It has been demonstrated that the clearance method can be applied in nonsteady state conditions (10, 13, 15). The total amount of albumin degraded over each period was obtained from the sum of the daily values of the amount of albumin degraded, as determined by the clearance method. During the control periods, the plasma albumin concentrations remained constant, and it may be assumed that steady state conditions, with respect to albumin metabolism, were satisfied, and that the quantity of albumin synthesized was equal to the quantity degraded. In previous studies the amount of albumin synthesized during an experimental period was calculated from the difference between the total amount degraded and the change in the total exchangeable albumin pool during the period. In this study the rabbits were “equilibrated” with the test substances before reinjection, and the experimental data for albumin degradation were derived from subsequent injections of albumin-$^{131}$I. Since the plasma albumin values changed only slightly following the reinjections, albumin synthesis was assumed to closely parallel albumin degradation. These observations do not permit an exact evaluation of degradation or synthesis during the period of equilibration prior to reinjection of albumin-$^{131}$I. However, the control and experimental values for albumin degradation and the changes in pool size are known and indicate the net albumin bal-

Fig. 2. Typical set of curves (Rabbit 10) showing distribution, plasma decay, and urinary excretion curves during the control period and following the administration of dextran and dextran and cortisone.

Fig. 3. Albumin distribution. The mean values (horizontal lines) and ranges (solid bars) for hematocrit value, plasma volume, total exchangeable albumin space and per cent of total exchangeable albumin located intravascularly during control, dextran and dextran and cortisone periods. See text and Table I.
ance as well as the direction of change in albumin degradation and synthesis during the equilibration period. Previous reports have dealt adequately with the use of albumin-131 as a tracer for endogenous albumin metabolism in both steady and nonsteady states (10, 11, 13, 15-19).

The significance of the differences between the mean values was determined according to the t test (20).

RESULTS

Data pertaining to albumin distribution are summarized in Table I and Figures 2 and 3. Weights of the animals showed no specific trend throughout any portion of the study. During dextran administration, mean hematocrit values declined in 12 animals by 27.6 per cent while the plasma volume increased by 23.2 per cent. Following institution of cortisone treatment in the dextran-treated animals, the mean hematocrit value decreased further by 16.5 per cent and plasma volume increased an additional 59.5 per cent. These changes in hematocrit values and plasma volume suggest a decrease in red cell mass or shrinkage of erythrocytes after dextran treatment and an increase in red cell production with cortisone treatment. However, alterations in the intravascular distribution of red cells and plasma could explain these findings as well. The mean apparent total exchangeable albumin "space" increased by 33.1 per cent on dextran treatment and a further 28.5 per cent increase was observed upon the addition of cortisone.

Significant changes in the intravascular-extravascular partition of albumin occurred. In control animals, 38.2 ± 0.5 per cent of the total albumin pool was located within the plasma space.

![Graph](image_url)

**FIG. 4.** TYPICAL ANIMAL EXPERIMENT (RABBIT 10). Following dextran administration, a slight rise in the renal clearance of plasma-131 occurred; plasma albumin concentration, albumin degradation and the exchangeable albumin pool decreased. Upon the addition of cortisone, the clearance of plasma-131 rose considerably, plasma albumin concentration rose slightly, and there was an increase in albumin degradation and the exchangeable albumin pool.
## TABLE II

**Albumin metabolism**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Total protein</th>
<th>Albumin</th>
<th>TEA</th>
<th>Albumin degradation</th>
<th>Days of study</th>
<th>Clearance</th>
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<td>D+C</td>
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</table>

Mean value: 6.74 ± 0.11

p Value: <0.001

Per cent change
(N - D)/N = 32.8
D - (D+C)/D = -0.4

*TD = total duration of dextran administration. TEA = total exchangeable albumin. N = control study. D = dextran study. D + C = dextran and cortisone study. SE = standard error of the mean. All p values are based on comparisons between the control (N) and experimental values (D and D + C).

† Rabbit 18 was studied while it was on saline injections between the control and dextran study. The experimental periods, however, are compared with the initial control values.
ministration, the mean total plasma protein fell 32.8 per cent, with essentially no change after cortisone therapy. Dextran administration resulted in an average decrease in albumin concentration of 35.8 per cent, while plasma globulin fell by only 28.4 per cent. This finding does not confirm previous reports which indicated a greater fall in the globulin than in the albumin fraction (2, 3, 21). After cortisone administration, the mean albumin concentration actually rose by 7.4 per cent. The mean total exchangeable albumin pool declined 15.5 per cent after dextran administration and rose 38.4 per cent upon the addition of cortisone.

A decrease in albumin degradation of 22.3 per cent was observed following the administration of dextran. Upon the addition of cortisone, albumin degradation increased by a mean of 49.0 per cent over control values and 91.8 per cent over prior dextran values. Dextran infusions resulted not

![Figure 5](Image)

**Fig. 5. Albumin metabolism.** The mean values (horizontal lines) and ranges (solid bars) for total protein, albumin concentration, total exchangeable albumin and albumin degradation during control, dextran, and dextran and cortisone periods. See text and Table II.

Following the administration of dextran, this fraction decreased slightly to 35.3 \pm 1.0 per cent, and in animals receiving cortisone and dextran the intravascular compartment increased to 43.3 \pm 1.7 per cent of the total exchangeable albumin.

The data for albumin metabolism are shown in Table II and Figures 4 and 5. After dextran administration, the mean total plasma protein fell 32.8 per cent, with essentially no change after cortisone therapy. Dextran administration resulted in an average decrease in albumin concentration of 35.8 per cent, while plasma globulin fell by only 28.4 per cent. This finding does not confirm previous reports which indicated a greater fall in the globulin than in the albumin fraction (2, 3, 21). After cortisone administration, the mean albumin concentration actually rose by 7.4 per cent. The mean total exchangeable albumin pool declined 15.5 per cent after dextran administration and rose 38.4 per cent upon the addition of cortisone.

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![](Image)

**Table III**

*Albumin distribution and metabolism*

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<tr>
<th>Animal</th>
<th>Weight</th>
<th>Hematocrit</th>
<th>Plasma volume</th>
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<th>Albumin partition</th>
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</tr>
<tr>
<td></td>
<td>kg</td>
<td>%</td>
<td>ml/kg</td>
<td>ml/kg</td>
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<table>
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<tr>
<th>Total protein</th>
<th>Albumin</th>
<th>TEA</th>
<th>Albumin degradation</th>
<th>Days of study</th>
<th>Clearance</th>
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<td>g/100 ml</td>
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</tr>
</tbody>
</table>

* N = control. E = experimental. TEAS = total exchangeable albumin space. TEA = total exchangeable albumin.
† Received no treatment during experimental periods which followed by 6 weeks (Rabbit 4) and 8 weeks (Rabbit 6) the discontinuation of dextran treatment in these animals.
‡ Received only daily saline injections during experimental period.
only in a decrease in the amount of albumin degraded but also in a mean decrease of total exchangeable albumin of 530 mg per kg. Thus, while degradation decreased, a diminution in synthesis must have taken place to an even greater extent to result in this loss of total exchangeable albumin. Upon the administration of cortisone, changes in the opposite direction occurred—namely, an increase in degradation and an increase in the exchangeable albumin pool by a mean of 1,100 mg per kg. Thus, during the 9 to 17 days of combined dextran-cortisone treatment, albumin synthesis exceeded degradation to a considerable degree. The clearance of plasma-\(^{131}\)I, resulting from albumin degradation, averaged 30.1 ± 4.9 ml per day during the control period. An increase to 35.5 ± 6.8 ml per day occurred following dextran administration, and a further more marked increase to 62.5 ± 3.0 ml per day was obtained following the administration of cortisone with dextran.

Concentrations of circulating dextran ranged between 1.2 and 2.1 g per cent during dextran administration and were not significantly altered in the presence of the expanded plasma volume following cortisone therapy.

Table III indicates the results in two animals given saline infusions and in two animals restudied 6 and 8 weeks, respectively, after discontinuing dextran. Neither group showed any marked changes from the control periods.

Most of the animals in the initial study were followed long enough before reinjection so that an accurate estimate of total excretion of radioactivity could be obtained. Between 93 and 106 per cent of the injected dose was accounted for in urine, stool, withdrawn blood, and that still present in the original total albumin space of distribution. No evidence for a very slowly exchanging albumin compartment, as has been suggested by others (19), was obtained from these studies.

**DISCUSSION**

While plasma volume expansion clearly follows the infusion of dextran (2-4), little is known

reached values 10.9 to 21.5 per cent greater than those observed with dextran alone. These results are similar to those previously reported after a single dose of albumin-\(^{131}\)I (10).

Proteinuria was not observed and the urinary 1st activity was not precipitable with trichloroacetic acid.
molecular weight of the circulating dextran was 188,000, the colloid osmotic pressure contributed by dextran alone would be only 2.1 mm Hg. However, the site of albumin production is most likely in direct contact with extracellular fluid rather than with plasma, and the results of these studies indicate that the total extravascular albumin suffered a lesser reduction than total plasma albumin during dextran treatment (Table IV). Unless the interstitial space increased even more than did the plasma volume, these results would indicate that the interstitial concentration of albumin suffered a lesser reduction than did the plasma albumin concentration. Thus it is possible that in certain critical areas adjacent to or within sites of albumin synthesis, the sum of interstitial dextran and albumin could have resulted in a colloid osmotic pressure high enough to inhibit albumin synthesis.  

Upon the addition of cortisone, albumin distribution and metabolism were again altered. Plasma volume was nearly doubled and plasma albumin concentrations rose (in four of six rabbits) indicating a return of albumin from extravascular locations to the plasma. The absence of any change in plasma dextran concentration, in spite of a marked increase in plasma volume during combined dextran-cortisone therapy, suggests that cortisone probably mobilized extravascular dextran as well. Cortisone administration has previously been shown to result in increased albumin catabolism (10) and this effect was observed again; however, albumin synthesis increased to a greater extent, resulting in a total exchangeable albumin pool even larger than that observed during the control study.

In the presence of dextran and a low albumin concentration, cortisone administration not only resulted in a more marked increase in albumin synthesis than when it was given without prior dextran therapy, but also caused a greater shift of extravascular albumin to the plasma than had been observed previously in the absence of dextran (10). In addition, cortisone therapy has been reported to cause an increase in extravascular volume (30, 31) even in the absence of weight gain (30). Thus it may be suggested that, following cortisone administration, there might have been a reversal of the elevated extravascular colloid concentration postulated under dextran administration, with a resultant augmented stimulus for albumin production. However, until it becomes possible to measure extravascular colloid concentration, these considerations must remain purely speculative.

Other factors must also be considered in attempting to interpret the observed changes in albumin metabolism. The depression of albumin synthesis by dextran might have been due to a specific toxic action unrelated to osmotic activity. However, the rapid return to normal following discontinuation of dextran indicates that such action, if it exists, is readily reversible. While no specific mechanism has been identified as responsible for the observed changes in albumin synthesis, it is clear that, in the presence of dextran, a low albumin concentration is not an adequate stimulus for normal albumin synthesis. Addition of cortisone results in a marked stimulation of albumin synthesis.

### SUMMARY

1. The effects of daily dextran infusions on the distribution and metabolism of albumin-\(^{14}C\) were studied in 12 female rabbits. Cortisone acetate was administered to 6 of the rabbits after prolonged dextran infusions and to 2 rabbits from the onset of dextran administration. Two rabbits were re-examined 6 and 8 weeks after dextran infusions were discontinued, and the effects of saline infusions were studied in 2 additional rabbits.

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Albumin partition</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Control</td>
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<tr>
<td>Intravascular albumin</td>
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<td>Mean value, g</td>
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<td></td>
<td>Change, %</td>
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</table>

It is recognized that if a disproportionately large number of smaller dextran molecules were present, then the calculated colloid osmotic pressure due to dextran would be higher than the computed value given above. However, such a change in the colloid osmotic pressure would seem to be applicable to both plasma and interstitial fluid and would not tend to refute the above hypothesis.
2. Under the influence of dextran, total exchangeable albumin was diminished, while plasma volume and total apparent space for albumin increased. The rate of albumin degradation decreased by 22.3 per cent and the rate of albumin synthesis by at least this much in the presence of a lowered plasma albumin concentration.

3. Upon the addition of cortisone, the plasma volume and total apparent space for albumin distribution increased markedly, with a shift of albumin stores from extravascular to intravascular sites. Albumin degradation increased 49 per cent over control values and 91.8 per cent above the value obtained during dextran infusions alone. The increment in albumin synthesis was probably more marked, since the total exchangeable albumin pool increased in the face of the increase in albumin degradation. Albumin synthesis seems unrelated to albumin levels per se.

4. Albumin synthesis may be regulated by the level of oncotic pressure in certain critical locations adjacent to or within sites of albumin synthesis.

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