EFFECTS OF LARGE INFUSIONS OF HETEROLOGOUS SERUM PROTEINS ON THE SERUM PROTEIN METABOLISM OF RABBITS*, ‡

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As part of a study of the immunologic consequences of large infusions of foreign serum proteins in rabbits (1), we observed some of the associated alterations in serum protein metabolism. Although the metabolism of serum proteins has been exhaustively studied (for recent review see reference 2), no detailed observations of the metabolic effects of large infusions of either homologous or heterologous serum proteins in adequately fed, normal animals have come to our attention. This report covers our observations on the concentrations and rates of turnover of both homologous and heterologous serum proteins during and after such infusions.

EXPERIMENTAL PROCEDURE

The heterologous serum protein infusions were calculated to provide the host over a period of many weeks with an amount of heterologous protein comparable to the amount of the corresponding autologous protein normally synthesized. The total serum protein space of the rabbit is approximately 80 ml. per kilo, the serum protein concentration about 6 gm. per 100 ml., and the albumin/globulin ratio averages slightly more than 3:1 with considerable individual variation. Most determinations of albumin and globulin half-lives in rabbits indicate values of 5 to 6 days (3). Therefore, approximately 0.6 gm. of serum albumin and globulin per kilo body weight is catabolized and replaced daily, an amount comparable to that introduced by our infusions of 10 cc. pooled human plasma per kilo per day six times a week. Infusions of a 5 per cent crystalline bovine serum albumin (Armour and Company Lot 29633) solution (10 cc. per kilo per day six times per week) were calculated to be approximately equivalent to the turnover of rabbit albumin.

Infusions were give by combined intravenous (one part) and subcutaneous (two parts) routes to avoid overloading the cardiovascular system.

Four groups of albino rabbits were infused as follows:—

1. Five adult albino male rabbits weighing from 2.2 to 2.4 kilos were infused as described above for a period of 53 days, human plasma adults (HPA).

2. A litter of 5 albino rabbits was infused as described above (except that infusions for

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first 4 weeks were made entirely subcutaneously) for a period of 112 days beginning the day after birth, human plasma "newborns" (HPN).

3. Six adult albino male rabbits weighing from 2.2 to 2.4 kilos were infused as described above for a period of 43 days, bovine albumin adults (BAA).

4. A litter of 3 albino rabbits was infused as described above (except that infusions were made entirely subcutaneously for first 4 weeks) for a period of 98 days beginning the day after birth, bovine albumin "newborns" (BAN).

Prior to, during, and after the infusion period the sera of these rabbits were analyzed by immunochemical methods to determine the amounts of various homologous and heterologous proteins present. The total serum protein was determined by the analysis of dissolved aliquots of trichloroacetic acid-precipitated serum. The Markham modification of the micro Kjeldahl method was used for nitrogen analyses (4). The concentrations of rabbit albumin, human albumin, and human gamma globulin, including some human alpha and beta globulins, in the human plasma rabbits, and rabbit albumin and bovine albumin in the bovine albumin rabbits were determined by quantitative immunochemical techniques (5). Chicken antirabbit albumin serum and rabbit antihuman albumin and antihuman gamma globulin sera were prepared by multiple injections of the appropriate alcohol separated serum protein fractions.[1] These were calibrated by the conventional techniques. For analyses employing chicken serum both the antigen or appropriate serum dilutions were made in 8 per cent NaCl adjusted to pH 7.5. The concentration of rabbit globulin was determined by subtracting the sum of the above proteins from the total protein. The rabbit globulin values in the human plasma rabbits may be slightly high since the rabbit antihuman gamma globulin serum would not precipitate all of the alpha and beta globulins along with the gamma globulins and the non-precipitated human alpha and beta globulins would be included with the rabbit globulins. However, since the concentration of human globulin in the rabbit sera was always small this source of error is unimportant. Total protein values and the value for the sum of rabbit albumin plus human or bovine albumin were also checked independently by the laboratory of Presbyterian Hospital, Pittsburgh. Their method involved the analysis of the serum and supernatant of Na_2SO_4-precipitated globulins in serum (albumins).

During and following the infusion period the rates of catabolism of some of the homologous and heterologous serum proteins in the rabbits were determined by injecting and tracing small amounts of these proteins labelled with I^{131} (3, 6). In the human plasma rabbits I^{131}-labelled rabbit albumin (I*RA), rabbit gamma globulin (I*RGG), human albumin (I*HA), and human gamma globulin (I*HGG) were traced, and in the bovine albumin rabbits I^{131}-labelled bovine albumin (I*BA), I*RA, and I*RGG were traced. The sizes of the plasma protein pools of the rabbits during the infusions were estimated by determining the dilution of these labelled proteins as indicated by their concentration in the plasma during the first 48 hours after injection.

In addition, qualitative capillary ring tests (5) were used to follow the last traces of the heterologous proteins in the serum during the postinfusion period.

RESULTS

First, in spite of the large protein infusions, only traces of protein at most were lost in the urine of these rabbits as determined by precipitin tests and protein-bound I^{131} measurements of the urine and by acidification (pH 5–6) and boiling of the urine. The only possible exception might have been in the terminal period of some of the rabbits of the HPA group which died during the

[1] These alcohol separations were kindly made by Armour and Company, Chicago.

course of infusions and from which urine samples were difficult to obtain. *Second*, during the period of infusions there were increases of from 20 to 50 per cent in the size of the rabbits' plasma protein pools as determined by dilution of injected I^{131}-labelled proteins. *Third*, with the exception of the HPA group all rabbits tolerated the infusions well and gained weight at normal or increased rates. *Fourth*, all rabbits made antibody responses to materials present in small concentration in the infusions and failed to make detectable antibody responses to the principal protein constituents. Discussion of the immunologic reactions of these rabbits to the infused materials is presented in the accompanying paper (1). And *fifth*, 2 of the HPA rabbits died during the infusions, one shortly thereafter and the remaining 2 were obviously sick during the infusion period. All these animals developed a marked anemia and those that died had a full blown serum sickness with arteritis, myocarditis, and endocarditis.

The detailed results of the immunochemical analyses of sera of each animal for the various homologous and heterologous proteins are given in Table I and summarized as group averages in Table II. In the HPA rabbits there was a marked increase in the total serum protein during the first 3 weeks of infusions, in some instances nearly doubling control values. After the 6th week of infusions the total serum proteins fell somewhat in spite of continued foreign protein administration but remained above normal levels for at least 5 weeks after infusions were stopped. In spite of the large infusions the human protein did not appear to account for much of the rise in serum proteins. At most the human proteins accounted for 10 to 20 per cent of the total serum proteins. The ratios of human albumin to human gamma globulin in the rabbit sera, although showing some variation, were approximately the same as or slightly higher than would be expected in human sera. Virtually all of the increase in total serum protein of the HPA rabbits could be attributed to a tremendous increase in rabbit globulins, in some rabbits reaching more than five times normal levels. Maximum globulin values were reached after 3 weeks of infusions and elevated levels were maintained throughout the period of observation. This increased rabbit globulin was probably associated with the immunologic response of these rabbits to the minor constituents of the human plasma (1). Although it was difficult to obtain reproducible quantitative values of rabbit gamma globulin employing calibrated chicken anti-RGG sera high values were obtained indicating that a high percentage of the increased rabbit globulin was rabbit gamma globulin. In all rabbits there was an associated drop in rabbit albumin accompanying the elevation in rabbit globulin. For the first 5 weeks after infusions the human proteins were lost from the sera of rabbits 10-75 and 10-77 at rates with average half-lives varying between 5 and 7 days which approximate the normal half-lives of rabbit serum protein (3). The rates of loss were most rapid during the first postinfusion week and were slowest during the 2nd and 3rd weeks.

TABLE I

Homologous and Heterologous Serum Protein Concentrations, Individual Values

Figures represent milligrams protein/milliliter serum—arrows indicate cessation of infusions.

A. Human plasma adults

Rabbit No.	Days after beginning of infusions	Total protein	Rabbit albumin	Rabbit globulin	Human albumin	Human gamma globulin
10-74	0	67	52.9	14.1	—	—
	7	67	41.6	19.0	5.3	1.1
	21	110	26.4	72.0	9.0	2.8
	42	82	32.7	39.2	8.4	1.7
	Died	—	—	—	—	—
10-75	0	59	45.7	13.3	—	—
	7	62	31.3	23.1	6.1	1.5
	21	84	25.6	47.9	8.2	2.3
	42	99	43.0	43.8	9.8	1.8
	→ 53	72	33.4	30.0	6.9	1.7
	60	46	23.5	20.3	1.8	0.4
	74	73	33.4	38.8	0.6	0.2
	88	74	32.1	41.8	0.06	0.03
10-76	0	55	42.3	12.7	—	—
	7	58	28.8	22.7	5.3	1.2
	21	101	27.2	63.9	7.9	2.0
	42	99	36.2	49.0	11.9	1.9
	→ 53	75	23.6	44.6	6.1	0.7
	Died	—	—	—	—	—
10-77	0	56	44.4	11.6	—	—
	7	56	30.0	17.6	7.3	1.1
	21	94	22.1	63.6	6.5	1.8
	42	88	35.5	45.6	5.3	1.6
	→ 53	87	25.2	53.2	7.2	1.4
	60	77	25.5	47.4	2.6	0.5
	74	69	40.2	27.9	0.7	0.2
	88	68	35.1	32.6	0.25	0.06
10-78	0	59	44.0	15.0	—	—
	7	56	30.9	19.0	5.0	1.1
	21	83	25.7	48.3	6.4	2.6
	42	67	32.0	23.0	9.1	2.9
	→ 53	59	29.1	22.7	6.1	1.1
	60	48	23.4	22.2	2.1	0.3
	Died	—	—	—	—	—

TABLE I—*Continued*

B. Human plasma newborns

Rabbit No.	Days after beginning of infusions	Total protein	Rabbit albumin	Rabbit globulin	Human albumin	Human gamma globulin
10-62	56	71.0	32.2	30.0	6.9	1.9
	70	76.0	40.0	29.0	5.4	1.6
	84	76.0	42.2	23.3	7.9	2.6
	98	70.0	39.0	21.7	6.9	2.4
	→ 112	82.0	37.6	36.1	6.5	1.8
	119	65.0	34.0	25.6	4.4	1.0
	133	74.0	45.8	27.7	0.4	0.1
	147	68.0	42.9	25.0	0.04	0.04
10-63	56	60.0	40.0	9.2	6.5	4.3
	70	70.0	43.6	18.0	6.1	2.3
	84	73.0	38.1	24.4	7.4	3.1
	98	56.0	19.0	33.1	3.4	0.5
	→ 112	58.0	20.9	33.3	2.9	0.9
	119	65.0	33.8	27.8	3.1	0.3
	133	68.0	50.7	16.7	0.5	0.1
	147	64.0	33.1	30.8	0.07	0.01
10-64	56	72.0	41.6	18.9	7.9	3.6
	70	69.0	47.1	12.1	7.9	1.9
	84	86.0	40.7	33.4	8.1	3.8
	98	76.0	32.5	34.5	6.5	2.5
	→ 112	73.0	45.8	19.4	6.5	1.3
	119	71.0	33.2	32.4	4.9	0.5
	133	83.0	34.5	47.3	1.0	0.2
10-65	56	70.0	40.1	18.6	7.7	3.6
	70	72.0	32.0	32.1	6.6	1.3
	84	71.0	35.4	25.6	8.6	1.4
	98	70.0	31.4	31.7	5.4	1.5
	→ 112	67.0	32.5	26.3	6.9	1.3
	119	68.0	32.7	31.1	3.8	0.4
	133	75.0	42.0	32.0	0.7	0.3
	147	68.0	36.5	31.3	0.1	0.07
10-66	56	67.0	36.0	19.7	7.3	4.0
	70	71.0	44.0	17.6	6.9	2.5
	84	72.0	40.6	21.6	6.7	3.1
	98	72.0	34.7	29.2	6.0	2.1
	→ 112	61.0	39.5	14.1	5.3	2.1
	119	67.0	34.7	30.4	1.6	0.3
	133	76.0	39.4	36.6	0.2	0.1
	147	86.0	31.8	54.1	0.04	0.05

TABLE I—*Continued*

C. Bovine albumin adults

Rabbit No.	Days after beginning of infusions	Total proteins	Rabbit albumin	Rabbit globulin	Bovine albumin
11-39	0	58.0	53.5	4.5	—
	7	71.0	49.6	8.3	13.1
	21	60.0	37.2	9.0	13.8
	→ 43	67.0	39.2	12.9	14.9
	56	67.0	45.4	18.4	3.2
	67	66.0	50.5	14.5	1.0
	84	64.0	47.5	16.4	0.1
11-40	0	54.0	47.0	7.0	—
	7	69.0	52.0	1.7	15.3
	21	66.0	30.7	20.9	14.4
	→ 43	68.0	37.5	16.3	14.2
	56	68.0	35.4	27.9	4.7
	67	62.0	39.2	21.3	1.5
	84	66.0	49.4	16.4	0.16
11-41	0	48.0	40.5	7.5	—
	7	68.0	48.9	7.3	11.8
	21	71.0	31.8	27.8	11.4
	→ 43	79.0	39.4	26.0	13.6
	56	87.0	36.0	47.1	3.9
	67	76.0	36.5	38.8	0.7
	84	82.0	50.6	31.4	0.01
11-42	0	58.0	42.3	15.7	—
	7	68.0	41.7	15.1	11.2
	21	77.0	38.5	21.8	17.7
	→ 43	67.0	34.8	20.7	11.5
	56	76.0	35.6	36.1	4.3
	67	79.0	35.1	42.8	1.1
	84	76.0	40.4	35.5	0.1
11-43	0	54.0	47.1	6.9	—
	7	68.0	45.5	9.4	13.1
	21	73.0	44.5	14.9	13.6
	→ 43	87.0	29.0	42.5	15.5
	56	70.0	42.9	22.3	4.8
	67	69.0	32.9	35.5	0.6
	84	—	—	—	—
11-44	0	53.0	47.5	5.5	—
	7	73.0	41.3	15.1	16.6
	21	72.0	35.8	18.9	17.3
	→ 43	76.0	38.0	23.3	14.7
	56	69.0	46.9	18.0	4.1
	67	67.0	55.6	10.8	0.6
	84	75.0	55.5	19.5	0.02

TABLE I—*Concluded*

D. Bovine albumin newborns

Rabbit No.	Days after beginning of infusions	Total proteins	Rabbit albumin	Rabbit globulin	Bovine albumin
11-14	56	53.0	36.0	6.7	10.3
	70	60.0	22.7	28.7	8.5
	84	68.0	39.4	20.8	7.8
	→ 98	63.0	33.5	22.4	7.1
	105	59.0	24.6	30.3	4.1
	126	72.0	31.1	40.5	0.4
11-15	56	47.0	30.0	7.3	9.7
	70	65.0	36.0	17.5	11.5
	84	65.0	34.9	17.2	12.9
	→ 98	66.0	27.0	23.4	15.6
	105	60.0	27.5	27.2	5.3
	126	64.0	43.5	20.1	0.1
11-16	56	55.0	37.1	9.2	8.7
	70	72.0	36.9	21.0	14.1
	84	62.0	31.4	17.4	13.2
	→ 98	67.0	41.0	11.4	14.6
	105	60.0	44.3	10.0	5.7
	126	72.0	37.6	33.8	0.6

The serum proteins of the HPN rabbits were not analyzed before these rabbits were 8 weeks old, having received injections of human plasma since birth. The 8 week sera had elevated total proteins, as compared with the pre-infusion values of the HPA and BAA groups. The elevations were approximately equal to the amounts of human protein found in the serum. Approximately 10 to 15 per cent of the total serum protein was human in origin. The ratios of rabbit albumin to rabbit globulin were much lower than those found in control determinations. Rabbit globulins were one and a half to two times normal while rabbit albumins were about five-sixths normal. Again, this globulin increase was probably associated with the immune response these rabbits were making to the minor constituents of the plasma. For the last 8 weeks of the infusion period the total serum protein concentration remained unchanged, the human protein and rabbit albumin concentrations diminished slightly, and the rabbit globulin concentration increased in most cases. Following the period of infusions there was an increase in the rabbit globulin and simultaneous decrease in rabbit albumin in rabbits 10-64 and 10-66 but the rest of the group showed no consistent change in rabbit protein concentrations. The human proteins were lost from the sera in the postinfusion period at rates with half-lives of 5 to 7 days for the most part, again approximating the normal serum protein half-lives in rabbits.

TABLE II

Homologous and Heterologous Serum Protein Concentrations, Group Averages

Figures are averages taken from individual values in Table I and represent milligrams protein/milliliter serum.

Group	Time after beginning of infusions	Total protein	Rabbit albumin	Rabbit globulin	Human albumin	Human gamma globulin
	days					
A	0	57.5	45.1	12.5	—	—
Human plasma adults (Rabbits 10-75 and 10-77 only)	7	59.0	30.7	20.4	6.7	1.3
	21	89.0	23.9	55.8	7.4	2.1
	42	93.5	39.4	44.7	7.6	1.7
	→ 53	79.5	29.3	41.6	7.1	1.6
	60	61.5	24.5	33.9	2.2	0.5
	74	71.0	36.8	33.4	0.7	0.2
	88	71.0	33.6	37.2	0.2	0.05
B	56	68.0	38.0	19.3	7.3	3.5
Human plasma newborns (5 rabbits)	70	71.6	41.3	21.8	6.6	1.9
	84	75.6	39.4	25.7	7.7	2.8
	98	68.8	31.3	30.0	5.6	1.8
	→ 112	68.2	35.3	25.8	5.6	1.5
	119	67.2	33.7	29.5	3.6	0.5
	133	75.2	42.5	32.1	0.6	0.2
	147	71.5	36.1	35.3	0.06	0.04
					Bovine albumin	
C	0	54.2	46.3	7.9	—	
Bovine albumin adults (6 rabbits)	7	69.5	46.5	9.5	13.5	
	21	69.8	36.4	18.9	14.7	
	→ 43	74.0	36.3	23.6	14.1	
	56	72.8	40.4	28.3	4.2	
	67	69.8	41.6	27.3	0.9	
	84	72.6	48.7	23.8	0.08	
D	56	51.7	34.4	7.7	9.6	
Bovine albumin newborns (3 rabbits)	70	65.7	31.9	22.4	11.4	
	84	65.0	35.2	18.5	11.3	
	→ 98	65.3	33.8	19.1	12.4	
	105	59.7	32.1	22.5	5.0	
	126	69.3	37.4	31.5	0.5	

The BAA rabbits showed a moderate increase in total serum protein during the infusion period, and this elevation was maintained during the first 6 weeks thereafter. There was an increase in the concentration of rabbit globulin during the infusions which was maintained or even further increased in some rabbits in the postinfusion period. The increase in globulin was accompanied by a

decrease in rabbit albumin during the infusions; thereafter, the albumin returned to normal levels. The bovine albumin made up as much as one-fifth to one-fourth of the total serum protein and as much as one-third of the total albumin in some rabbits during the infusion period. After the infusions the

TABLE III

*Half-Lives of Homologous and Heterologous Proteins during Infusions**

Figures indicate half-lives of I^{131}-labelled proteins in days.

Group No.		Rabbit albumin (Norm 5.8 days)		Rabbit gamma globulin (Norm 5 days)		Human albumin		Human gamma globulin	
Human plasma adults	10-74	—	average 2.7	2.7	average 2.0	2.0	average 2.5	2.1	average 2.0
	10-75	2.3		1.7		2.9		2.2	
	10-76	—		1.8		2.7		1.9	
	10-77	3.2		2.5		2.8		2.1	
	10-78	2.6		1.4		2.2		1.8	
Human plasma newborns	10-62	4.1	average 3.7	2.2	average 2.2	2.9	average 2.9	2.6	average 2.5
	10-63	3.0		2.1		2.1		2.7	
	10-64	3.7		2.3		3.4		2.5	
	10-65	3.6		2.1		2.4		2.0	
	10-66	4.0		2.4		3.7		2.5	
						Bovine albumin			
Bovine albumin adults	11-39	3.7	average 4.1	—		4.0	average 4.0		
	11-40	3.8		—		3.8			
	11-41	4.3		—		4.6			
	11-42	4.4		—		3.5			
	11-43	4.2		—		4.3			
	11-44	4.2		—		3.9			
Bovine albumin newborns	11-14	4.2	average 4.0	3.0	average 3.0	3.6	average 3.3		
	11-15	4.0		2.8		3.3			
	11-16	3.9		3.2		3.0			

* Half-lives of human plasma groups are based on 4 or 5 day periods of observation and those of bovine albumin groups 8 or 9 day periods which may account in part for the generally shorter half-lives seen in the former.

bovine albumin disappeared from the serum at rates with half-lives comparable to the normal half-life of rabbit albumin.

At the age of 8 weeks the three BAN rabbits which had been infused since birth had total protein, globulin, and total albumin concentrations within normal range. The total albumin consisted of three to four parts rabbit albumin and one part bovine albumin. During the remainder of the infusion period the concentration of globulin increased considerably while the bovine albumin

concentration in 2 rabbits increased appreciably and the rabbit albumin showed no consistent changes. In the postinfusion period the globulin levels were elevated, rabbit albumin levels were not consistently changed, and the bovine albumin disappeared at rates comparable to the normal half-life of rabbit albumin.

The half-lives of various I^{131} trace-labelled homologous and heterologous protein fractions injected serially during the period of infusions are presented in Table III. It should be noted that the short periods during which the labelled proteins were followed in the human plasma groups were probably in part responsible for the somewhat shorter half-lives seen in those two groups. In the HPA group the order of administration was: I*RGG end of 3rd week, I*HGG end of 5th week, I*HA end of 6th week, and I*RA end of infusion period. As can be seen in Table III there were no significant differences between the half-lives of either homologous or heterologous albumins or homologous or heterologous gamma globulins. However, all half-lives are approximately one-half or less those of homologous albumin and gamma globulin in normal rabbits. In the HPN group order of administration was: I*RGG during 8th week, I*HGG during 10th week, I*RA during 12th week, and I*HA during 14th week of infusions. Here there was a somewhat longer half-life of I*RA (3.7 days) than I*HA (2.9 days) but no significant difference between the gamma globulin half-lives. Again all half-lives were considerably shorter than homologous serum protein half-lives in normal rabbits. In the BAA group the half-lives of I*RA given during the 2nd week of infusions and I*BA given during the 4th week were virtually identical and approximately two-thirds of the normal rabbit albumin half-life. In the BAN group the I*RA given during the 8th week of infusions had a slightly longer half-life (4.1 days) than the I*BA given during the 10th week (3.3 days). Again, both the albumin and globulin half-lives where shorter than normal homologous serum protein half-lives.

Finally, precipitin ring tests with appropriate antisera were carried out during the postinfusion period to see how long the foreign proteins could be detected in the serum of animals in HPA, HPN, and BAN groups. In the HPA group human albumin was last detected 81 days after cessation of infusions and human gamma globulin, 68 days after. In the HPN group human albumin and gamma globulin were last detectable at 75 days. In the BAN group the bovine albumin was detectable for at least 87 days, after which no further tests were made.

DISCUSSION AND CONCLUSIONS

It is apparent from these observations that additions of heterologous serum proteins to the plasma protein pool, large enough to replace virtually the entire loss of corresponding autologous proteins, greatly increased the rate of serum protein catabolism, with corresponding reduction in protein half-lives to one-half to two-thirds normal values. The rates of catabolism of corresponding homologous and heterologous proteins were remarkably similar. Only in the

HPN and BAN groups did the homologous albumin have a longer half-life than the heterologous albumin, a difference certainly not significant on the basis of the number of present observations. That the increased rate of catabolism of both homologous and heterologous proteins was the direct result of the protein infusions seems likely since the rates of catabolism of heterologous proteins promptly approached the normal values for corresponding homologous proteins in the postinfusion period, Table I. Whether comparable infusions of homologous protein would result in similar metabolic adjustments is under study at present.

In estimating changes in serum protein synthesis resulting from the foreign protein infusions two factors had to be considered: first, that the proportion of albumin synthesis to globulin synthesis was probably affected to a considerable degree by the occurrence of antibody responses to minor constituents of the infusions, and second, that an increase in the size of the plasma protein pool accompanied the infusions. In the BAA and BAN groups the situation was least complicated by an immune response. Here the rabbit albumin concentrations in the serum during the period of infusions fell to approximately two-thirds normal, the plasma protein pools increased one-fourth to one-third in size, and the half-lives of rabbit albumin were about two-thirds normal. This increased rate of albumin catabolism in the presence of an only slightly reduced total amount of rabbit albumin in the rabbits suggests a normal or slightly increased rate of albumin synthesis. Thus, it would appear that adjustment to the heterologous protein infusions involved an increased rate of protein catabolism, an increased plasma protein pool, and an unchanged or even slightly increased rate of protein synthesis.

Adding heterologous protein to the plasma protein pool in amounts sufficient to replace the normal loss of serum proteins did not result in such large concentrations of these foreign proteins in the serum as might have been expected. While the infusions did expand the plasma protein pool the foreign proteins did not reach more than one-third to one-half the serum concentration of corresponding autologous serum proteins and usually were considerably less. How much of this failure of infused protein to be present in high concentrations in the serum was the result of the route of injection, *i.e.* one-third intravenous and two-thirds subcutaneous, could not be determined since larger intravenous injections were not tolerated well by the rabbits. In some instances after repeated injections the human plasma tended to form local subcutaneous pools which persisted from several hours to a day, but the bovine albumin was always rapidly absorbed from the injection site. It is possible that antibodies to constituents of the rabbit might have been present in the human plasma which would have interfered with the expected equilibration of human globulin in the rabbits. However, there is no apparent reason why the bovine albumin or the human albumin should not have equilibrated freely in the plasma protein pool.

The hyperproteinemia which developed to some extent in all the rabbits was caused primarily by marked increases in the rabbit globulin fraction and to a lesser extent by the presence of foreign proteins. As might be expected, the greatest rises in rabbit globulin were seen in the HPA rabbits in which there was a considerable antibody response to the minor constituents of the plasma. The animals receiving whole plasma invariably made antibody responses to a variety of minor constituents but not to the albumin and gamma globulins. The animals receiving bovine albumin made antibody responses to the bovine globulin contaminants in the preparation but not to the albumin. Thus, the hyperproteinemia associated with these infusions was principally the result of globulin synthesis by the host presumably associated with antibody production called forth by minor constituents of the preparations. Coincident with the increased rabbit globulin levels there was in most instances a decrease in rabbit albumin.

A marked hyperalbuminemia which developed in all the BAA rabbits early in the course of the infusions then disappeared in the postinfusion period. During the greatest hyperalbuminemia the ratio of rabbit albumin to bovine albumin was two or three to one. No definite hyperalbuminemia developed in the other groups, and actually a hypoalbuminemia occurred in the HPA group coincident with the hyperglobulinemia.

SUMMARY

Infusions of heterologous serum proteins large enough to replace the entire normal catabolic loss of the corresponding autologous proteins in the recipient rabbits caused increased rates of plasma protein catabolism, an increase in the size of the plasma protein pool and normal or even slightly increased rates of plasma protein synthesis. The principal proteins in these infusions were catabolized at rates similar to those for corresponding homologous proteins. The most marked hyperproteinemias which developed were caused principally by increases in the host's own globulin and to a lesser extent by the presence of foreign protein in the circulation.

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