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Research Article

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Augmentation of Albumin but Not Fibrinogen Synthesis by Corticosteroids in Patients with Hepatocellular Disease

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ABSTRACT Simultaneous studies of albumin and fibrinogen metabolism have been conducted using the carbonate-^{14}C method before and after a 13 day course of prednisolone in eight patients with hepatocellular disease. Initially six patients were hypoalbuminemic. The mean plasma albumin and fibrinogen concentrations and albumin and fibrinogen synthetic rates were all lower than the corresponding values in a group of control subjects. Prednisolone therapy was associated with significant increases in the plasma concentration and synthetic rate of albumin but changes in the intravascular albumin pools were not significant. It is inferred that a low synthetic rate of albumin in a patient with liver disease does not necessarily represent the maximum capacity of the diseased liver to synthesize this protein. Changes in the plasma concentration, intravascular pool, and synthetic rate of fibrinogen were small and inconsistent. The data are compatible with a selective action of corticosteroids on hepatic protein metabolism and with the existence of different mechanisms for the control of albumin and fibrinogen synthesis.

INTRODUCTION

Corticosteroids are often administered to patients with hepatocellular disease. However, there have been few studies of the effects of these drugs on specific functions of the liver cell. These functions include the synthesis of plasma proteins other than the immunoglobulins. The carbonate-^{14}C method for direct measurement of the synthetic rate of liver-produced plasma proteins is particularly appropriate for studying the effects of drugs on the metabolism of these proteins over a short period (1, 2). To obtain data on the effects of corticosteroids on hepatic plasma protein metabolism in liver disease, this technique was used to measure albumin and fibrinogen synthesis in eight patients before and after the administration of corticosteroids for only 2 wk. The results of the studies indicate that this treatment is usually associated with appreciable augmentation of the synthetic rate of albumin but only small and inconsistent changes in fibrinogen metabolism. These findings suggest a selective action of corticosteroids on hepatic protein metabolism and different mechanisms for the control of albumin and fibrinogen synthesis.

METHODS

Patients. Clinical data and serum biochemistry of the eight patients are given in Table I. Their ages varied between 25 and 71 yr. There were five females and three males. All patients had hepatocellular disease established by needle biopsy. Five had cirrhosis. Of these, three (Nos. 2, 6, and 7) had a previous history of chronic active hepatitis and one (No. 1) was an alcoholic. Two patients had chronic hepatitis (No. 3, chronic aggressive hepatitis; No. 4, chronic persistent hepatitis) (3). The duration of illness based on clinical history and biochemical tests of liver function varied between 0.3 and 15 yr. In all cases serum biochemical changes were consistent with hepatocellular disease. Total serum bilirubin concentrations varied between < 0.5 mg/100 ml and 26 mg/100 ml. The conjugated bilirubin varied between < 0.5 mg/100 ml and 22 mg/100 ml. Three patients (Nos. 2, 3, and 5) were deeply jaundiced. The alkaline phosphatase ranged between 16 and 57 King-Armstrong units. The aspartate transaminase (SGOT) varied between 20 and 520 IU/liter.

At the beginning of the studies all patients were considered to be in a metabolically steady state with particular reference to body weight, hematocrit, and serum bilirubin, urea, and albumin concentrations. Three patients (Nos. 2, 6, and 8) had had fluid retention and were receiving restricted sodium intake and diuretics. In two (Nos. 2 and 6) there was a history of gastrointestinal hemorrhage but none had bled during the 6 months prior to the

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TABLE I

Patients Studied and Serum Biochemistry before and after Prednisolone

Patient No.	Age	Sex	Diagnosis	Duration of illness	Bilirubin				Alkaline phosphatase		Aspartate transaminase	
					Total		Conjugated					
					Before	After	Before	After	Before	After	Before	After
	yr			*yr*	*mg/100 ml*				*K.A. Units*		*IU/liter*	
1	43	F	Cirrhosis of alcoholic	4	<0.5	<0.5	<0.5	<0.5	18	10	40	10
2	25	M	Cryptogenic cirrhosis	15	14.0	11.5	8.0	9.2	27	28	38	66
3	39	M	Chronic hepatitis	0.4	26.0	23.5	22.0	22.0	23	18	520	125
4	27	F	Chronic hepatitis	0.3	5.0	4.0	4.0	2.5	16	12	52	30
5	63	M	Cholestatic hepatitis	2	13.0	3.2	10.5	3.0	30	22	22	16
6	63	F	Cryptogenic cirrhosis	5	3.5	3.5	3.0	3.0	57	50	45	64
7	28	F	Cryptogenic cirrhosis	10	2.2	6.5	2.0	3.5	22	45	20	26
8	71	F	Cryptogenic cirrhosis	0.3	1.3	2.3	0.8	1.2	23	28	52	28
Normal range					<0.5		<0.5		<13		<17	

studies. There were no clinical features of bleeding diathesis or clotting abnormalities. Also none had evidence of gastrointestinal disease known to affect plasma protein metabolism and none had proteinuria. Corticosteroids had not been administered to any of the patients during the previous 6 months.

Materials. Sodium carbonate-^{14}C was obtained from The Radiochemical Centre, Amersham, England in ampoules containing 200 μCi in 3 ml of 0.9% saline under nitrogen.

Urea-^{13}C was prepared from barium carbonate-^{13}C in the Department of Biophysics, National Institute for Medical Research, Mill Hill, London, N.W. 7. The enrichment of the batches was 51.1 and 65.5 atoms per 100 atoms excess, and the purity was 90 and 96%, respectively.

Behringwerke (Marburg) human serum albumin and Kabi (Stockholm) human fibrinogen were trace labeled with ^{131}I and ^{125}I, respectively, by the iodine monochloride method of McFarlane (4). More than 99% of the radioactivity in a preparation was precipitable by 20% trichloroacetic acid. The degree of iodination of each preparation was statistically less than 1 atom of iodine per molecule of protein.

Design of studies. The studies were carried out with the fully informed consent and cooperation of each patient.

48 hr before isotopically labeled substances were given and daily thereafter, 200 mg of potassium iodide were given. This was continued for at least 3 wk to block uptake of nonprotein-bound radioiodine by the thyroid. 12 hr before and throughout the 10-12 hr period of each study, all patients received a low protein diet (10 g protein/day) to minimize postprandial fluctuations in the synthetic rate of urea (2).

At zero time sodium carbonate-^{14}C (200 μCi), urea-^{13}C (50–100 mg), albumin-^{131}I (approximately 50 μCi), and fibrinogen-^{125}I (approximately 50 μCi) were simultaneously injected intravenously. The mass of urea-^{13}C and the volume of the labeled albumin and fibrinogen solutions administered were accurately weighed. Similar weighed volumes of the labeled protein solutions were used to make standard solutions.

Without stasis 10 accurately timed specimens of venous blood (20 ml) were taken into heparinized tubes from the arm opposite to that used for injecting the isotopically labeled substances. The first specimen was taken at 5 min. The intervals between the remaining specimens varied between 15 min initially to about 2 hr near the end of the study. Commencing at 1 hr extra blood (40 ml) was taken into 4 ml of 3.8% sodium citrate when drawing six of the heparinized specimens.

The morning after the first study, orally administered prednisolone was begun in a dose of 1 mg/kg body weight per day except in patient No. 7 who received 0.75 mg/kg body weight daily. On the 13th day of treatment a second study was conducted. Immediately prior to the second study, a base line specimen of blood was taken to determine residual concentrations of isotopically labeled substances in the plasma. After the second study the dose of prednisolone was reduced over 2 wk to a maintenance dose of less than 15 mg/day.

Laboratory procedures. Plasma albumin and fibrinogen concentrations were estimated at the beginning of the first and second studies and twice weekly before, during, and after the 2 wk period as long as the patient was hospitalized. Plasma albumin concentrations were measured electrophoretically (5) and plasma fibrinogen concentrations by the method of Jacobsson (6).

Heparinized plasma samples were used to determine urea-^{14}C specific activity in duplicate, urea-^{13}C enrichment, and ^{131}I and ^{125}I radioactivity. Plasma from the citrated samples was used to determine the ^{14}C specific activity of the guanidine carbon of arginine in albumin (in duplicate) and fibrinogen.

The methods used for measuring the ^{14}C specific activity of urea carbon and the guanidine carbon of arginine in albumin were those described by Tavill, Craigie, and Rosenoer (2). The method for determining ^{14}C specific activity of the guanidine carbon of arginine in fibrinogen was that described by McFarlane (1). Urea-^{13}C enrichment was measured by mass spectrometry. Aliquots of the same specimen of carbon dioxide derived by enzymatic hydrolysis of urea were used to measure both ^{13}C enrichment and ^{14}C specific activity (7).

2-ml aliquots of plasma and appropriate standard solutions were counted for 200 sec in the well of a two channel Packard Autogamma Counter. The gains and windows of the two channels were set for counting ^{131}I and ^{125}I radio-

activity. No ^{125}I counts appeared in the ^{131}I channel, but about 20% of the ^{131}I counts appeared in the ^{125}I channel. The ^{125}I radioactivity content of an aliquot was determined by subtracting the counts due to ^{131}I from the total counts in the ^{125}I channel.

Calculations. The value for the concentration of each of the different isotopes in urea and the two proteins in the plasma, measured immediately prior to the commencement of the second study, was subtracted from all estimates of the concentration of the same isotope in the same substance determined during the second study.

Plasma volumes were derived by calculating the initial volume of distribution of albumin-^{131}I assuming no losses and uniform distribution throughout the plasma at 5 min after its intravenous injection. Intravenous protein pools were calculated by multiplying the plasma volume by the plasma concentration of the protein.

The ^{14}C specific activity curves were fitted to four exponential functions and the ^{13}C enrichment and ^{131}I and ^{125}I radioactivity curves to three exponential functions by an adaptive ("hill-climbing") technique which minimizes the root mean square error (8).

The derivation of plasma protein synthetic rates utilizing the carbonate-^{14}C method depends on the application of the labeled precursor-product relationship to the hepatic pool of guanidine carbon of arginine (1, 2). This relationship enables the derivation of a simple equation for the fractional synthetic rate of a liver-produced plasma protein (see Appendix).

$$K_p = K_u \times \frac{P(t)}{U(t)} \quad (1)$$

Where

K_p = the fraction of the intravascular (plasma) pool of the protein synthesized per unit time;
K_u = the fractional turnover rate of the initial mixing pool of intravenously injected urea per unit time;
$U(t)$ = the plasma ^{14}C specific activity of urea carbon corrected for losses at time t (dpm/mg C); and
$P(t)$ = the plasma ^{14}C specific activity of the guanidine carbon of arginine in the protein corrected for losses at time t (dpm/mg C).

To make due allowance for the multicompartmental nature of urea metabolism in man (9), K_u was calculated by multiexponential analysis of the fitted urea-^{13}C curve (see Appendix). $U(t)$ was derived by using the plasma urea-^{13}C curve to correct the plasma biosynthesized urea-^{14}C specific activity curve for losses of urea-^{14}C, which occur from the initial mixing pool of urea due to distribution, catabolism, and excretion (see Appendix). Similarly $P(t)$ was derived by using the plasma radioiodinated protein curve to correct the plasma ^{14}C specific activity curve of the same protein for losses of the ^{14}C-labeled protein from the plasma due to distribution and catabolism (see Appendix). The ratio $P(t)/U(t)$ was determined from appropriately corrected ^{14}C specific activity values 300 min after the injection of carbonate-^{14}C.

The fitting of the experimental curves and the mathematical procedures required to correct the fitted ^{14}C specific activity curves for losses (see Appendix) were carried out using a digital computer.

The absolute synthetic rate of a protein was calculated by multiplying its intravascular pool by its fractional synthetic rate.

The proportion of the injected dose of ^{14}C incorporated into the guanidine carbon of arginine in albumin by 300 min (F) can be calculated from the following equation.

$$F = \frac{A(t)cI}{K} \quad (2)$$

where

$A(t)$ = the ^{14}C specific activity of the guanidine carbon of arginine in albumin corrected for losses at 300 min (dpm/mg C);
c = milligrams guanidine carbon of arginine/gram albumin;
I = intravascular pool of albumin (grams); and
K = injected dose of ^{14}C (dpm).

The ratio of the proportion of the injected dose of ^{14}C incorporated into the guanidine carbon of arginine in albumin (at 300 min) after corticosteroids (F_a) to that before corticosteroids (F_b) was calculated from the appropriate paired values of $A(t)$ and I (values for c and K cancelling).

RESULTS

Body weight, plasma volume, plasma albumin concentration, intravascular albumin pool, and albumin synthetic rate before and after prednisolone are given in Table II. The control data for the synthetic rate of albumin, obtained from hospitalized patients without liver disease using the carbonate-^{14}C method, agree satisfactorily with data on the catabolic rate of this protein measured with albumin-^{131}I in controls (10).

Changes in body weight associated with the course of prednisolone were small and inconsistent. One patient (No. 1) had an appreciably elevated plasma volume. The plasma volume in the remainder fell either within or just above the normal range. The mean value for 19 hospitalized patients without liver disease (44.6 ml/kg) was less than that for the eight patients before prednisolone treatment (49.3 ml/kg). Changes in the plasma volume also were small and inconsistent.

The plasma concentration of albumin was subnormal in six, and in the lower range of normal in the remaining two. However, the sizes of the intravascular pools of albumin in the patients were similar to those in the controls. The fractional synthetic rate of albumin was rather high in two (Nos. 1 and 3) and particularly low in three (Nos. 4, 7, and 8). The absolute synthetic rate of albumin was rather high in one (No. 1) and was low in four (Nos. 4, 6, 7, and 8). Both the mean fractional (9.7%/day) and absolute (8.3 g/day) synthetic rates of albumin were lower than the corresponding control values.

Prednisolone was not associated with significant changes in the size of the intravascular albumin pool. However, there were increases in the plasma concentration of albumin in six patients. The proportion of the injected dose of ^{14}C incorporated into albumin was higher (F_a/F_b greater than unity, Table II) after prednisolone in all eight patients and the calculated fractional and ab-

TABLE II

Body Weight, Plasma Volume, and Albumin Metabolism before and after Prednisolone

Patient No.	Body weight		Plasma volume		Plasma albumin concentration		Intravascular albumin pool		Albumin synthetic rate				F_a/F_b*
									Fractional		Absolute		
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	
	kg		*ml/kg*		*g/100 ml*		*g*		*% i.v. pool/day*		*g/day*		
1	39.7	42.4	65.5	62.7	2.9	3.2	74.4	83.8	18.7	26.2	13.9	22.0	1.18
2	69.8	65.2	56.0	56.0	2.6	2.7	100.0	97.5	9.4	9.1	9.4	8.9	1.51
3	57.6	58.2	48.0	44.6	3.0	3.0	82.5	77.4	15.2	20.5	12.5	15.9	1.04
4	68.8	67.3	44.7	45.9	2.7	2.8	84.3	87.2	4.3	7.8	3.6	6.8	1.54
5	70.1	70.0	38.2	44.1	3.4	3.8	91.4	116.2	10.3	26.2	9.4	30.4	1.92
6	67.8	65.2	50.0	45.4	2.7	3.0	92.8	88.2	9.0	29.5	8.4	26.0	1.33
7	81.9	85.0	48.0	44.0	2.7	3.1	104.2	115.1	6.8	16.1	7.1	18.5	1.63
8	53.4	50.6	43.7	39.9	2.5	2.5	58.3	50.5	3.6	8.6	2.1	4.3	1.70
Normal range					3.0 to 4.6								
Control data													
Mean			44.6				91.7		11.9		10.9		
SEM			1.33				5.9		1.5		1.7		
Number			19				6		6		6		

* The ratio of the total ^{14}C radioactivity incorporated into albumin by 300 min after corticosteroids (F_a) to that before corticosteroids (F_b).

solute synthetic rates of albumin were higher in seven. The only patient (No. 2) in whom there was no appreciable change in the synthetic rate of albumin had the longest history and was the most ill clinically. In the other seven patients, the increases in albumin synthetic rate were unequivocally greater than the changes in this rate observed over the same time interval by Tavill et al. (2) using the carbonate-^{14}C method in cirrhotic patients on no specific therapy. The methods of calculation used by Tavill et al. (2) and those used in this study are not identical. However, neither method of calculation is likely to result in any appreciable error in the derived value for the albumin synthetic rate (9) and good agreement using both methods of calculation has been obtained between the synthetic rate of albumin and the catabolic rate of this protein using albumin-^{131}I in the same patients in a steady metabolic state (2).[1]

After prednisolone the synthetic rate of albumin (both fractional and absolute) was high in five patients. The largest increase (21.0 g/day) occurred in one (No. 5) of the two patients in whom the hepatocellular disease was potentially reversible. Paired Student t tests indicated that the increases in both plasma albumin concentration ($P < 0.025$) and the synthetic rate of albumin ($P < 0.025$) were significant.

Data on the plasma concentration, intravascular pool, and synthetic rate of fibrinogen before and after prednisolone are given in Table III. The control data for the synthetic rate of fibrinogen, obtained in hospitalized patients without liver disease by use of the carbonate-^{14}C method, are in satisfactory agreement with data on the catabolic rate of this protein measured with fibrinogen-^{131}I in controls (11). The plasma fibrinogen concentration and the intravascular fibrinogen pool were low in patient No. 2. This patient had a rather high fractional synthetic rate of fibrinogen. In general, the plasma fibrinogen concentrations, while tending to be low, were relatively less depressed than the plasma albumin concentrations. But, like albumin, the sizes of the intravascular pools of fibrinogen were similar to those in the controls while both the mean fractional (26.6%/day) and absolute (1.6 g/day) synthetic rates were lower (16 and 23%, respectively) than the corresponding control values. In contrast McFarlane, Todd, and Cromwell (11), using fibrinogen-^{131}I, found that the mean fractional and absolute (grams/day) catabolic rates of fibrinogen were, respectively, 8 and 28% higher in a group of cirrhotic patients than in a group of controls. However, in neither the study of McFarlane et al. (11) nor in the present study were these differences between mean values in cirrhotic and control patients statistically significant. Treatment with prednisolone was not associated with consistent changes in the plasma fibrinogen concentration, the intravascular fibrinogen pool, or the fibrinogen synthetic rate.

DISCUSSION

Hypoalbuminemia in liver disease. Although six of the eight patients had hypoalbuminemia, the intravascular pools of albumin were relatively well maintained. This finding is probably due to the plasma volume tend-

[1] Craigie, A., and E. A. Jones. 1968. Unpublished data.

TABLE III

Fibrinogen Metabolism before and after Prednisolone

Patient No.	Plasma fibrinogen concentration		Intravascular fibrinogen pool		Fibrinogen synthetic rate			
					Fractional		Absolute	
	Before	After	Before	After	Before	After	Before	After
	mg/ml		*g*		*% i.v. pool/day*		*g/day*	
1	2.0	1.0	5.3	2.7	28.2	43.3	1.5	1.2
2	0.7	0.7	2.8	2.6	49.6	27.1	1.4	0.7
3	2.8	3.4	7.7	8.9	29.6	54.2	2.3	4.8
4	2.2	3.1	6.9	9.5	16.6	17.9	1.1	1.7
5	2.2	2.6	6.0	8.1	23.6	39.6	1.4	3.2
6	2.9	3.3	9.9	9.8	19.5	23.4	1.9	2.3
7	2.0	1.1	7.8	4.1	18.5	30.6	1.4	1.3
8	3.4	2.3	7.8	4.7	26.8	41.8	2.1	2.0
Normal range 2.0–5.0								
Control data								
Mean			6.58		31.6		2.12	
SEM			0.90		4.9		0.48	
Number			6		6		6	

ing to be increased in patients with liver disease (12–15). Only one of our patients had an unequivocally elevated plasma volume, but the mean plasma volume for the group was higher than that for the controls.

In most of the patients, the fractional synthetic rate of albumin was either normal or low. These results are consistent with the studies of Wilkinson and Mendenhall (12), Hasch, Jarnum, and Tygstrup (14), and Dykes (15) who found normal or low fractional catabolic rates of this protein in cirrhotics using albumin-^{131}I. These data suggest that excessive catabolism or loss of albumin is not a major factor contributing to hypoalbuminemia in cirrhotics.

Initially all but one of our patients had either normal or low absolute synthetic rates of albumin. Tavill et al. (2) found similar results in uncomplicated cirrhotics using the carbonate-^{14}C method. However, one of our patients had a rather high absolute synthetic rate particularly when expressed in terms of body weight. Furthermore, Rothschild, Oratz, Zimmon, Schreiber, Weiner, and Van Caneghem (16) reported high synthetic rates in 5 out of 19 cirrhotic patients with ascites by use of the carbonate-^{14}C method. All of these patients with high synthetic rates had cirrhosis associated with alcoholism. These results may be due in part to the effects of better nutrition and withdrawal from alcohol after hospitalization. Nevertheless, most of the available data indicate that hypoalbuminemia in liver disease is due to a reduced absolute synthetic rate and (or) an increased plasma volume.

Corticosteroids and albumin metabolism. In our series the treatment with corticosteroids was usually associated with an increased plasma albumin concentration and an augmentation of the synthetic rate of albumin. It is possible that even greater increases may have been found had the timing of the second study been different. Hasch et al. (14) conducted paired studies of albumin metabolism, using albumin-^{131}I, in three patients with cirrhosis, before and after a 3–5 month course of prednisone. The dose given was about one-third the dose of prednisolone given in the present study. In all three instances the absolute catabolic rate of albumin, and hence, by inference, the absolute synthetic rate of this protein, was found to be higher after corticosteroid therapy than before. However, in contrast to the large increases found in most cases in the present study, the increases found in their sutdy were relatively small (0.2–2.1 g/day). Clearly further studies are required to ascertain fully how quickly and for how long albumin metabolism can be modified by corticosteroids. The results of this study and that of Hasch et al. (14) indicate that the subnormal synthetic rates of albumin often found in chronic liver disease do not necessarily represent the maximum capacity of the diseased liver to synthesize this protein. It appears that the cirrhotic liver can respond to an appropriate stimulus by increasing the synthetic rate of albumin. The present study, but not that of Hasch et al. (14), indicates that such increases can be appreciable and may sometimes be to supranormal values.

Augmentation of the synthetic rate of albumin by corticosteroids is almost certainly not confined to subjects with liver disease. Results of paired and unpaired studies, using albumin-^{131}I in patients without liver disease, normal volunteers, and normal rabbits, all of whom were assumed to be in a metabolically steady state, have

indicated that the administration of corticosteroids or adrenal corticotrophic hormone and excessive endogenous secretion of corticosteroids in patients with Cushing's disease are associated with increased absolute catabolic rates of albumin, and hence by inference with increased absolute synthetic rates of this protein (17–20).

Corticosteroids may influence the synthesis of albumin by more than one mechanism. These hormones may exert their effects directly on the liver cells by affecting one or a number of the many subcellular processes involved in protein synthesis. Alternatively the changes in albumin synthesis could be induced indirectly, occurring secondary to a selective augmentation of the catabolic rate of one or more specific proteins such as albumin and (or) to an increased supply of amino acids to the liver cell from peripheral tissues which have undergone a relatively nonselective increase in protein catabolism (21, 22) and (or) to an increased secretion of insulin (23). A combination of direct and indirect phenomena could be reflected in the increased synthesis of albumin found in our patients. Sellers, Bonorris, and Katz (24), using the carbonate-^{14}C method in isolated perfused rat livers, have reported that corticosteroids appear to inhibit the synthesis of albumin and John and Miller have shown that these hormones decrease the incorporation of lysine-^{14}C into total hepatic protein of the isolated perfused rat liver (23). These findings, if confirmed, suggest that the increased synthesis induced by these drugs in vivo is more likely to be mediated by an indirect mechanism.

The selective action of corticosteroids. It cannot be concluded from the data presented that corticosteroids are without effect on fibrinogen synthesis. A consistent effect of these drugs on fibrinogen synthesis may have been observed if the timing of the second study had been different or had normal subjects been studied. It has been demonstrated that the rate of synthesis of fibrinogen by the isolated perfused rat liver is critically dependent on the presence of cortisol (23). However, the observation that the course of corticosteroids in these particular studies was associated with an augmentation in the synthetic rate of albumin but not fibrinogen indicates that these drugs, in pharmacological doses, probably have a selective effect on hepatic protein metabolism. This conclusion is in agreement with the data of John and Miller on the action of cortisol on the isolated perfused rat liver (23). Other data are also consistent with this conclusion. Corticosteroids induce certain hepatic enzymes but not others and they have quantitatively different and sometimes opposite effects on various fractions of hepatic messenger RNA profiles (25, 26).

The selective action of corticosteroids on albumin and fibrinogen metabolism found in these studies suggests that there are probably different mechanisms involved in the control of albumin and fibrinogen synthesis in these patients. That there are fundamental differences in the control of the catabolism of these two proteins has already been demonstrated. Whereas the fractional catabolic rate of albumin is proportional to its plasma concentration, that of fibrinogen is independent of its plasma concentration (11, 27, 28).

APPENDIX

The application of the labeled precursor-product relationship to the hepatic pool of guanidine carbon of arginine after the intravenous injection of carbonate-^{14}C (1, 2) enables the following simple equation for the synthetic rate of a liver cell–produced plasma protein to be written

$$M_p = M_u \times \frac{R_p}{R_u} \tag{1}$$

where

M_p = the mass of guanidine carbon of arginine in the protein synthesized per unit time (mg C/unit time);
M_u = the mass of urea carbon synthesized per unit time (mg C/unit time);
R_p = total radioactivity incorporated into the guanidine carbon of arginine in the protein up to time t (dpm); and
R_u = total radioactivity incorporated into urea carbon up to time t (dpm).

The absolute synthetic rate of urea (M_u) is given by the product of the initial mixing pool of intravenously injected urea (P_u mg urea C) and the fractional turnover rate of this pool per unit time (K_u) (9).

$$M_u = P_u K_u \tag{2}$$

K_u is derived from multiexponential analysis of the plasma disappearance curve of urea-^{13}C.

$$K_u = \frac{1}{\frac{C_1}{b_1} + \frac{C_2}{b_2} + \frac{C_3}{b_3}} \tag{3}$$

where b_1 b_2, and b_3 are the rate constants and C_1, C_2, and C_3 are the ordinate intercept values of the first, second, and third exponentials, respectively, the ordinate intercept values having been normalized so that $C_1 + C_2 + C_3$ equaled unity.

R_u is given by the product of the initial mixing pool of urea (P_u mg C) and the plasma urea-^{14}C specific activity (U(t) dpm/mg C at time t) had no losses of urea-^{14}C occurred from this pool due to distribution, catabolism, and excretion.

$$R_u = P_u U(t) \tag{4}$$

U(t) can be derived from the two experimentally determined plasma labeled urea curves: the urea-^{13}C curve (G(t) atoms per 100 atoms excess) and the urea-^{14}C curve (X(t) dpm/mg C). The relationship between these two curves is given by the following equation:

$$X(t) = \frac{1}{G(0)} \int_0^t M(t - T)G(T)dT \tag{5}$$

where M(t) = the rate of change of ^{14}C specific activity of newly synthetized urea (dpm/mg C/unit time). Equation 5 can be solved for M(t) by numerical inversion (9). U(t) can then be derived by integrating M(t) with respect to time.

$$U(t) = \int_0^t M(t)dt \tag{6}$$

R_p is given by the product of the plasma pool of the protein (P_p mg guanidine C) and the plasma ^{14}C specific activity of

the protein (P(t) dpm/mg guanidine C at time t) had there been no losses of ^{14}C-labeled protein from the plasma due to distribution and catabolism.

$$R_p = P_p P(t) \quad (7)$$

P(t) can be derived from the two experimentally determined plasma labeled protein curves: the radioiodinated protein curve (per cent of value at 5 min) and the ^{14}C specific activity curve of the same protein (dpm/mg C) by an analysis analogous to that described for determining U(t).

Substituting the expressions for M_u, R_u, and R_p in equation 1

$$M_p = K_u \times \frac{P_p P(t)}{U(t)}. \quad (8)$$

By dividing both sides of equation 8 by P_p, the expression for the fraction of the plasma pool of the protein synthesized per unit time (K_p) is derived:

$$K_p = K_u \times \frac{P(t)}{U(t)}. \quad (9)$$

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