CLINICAL MEASUREMENT OF PLASMA-PROTEIN SYNTHESIS

Hassan K. Awwad* and E. James Potchen

The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo.

To a large extent, the clinical isotopic study of plasma-protein (PP) metabolism has been limited to measuring the distribution kinetics and metabolism of the principal PP components. Radioiodinated proteins have been the principal tracer substances employed, and their use has promoted greatly our knowledge of PP metabolism in health and disease. During the past few years, more efforts have been directed at developing clinical isotopic methods to measure quantitatively the synthesis of PP. These efforts were largely motivated by the recognition of certain shortcomings and limitations in the radioiodinated-protein methods, particularly in studying protein synthesis in a changing metabolic system. The present article is an attempt to appraise the radioisotopic methods which are currently available for measuring PP synthesis in man. The principal aim is to present the theoretical and conceptional principles on which these methods are based.

METABOLIC SYSTEM OF PLASMA PROTEINS

The physiological metabolic system of PP is generally considered to be composed of the following components:

1. **Synthesis sites.** Plasma albumin and fibrinogen are exclusively formed in the liver (*1–3*). The greater part of alpha- and beta-globulins are synthesized in the liver. It has been estimated that 10% of $alpha_1$-globulin, 25% of $alpha_2$-globulin and 50% of beta-globulin are formed extrahepatically (*4*). Most, if not all, of the gamma-globulin is formed by the lymphocytic and plasma cells (*5*).

Present evidence indicates that the free intracellular amino acids are the immediate precursors of the same acids incorporated into protein (*6*). The time necessary for the completion of intracellular protein synthesis is quite short—3 min in the case of mouse serum albumin (*7*). Because very little PP produced in the liver is stored there, newly formed protein emerges rapidly in the venous blood or hepatic lymph. Liver-produced PP appears in the plasma within 15–30 min in various animal species (*3–14*). This contrasts with the much slower transfer of new gamma-grobulin from extravascular synthesis sites to plasma by the lymphatic system (*15*).

2. **Intravascular plasma pool.** The plasma-protein pool constitutes a well-mixed compartment that can be adequately sampled during the course of a radiotracer experiment without seriously altering its size or disturbing the equilibrium of the system.

3. **Extravascular interstitial protein pool.** Because PP passes outward across the capillary wall into the interstitial tissue spaces, the distribution of extravascular protein is a function of capillary permeability. Capillaries of the liver, spleen and intestines exhibit high permeability in contrast to low values found for capillaries of muscle and skin (*16,17*). It is generally believed that protein flow between blood and lymph is an unidirectional process (*18–20*) in which proteins circulate into the highly ramified tissue spaces and small lymphatics and thence to plasma (*21*).

4. **Breakdown sites.** The exact site of PP catabolism is not known. However, various theoretical and experimental considerations suggest that the catabolic sites must be functionally close to the intravascular pool (*22–29*). The products of protein catabolism are amino acids that can re-enter the precursor pool for reutilization in the synthesis of various tissue and blood proteins (*30*).

PP METABOLISM STUDY BY TRACER TECHNIQUES

A complete kinetic description of the metabolism of a specific plasma protein should include estimates of the total exchangeable protein, its partitioning into intravascular and extravascular compartments and the rates of intercompartmental exchange. The rates of synthesis and catabolism of the protein should also be given.

Tracer experiments can be directed towards either the anabolic or catabolic components of PP metabolism.

Received March 9, 1967; accepted Oct. 19, 1967.

* Present address: Faculty of Medicine, University of Alexandria, U.A.R.

Radiotracer study of PP synthesis involves the introduction of a labeled amino acid into the precursor pool. Some method is then needed to evaluate the specific activity of the intracellular amino-acid pool as well as the product protein. The realization of these two measurements and their use in the calculation of the absolute synthesis rate of protein will be discussed later.

In the most commonly used *catabolic-type radiotracer study* an aliquot of a preformed plasma protein is labeled *in vitro* with radioiodine; it is then reintroduced into plasma, and its disappearance is recorded for a given time. The distribution of the labeled protein and its catabolic rate can then be deduced.

Both anabolic and catabolic types of radiotracer studies are technically feasible in clinical applications. However, each has its own specific merits and limits of applicability.

Studies of synthesis require the existence of a single well-defined precursor pool for the specific plasma protein. Albumin and fibrinogen, for example, are formed exclusively in the liver and are therefore particularly suitable for synthesis studies. Gamma-globulin, on the other hand, is synthesized by the widely distributed lymphocytic cells and the precursor pool is too diffuse for the effective use of anabolic tracer methods.

A catabolic study can give the kinetics of distribution of the labeled protein as well as its catabolic rate. The synthesis rate can be equated to that of catabolism in an equilibrated system. A study of synthesis, on the other hand, gives the anabolic rate directly but does not indicate the distribution of protein.

Catabolic studies which last 2 or 3 weeks require the assumption of a steady state. A study of synthesis, in contrast, can be completed in a few hours and an unsteady state can be tolerated because the metabolic activities are unlikely to alter dramatically during the course of a few hours. This method is therefore applicable during the expansion or disintegration of the protein system before the full activation of feedback and homeostatic factors alter the metabolic state to a new equilibrium. Such disequilibrium states are of considerable interest from the standpoint of understanding basic physiologic functions as well as of clarifying mechanisms involved in the changing protein system.

Attempts have been made recently to extend the mathematical formulation of the catabolic studies with radioiodine-labeled proteins beyond the steady state (*31,32*). The difficulties that such an approach encounters are not only in the mathematical formulations, but also in the adequate physical description of the prevailing physiologic processes in the unsteady metabolic system. This is particularly critical when the feedback and homeostatic regulatory mechanisms have to be considered (*32*).

METHODS OF EVALUATING PLASMA-PROTEIN SYNTHESIS RATE

Direct method. The use of labeled amino acids for measuring synthesis of PP depends on the precursor-product relationships defined by Zilversmit (*33*) and Reiner (*34*). These methods are applicable only in the case of liver-produced PP as will be shown below.

When a labeled amino acid is injected, the absolute rate of synthesis of a specific protein product is given by

$$\text{synthesis rate} = f/ta\bar{S} \quad \text{gm/hr} \qquad (1)$$

in which f is the fraction of the injected radioactivity appearing in protein in the course of t hours, a is the mass in grams of the particular amino-acid residue in 1 gm protein and $\bar{S}$ is the mean specific activity of the intracellular free amino acid at the site of synthesis expressed as a fraction of the injected radioactivity per gram amino acid. The value of f in Expression 1 is given by

$$f = a\left[s(t) + k\int_0^t s(b)\,db\right]\frac{1}{P} \qquad (2)$$

where s(t) is the specific activity of the employed amino acid in protein at time t, k is the fraction of labeled protein formed at time b and lost in the interval t-b through diffusion into the extravascular space or catabolism, b is any time between $0 \leq b \leq t$ and p is the total mass of intravascular protein. In tracer synthetic studies lasting only a few hours no correction for the return of labeled protein from the extravascular space is needed. Moreover reutilization of the labeled amino acid released from the breakdown of labeled proteins can be neglected in such short-term studies (*35*).

The value of f in Eq. 2 can be determined directly by specific-activity measurements of the circulating protein, provided that the amino-acid precursor used is not readily converted into other amino acids so that the radioactivity in protein remains associated with one amino acid only. However, the metabolism of most labeled amino acids used in clinical and experimental studies results in secondary labeling of other amino acids, e.g., labeling of serine from injected ^{14}C-glycine (*36*) or labeling of cysteine and cystine after the injection of ^{35}S- or ^{75}Se-labeled methionine (*37,38*). The usual practice, therefore, involves the hydrolysis of the purified plasma protein and the isolation of the amino acid

from the hydrolysate for specific-activity determination (*39*).

The integral in Eq. 2 is determined by graphic integration of the plot of the specific activity of the amino acid in protein hydrolysate as a function of time. The value of k in the same equation has to be determined by an independent method, e.g., from the plasma disappearance curve of the radioiodinated protein (*35,39*).

The major remaining problem is the determination of the specific activity of the intracellular precursor pool. This can be realized directly in experimental animals by measuring the tissue free-amino-acid pool (*36,37*). However, only indirect methods can be used in man since the precursor amino-acid pool cannot be adequately sampled. Direct or indirect determinations can only yield average values for the specific activity of the intracellular pool prevailing at any one time. It is not certain whether such an average does in fact represent the specific activity at the exact locus of synthesis. Subcellular particles may have different specific activities by virtue of differences in their permeability or in the size of their amino-acid pool (*40*).

Indirect methods. The following sections will deal with the available indirect methods for evaluating the specific activity of the precursor pool in man.

External indicators of precursor specific activity: general principles. Derivatives of certain amino acids are formed exclusively in the liver and are excreted in urine. Such derivatives can be used as indicators of the intrahepatic specific activity of precursor amino acids.

Let the amino-acid pool be represented by X and its specific activity at time t following the intravenous injection of its labeled counterpart by x(t). Suppose that the derivative exists as a single pool I, with a specific activity i(t) at time t. The excretion of the indicator derivative can be schematically represented as:

$$\longrightarrow X \xrightarrow{F_I} I \xrightarrow{E_I}$$

where F_I is the rate of formation of the indicator and E_I is the rate of its excretion in urine. Under equilibrium conditions $E_I = F_I$ and the rate of increase of the amount of radioactivity associated with the pool I is given by

$$I\frac{di}{dt} = F_I\,x(t) - E_I\,i(t) = E_I\left[\,x(t) - i(t)\,\right] \quad (3)$$

$$\text{and } x(t) = i(t) + \frac{I}{E_I}\frac{di}{dt}. \quad (4)$$

In Eq. 4 i(t) and di/dt are obtained from the specific-activity curve of the indicator excreted in urine. The value of I/E_I is the reciprocal of the fractional excretion rate of an intravenously injected quantity of the indicator substance, i.e., the reciprocal of E_I/I. A specific example of this method follows.

Urinary hippurate as an indicator of hepatic glycine specific activity. Hippuric acid is formed in the liver by the conjugation of benzoic acid with glycine. Urinary hippurate can therefore be used as an indicator of hepatic glycine specific activity following administration of ^{15}N or ^{14}C-glycine (*41*). The ^{15}N-label is extremely labile since transamination results in the transfer of labeled-NH_2 groups to other amino acids. It has been shown, however, that this transfer is not as rapid as the rates of other metabolic reactions of amino acids (*42*). The label of ^{14}C-glycine is less labile, but glycine is transformed rapidly and reversibly into serine and glutathione. The reversibility of these reactions results in the persistence of the labeled glycine precursor in the free amino-acid pool for a comparatively long time (*36*). In man, excretion of hippuric acid of a high specific activity continues for 20–30 days following the injection of ^{14}C-glycine (*43*).

Weissman *et al* (*43*) reintroduced the hippuric acid method for the measurement of the synthesis of serum albumin. The theoretical arguments of their method are of interest although the procedure itself is too complicated for routine clinical use.

In actual practice the hepatic glycine specific-activity curve (as indicated by urinary hippurate) is resolved graphically into three components. The specific-activity curve of glycine in serum albumin also can be resolved graphically into a number of components after correction for overlap of components. Weissman and co-workers (*43*) could resolve one such curve into five distinct components. Three of the five exponents could be matched and identified with the three decay constants of the hepatic glycine specific-activity curve.

The method is cumbersome and involves laborious graphic resolution of two specific-activity curves over a period of about 20 days. The physiologic significance of the decay constants and their coefficients has not been determined. It is also assumed that the hepatic glycine pool is constant throughout the study, an unrealistic assumption even under normal physiologic conditions. Moreover, advocates of the method did not consider the possibility of some degree of reutilization of the glycine label occurring during the 20-day period of sampling.

Other amino-acid derivatives that are formed in the liver and excreted in urine include 1-phenacylglutamine, a derivative of glutamine, the conjugate of cysteine and bromobenzene and urea (from the guanido carbon of arginines). This last reaction has

proved to be of practical use and will be discussed in detail.

Precursor-product relationships circumventing the necessity of measuring the specific activity of the precursor pool: The general scheme. Let A be a precursor compound whose pool size at time t is given by A(t). Consider two products, B and C, which are exclusively formed from A in one and only one metabolic system, and let A, B and C possess a common chemical site, s, which can be effectively labeled. If k_b and k_c are, respectively, the two rate constants of the two reactions A → B and A → C expressed as fractions of A per unit of time, then the masses of the products B and C formed from A during a time interval t_0,t_1 are given, respectively, by

$$B(t_0,t_1) = nk_b \int_{t_0}^{t_1} A(t)\,dt \qquad (5)$$

$$\text{and } C(t_0,t_1) = mk_c \int_{t_0}^{t_1} A(t)\,dt \qquad (6)$$

where n and m are, respectively, the ratios of the number of grams of B and C to the number of grams of A in B or C in the event that precursor A is incorporated intact in B or C. Alternatively, if the products are simple chemical modifications converting A into the two products with preservation of the specific locus s, then n and M represent, respectively, the ratios of 1 gm of the product to the mass of A in grams necessary to synthesize 1 gm of the product.

It is noted that Expressions 5 and 6 permit the possibility that the pool A is variable and is hence given as a function of time. This contrasts with the expression for the glycine pool size where it is assumed to be constant.

The ratio of the masses of the products formed during t_0,t_1 is given by

$$\frac{B(t_0,t_1)}{C(t_0,t_1)} = \frac{nk_b}{mk_c}. \qquad (7)$$

If a radioactive precursor A* labeled in the specific locus s is introduced into the reaction system, radioactivity will eventually appear in B and C. During the time interval t_0,t_1, the radioactivity B* appearing in B is given as

$$B^*(t_0,t_1) = k_b \int_{t_0}^{t_1} A(t)\,a(t)\,dt. \qquad (8)$$

Similarly the radioactivity C* appearing in C is given by

$$C^*(t_0,t_1) = k_c \int_{t_0}^{t_1} A(t)\,a(t)\,dt \qquad (9)$$

where a(t) in both expressions represents the instantaneous specific activity of A. The ratio B*/C* is given by

$$\frac{B^*(t_0,t_1)}{C^*(t_0,t_1)} = \frac{k_b\ B(t_0,t_1)\ m}{k_c\ C(t_0,t_1)\ n}. \qquad (10)$$

The last expression can be written in an alternative way:

During the interval (t_0,t_1).

$$\frac{\text{Radioactivity entering B}}{\text{Radioactivity entering C}} \qquad (10a)$$

$$= \frac{\text{Mass of A entering (or converted into) B}}{\text{Mass of A entering (or converted into) C}}$$

or

$$\text{Mass of A entering B} = \frac{\text{Radioactivity entering B}}{\text{Radioactivity entering C}} \times \text{Mass of A entering C} \qquad (10b)$$

If B is a liver-produced PP and A is a precursor amino acid which can be labeled in a specific site, the problem of measuring protein synthesis will resolve itself into finding a product C that is exclusively formed in the liver to which the radioactive marker can be transferred by a specific metabolic reaction and whose synthesis can be measured by some relatively simple independent method. Examples of this method are as follows.

1. The arginine urea system: Urea synthesis in the liver proceeds according to the following reactions:

CO_2 + ammonia + ornithine → Citrulline

Citrulline + ammonia ——→ Arginine

Arginine + arginase ——→ Urea + ornithine.

These reactions take place exclusively in the liver. Arginine represents precursor A in the general scheme whereas the carbon atom in the 6-guanido position of arginine corresponds to the specific locus s which can be substituted by ^{14}C and which is the origin of urea carbon. Products B and C in this system are, respectively, a liver-produced PP (e.g., albumin or fibrinogen) and urea.

A specialized form of Relation 10b can be written:

$$\text{Arginine guanido C entering albumin} = \frac{\text{Radioactivity entering albumin}}{\text{Radioactivity entering urea}} \times \text{Guanido C used in urea synthesis.} \qquad (11)$$

Dividing both sides of this equation by the mass of guanidine carbon in the arginine of the total serum albumin we obtain in a given time interval:

Fractional synthesis of protein

$$= \text{Urea synthesis (gm) urea carbon} \times \frac{\text{Spec. act. of quanido C in arginine of protein}}{\text{Total activity associated with urea}} \quad (12)$$

The arginine-urea system was first used in the study of PP metabolism by Swick (*44*). It could be demonstrated that urea carbon emerging from the liver of rats fed for several days on a diet containing constant amounts of $Ca^{14}CO_3$ could be used as an indicator of the specific activity of guanido carbon of free hepatic arginine. McFarlane (*45*) substituted a single injection of ^{14}C-carbonate for the continuous feeding procedure of Swick with the advantage that only a minute fraction of the ^{14}C-label is incorporated as guanidine carbon in liver-produced PP, whereas the feeding procedure will result in extensive labeling of blood and tissue proteins. Reeve and co-workers used a single intravenous injection of 6-^{14}C-arginine with the advantage of a higher utilization efficiency in protein synthesis (*35*). The carbonate method has a lower utilization efficiency, yet there is preferential labeling of liver-produced PP because 6-^{14}C-arginine is exclusively formed in the liver (*39*).

The actual procedure takes 4–6 hr and involves separation of albumin or fibrinogen from 4–6 sequential plasma samples, protein hydrolysis and isolation of arginine on an ion-exchange resin. The specific activity of guanido carbon of arginine is determined after its conversion into CO_2 by incubation with arginase (*39*). Urea carbon specific activity is also determined as CO_2 liberated through the action of urease (*46*). From these specific-activity measurements the total activity associated with urea can be calculated. This included both the urea excreted in urine during a given time interval as well as urea retained in body water.

The specific activity of guanido carbon of arginine in protein should be corrected for the fraction of labeled protein lost by diffusion and catabolism.

This loss can be estimated by the injection of the corresponding radioiodinated human protein simultaneously with the ^{14}C-label. Alternatively an approximate correction can be introduced by increasing the apparent synthetic rate by 10% for both albumin and fibrinogen when the interval used is 3.5–4.4 hr and by 15% for intervals between 5.9 and 6.6 hr (*39*). This correction does not take into consideration individual variations of these values.

The main difficulty of the urea-arginine method is the estimation of urea synthesis used in expression (*12*). In the original procedures of Reeve (*35*) and McFarlane (*39*) urea synthesized in the interval t_0,t_1 was equated with

Urea excreted in urine during the interval
= Urea in body water at t_1
− Urea in body water at t_0.

It was soon realized that such an estimate is not accurate in view of certain pecularities of urea metabolism (*46*). Endogenous decomposition of urea, a phenomenon that was demonstrated in the forties (*47,48*) can lead to an underestimate of urea synthesis if calculated from the above formula. Most of the degradation of urea takes place through the urease activity of micro-organisms (*49–52*) although some urease activity is also found in the liver, kidney and gastric mucosa (*49,53,54*). Endogenous degradation can be minimized by the administration of neomycin (*46*). Extrahepatic synthesis of urea is another source of error. Arginase activity has been demonstrated in the skin (*55*), brain (*56*) and intestinal coliform bacteria (*57*). Protein-synthesis measurement then will be in error in proportion to the extent of extrahepatic urea synthesis.

In an attempt to circumvent these difficulties, McFarlane derived the fractional synthetic rate of urea from the disappearance curve of injected ^{13}C-urea, whose slope k gives the fractional catabolic rate which can be equated to that of synthesis in an equilibrated urea system (*58*). The disappearance curve of endogenously labeled ^{14}C-urea following the administration of ^{14}C-carbonate or ^{14}C-arginine cannot be used to derive the fractional catabolic rate. The continued synthesis of urea from hepatic arginine and the demonstration of the occurrence of significant reutilization of the ^{14}C-label in the synthesis of both urea and protein (*58*) will result in an underestimation of urea degradation. The situation is even worse if ^{15}N-urea is used as an indicator of urea catabolism (*58*). It would seem, therefore, that the best estimate of urea degradation is that derived from the disappearance of intravenously injected ^{13}C-urea.

To convert the urea fractional synthetic rate into mass of urea, k has to be multiplied by the urea pool size. The estimate of the pool size, however, has its own difficulties. One of these is that urea concentrations within the different compartments of body water might differ from that of plasma (*60,61*). A second difficulty is the recent demonstration of the existence of a renal urea pool not exchangeable with total-body urea and accounting for 2–15% of the total pool (*46*). In view of these considerations, an expression for protein synthesis can be derived by rewriting Eq. 12 as follows:

Fractional rate of synthesis of protein

$$= \text{Fractional rate of synthesis of urea} \times \quad (13)$$

$$\frac{\text{Spec. activity of guanido C in protein at } t_0}{\text{Spec. activity of guanido C in urea at } t_0}.$$

The new expression for rate of protein synthesis of urea equals 1.02 times the apparent slope of the ^{13}C-urea disappearance curve. The factor 1.02 allows for the net transfer of activity from extravascular urea since plasma urea specific activity decreases faster than that of extravascular urea with consequent transfer of label (*58*). The specific activity of urea at t_0 is obtained by extrapolating the disappearance curve of the endogenously labeled ^{14}C-urea back to zero time. The specific activity of guanido carbon in protein at t_0 is obtained from the observed specific activity at the end of the chosen time interval after correction for losses by diffusion or catabolism as described before.

To minimize urea reabsorption through the urinary bladder mucosa, frequent urine collection, possibly with help of an indwelling catheter, is recommended.

The final test of the feasibility of the urea-arginine method, and indeed of any other synthetic procedure, is to compare the synthetic rate obtained by the method with the catabolic rate of the corresponding radioiodinated protein in the same subject while in equilibrium. Such comparisons were reported by McFarlane (*58*) and by Reeve (*35*). Both groups of workers obtained agreement between synthetic rate and catabolic rate with 4–25% variation for albumin, and 2–35% variation for fibrinogen. In addition to the experimental errors involved, part of these differences can be related to the theoretical assumptions implicit in each type of measurement. Extrahepatic synthesis of urea is a contributing factor to the error involved in the measurement of synthesis.

2. The cyst(e)ine-sulfate system: For all practical purposes cysteine and cystine can be considered as one amino acid, and both will be referred to as cyst(e)ine. They are found incorporated into protein and their sulfur can be oxidized into inorganic sulfate, the highest oxidation product of sulfur in the mammalian organism. The only alteration that inorganic sulfate can undergo is its conjugation to form ethereal sulfates (*62*).

Thus, inorganic sulfate can represent product C of the general scheme whereas cyst(e)ine corresponds to the precursor A with sulfur as the specific locus.

In contrast to urea, endogenous sulfate synthesis can be measured after a period of a few hours of withdrawal from food and fluids by measuring the urinary output and adjusting for concentration changes in the sulfate space, with fasting continued during the period of blood sampling and urine collection (*63*).

However, it is still to be shown that endogenous sulfate is either exclusively formed in the liver from cyst(e)ine sulfur or that extrahepatic sulfate formation does not exceed 10–20% of the total sulfate production.

Work in this area is still in its early stages and results have not yet been reported.

Catabolic-Anabolic Balance Method. As was mentioned earlier the radioiodinated protein method essentially gives the catabolic rate of the labeled protein. This can be considered to equal synthesis rate in an equilibrated system. Grossman (*64*), however, developed an expression for synthesis from the plasma specific-activity curve of radioiodinated albumin independent of the existence of a steady state.

The measurement of PP anabolism from the radioiodinated protein specific activity curve. Following the distribution of the injected labeled protein, the specific activity of plasma albumin P is assumed to be equal to the mean specific activity of body albumin. At equilibrium the following relation holds for the total retained radioactivity A:

$$A = PQ \qquad (14)$$

in which Q is the total exchangeable body albumin.

In absence of albuminuria the urinary excretion of radioiodinated albumin a can be equated to the rate of change of retained radioactivity dA/dt. If the catabolic rate of albumin is c gm/day, then

$$a = dA/dt = -Pc. \qquad (15)$$

Differentiating Eq. 14,

$$\frac{dA}{dt} = \frac{dP}{dt}Q + \frac{dQ}{dt}P = sQ + qP \qquad (16)$$

for s = rate of change of plasma albumin specific activity and q = rate of change of total exchangeable albumin.

Substituting 16 in 15,

$$a = dA/dt = sQ + qP = -Pc. \qquad (17)$$

But q = f—c for f = rate of albumin synthesis in gm/day. In steady states, q = f—c = 0, and in unsteady states we can substitute f—c for q in Eq. 17 to get

$$sQ + qP = sQ + (f—c)\,P = -Pc. \qquad (18)$$

By rearrangement we have

$$sQ + (f—c)\,P + Pc = 0$$

and

$$sQ + fP = 0$$

or

$$\frac{f}{Q} = \frac{-s}{P} = \frac{-dP}{P\,dt} = \frac{-d(\ln P)}{dt}. \qquad (19)$$

In other words, the fractional catabolic rate of albumin is the negative slope of the natural log of the curve obtained by plotting the natural log of

serum albumin specific activity as a function of time after the preliminary equilibrium period.

The fundamental premise of this method is the assumption of equality of the serum albumin specific activity with the average specific activity of body albumin so that the fall of the latter's specific activity is a function of the rate of formation of new unlabeled albumin. More rigorous mathematical description of the kinetics of iodoalbumin (*20,65*), however, shows a net transfer of labeled albumin from the extravascular space back to plasma where it is catabolized. The existence of specific-activity differences between plasma and interstitial albumin would affect the slope of the serum-albumin specific-activity curve unrelated to synthesis of unlabeled albumin. Moreover, a knowledge of the relative pool size of the plasma and extravascular protein and the changes that may occur during the period of measurement are required. The advantage of the method, however, is that it gives estimates of both the catabolic and anabolic components of the metabolism of the labeled protein with the use of a single tracer.

CONCLUSION

The theoretical rationale and methodology for the clinical assessment of plasma-protein synthesis has been discussed. The catabolic-anabolic balance methods are the simplest to perform on a routine basis, but they suffer from the necessity of assuming a steady state and prolonged observation time which cause rapid or short-term alterations in plasma-protein anabolism to be obscured. The indirect methods relying on precursor-product relationship which avoid the necessity of measuring the specific activity of the precursor pool are the most practical means of determining plasma-protein synthesis on a short-term basis. Of these techniques, the arginine-urea system advocated by McFarlane currently provides the most reliable assessment of albumin and fibrinogen biosynthesis, notwithstanding the limitation of extrahepatic urea formation. The proposed cyst(e)ine-sulfate system offers advantages over the current methods from both a technical and theoretical point of view. However, the site of endogenous sulfate formation must be clearly defined before this method can achieve routine clinical application.

ACKNOWLEDGMENT

This project was supported in part by U.S. Atomic Energy Commission, Contract AT(30-1) 3442 under which this manuscript becomes Document NYO 3442-20.

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