Multiple myeloma is an invariably fatal tumor of the plasma cells, which are thought to be involved in antibody production. The disease is generally accompanied by hyperglobulinemia, Bence-Jones proteinuria, or both aberrations in protein synthesis. Although both the myeloma serum globulin and the unique urinary protein are thought to be formed within the tumor cell, no metabolic relationship has yet been demonstrated between the two types of abnormal proteins. Furthermore, accumulating evidence indicates not only that different patients produce individually characteristic globulins that are related to normal serum proteins (1, 2), yet distinguishable from them, but also that the Bence-Jones proteins excreted by different patients are not identical (3, 4). Previous study with N16-glycine and with glycine-1-C¹³ has refuted the hypothesis that the Bence-Jones proteins are derived by renal cleavage of the abnormal serum globulins and has suggested that the two types of pathological proteins may be synthesized independently (5, 6). These experimental results, since confirmed (7–9), did establish that the urinary protein is rapidly formed from the administered amino acids and is rapidly excreted. In order to investigate further whether the synthesis of Bence-Jones protein is related to that of the myeloma globulin, 450 μc. of DL-glutamic acid-1-C¹⁴ were injected into a patient who was catheterized to permit frequent withdrawal of blood and urine specimens. The accompanying paper (10) has described the subject and protocol of the experiment and the metabolic fate of the racemic amino acid; this communication reports the data relevant to the biosynthesis of the abnormal proteins. Significant radioactivity was not detected in either the Bence-Jones protein or the myeloma globulin until about 40 minutes after injection. The subsequent time-course of radioactivity is discussed in terms of possible biosynthetic relationships between the two abnormal proteins.

* Aided by research grants from the National Cancer Institute, National Institutes of Health (No. C-1331-C4), and from the American Cancer Society.
EXPERIMENTAL

Methods and Procedures

Radioactivity Measurements—Specific activity rate curves were obtained for four non-protein metabolic products of the injected amino acid, namely (a) expiratory CO₂ (10), (b) the urinary urea CO₂ liberated by urease (10), (c) the CO₂ released by ninhydrin from urinary amino acids, chiefly D-glutamic acid (10), and (d) the CO₂ liberated from L-glutamic acid of serum by the optically specific glutamic acid decarboxylase from Escherichia coli (Table I). Rate data were also obtained for two fractions of the Bence-

TABLE I
Summary of Radioactivity Measurements after Injection of DL-Glutamic Acid-1-C¹⁴

<table>
<thead>
<tr>
<th>Material</th>
<th>Source</th>
<th>Period of study</th>
<th>Time of maximal activity</th>
<th>Approximate half time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. L-Glutamic acid</td>
<td>Serum</td>
<td>12</td>
<td>0.1 (Ca.)</td>
<td>0.75</td>
</tr>
<tr>
<td>2. Expiratory CO₂</td>
<td>Breath</td>
<td>8</td>
<td>0.4</td>
<td>1.5</td>
</tr>
<tr>
<td>3. p-Glutamic acid</td>
<td>Urine</td>
<td>24</td>
<td>0.5† (Ca.)</td>
<td>1.4</td>
</tr>
<tr>
<td>4. Urea</td>
<td>&quot;</td>
<td>42</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>5. Residue‡</td>
<td>&quot;</td>
<td>19</td>
<td>3.5</td>
<td>8</td>
</tr>
<tr>
<td>6. Bence-Jones protein</td>
<td>Soluble (S)</td>
<td>&quot;</td>
<td>4</td>
<td>7, 10, 32</td>
</tr>
<tr>
<td></td>
<td>Ppt. (P)</td>
<td>&quot;</td>
<td>5</td>
<td>7.5, 21</td>
</tr>
<tr>
<td>7. γ-Globulin</td>
<td>Serum</td>
<td>50</td>
<td>10</td>
<td>&gt;48</td>
</tr>
</tbody>
</table>

* In most cases the decline was not strictly exponential. For Bence-Jones protein the curve has been broken down into several segments.
† Refers to the time of maximal counts per minute excreted per minute, not to maximal sample activity.
‡ The material remaining after ninhydrin treatment of the urine specimen.

Jones protein that differed in solubility and for the myeloma serum globulin prepared by salt precipitation. The radioactivity of the proteins was measured as previously described (10) with the data expressed as counts per minute (c.p.m.) per mg. of protein.

Serum Proteins—By chemical analysis the total serum protein was 8.1 gm. per cent, with an albumin-globulin ratio of 0.7. Electrophoretic analysis by the Tiselius method revealed a sharp peak in the γ-globulin region characteristic of myeloma globulin. This component had a mobility of 1.5 X 10⁻⁴ cm.² sec.⁻¹ volt⁻¹ and comprised 30 per cent of the total serum protein (Fig. 1). The percentage distribution of the remaining serum proteins was as follows: albumin 39, α₁-globulin 6, α₂-globulin 10, and β-globulin 15.

The myeloma globulin from 10 to 15 ml. aliquots of the nineteen serum
samples of the first 24 hours was precipitated in separate sacs by simultaneous dialysis against several changes of 1.6 M ammonium sulfate at pH 6.5 in the cold. The precipitates were washed with the salt solution, dialyzed until free of sulfate ion, and lyophilized. Ultracentrifugal analysis of representative samples demonstrated a predominant component with a sedimentation constant \( (s_{20,w}) \) of 6.55 Svedberg units at infinite dilution and only a very small amount of higher molecular weight globulin. About 95 per cent of the protein migrated as a single component at pH 8.6 in the Tiselius apparatus. Serum fractions corresponding to albumin, \( \alpha_1 \) plus \( \alpha_2 \), \( \beta \), and \( \gamma \)-globulins were also obtained by starch zone electrophoresis (11) of 1 to 2 ml. samples. The starch zone patterns almost duplicated those obtained by free electrophoresis, and the physical constants

and the homogeneity of the electrophoretically isolated and the salt-precipitated globulin were closely similar.

**Bence-Jones Protein**—The Bence-Jones protein was prepared from forty-nine consecutive urine samples representing a complete collection up to 234 hours after the injection. The protein was precipitated by dialysis in separate sacs against several changes of 3 M ammonium sulfate at pH 5 in the cold. The precipitates were washed with the salt solution, dispersed in water, and dialyzed against distilled water until free of sulfate. Both sometime prior to and several months after the experiment, the patient's urine, when treated by this procedure, yielded a protein that was soluble in distilled water and migrated in the Tiselius apparatus at pH 8.6 with a single major boundary (about 90 to 95 per cent). However, in every urine sample in the tracer experiment some of the labeled protein formed a gray-brown precipitate on dialysis against distilled water. Since this precip-

---

**Fig. 1.** Electrophoretic diagram of the serum in Veronal buffer, pH 8.6, after migration for 200 minutes at 16 ma. The arrows designate both the direction of migration and the myeloma globulin peak.
stitute was insoluble in common buffers, it was removed by centrifugation and lyophilized (designated P). The supernatant solution (S) likewise was lyophilized. Thus, some 100 samples of Bence-Jones protein were prepared for counting. Uniform deposition on planchets was accomplished by dissolving both S and P samples with 0.02 N NaOH. A variety of tests including comparison of rate activity curves, dialysis, and the reaction with ninhydrin and with glutamic decarboxylase assured that the Bence-Jones protein was not labeled spuriously by adsorption (10).

It was established that neither the S nor the P fractions were homogeneous by ultracentrifugal or electrophoretic analysis. Subsequently, an electrophoretic study was made of representative specimens of the frozen urine from this experiment, for the urine did not yield much precipitate on equilibration with Veronal buffer, pH 8.6, at 4°. This study revealed a remarkable progressive change in the electrophoretic pattern during the brief course of the experiment. The apparent number of components varied from two at 35 minutes to four at 36 hours. This Bence-Jones protein (He), alone of thirteen studied, could not be typed serologically because of heterogeneity; it also was the most heterogeneous specimen on the basis of N-terminal group analysis (4). The qualitative heat coagulation test was positive at 56°, but the protein was not completely soluble at 100°. No albumin was detectable by electrophoretic or ultracentrifugal analysis. The cause of the unexpected heterogeneity of the Bence-Jones protein was not determined, but it may have been the result of therapeutic x-radiation of the patient several days before the experiment.

Results

The specific activity-time curve for the Bence-Jones protein has four characteristics: (1) a short lag of about 40 minutes to be denoted the "transit time" (Fig. 2), (2) a rapid and nearly linear rise to a sharp maximum (period of constant incorporation) (Fig. 2), (3) a somewhat slower decline, the "excretion curve" (Fig. 3), and (4) a flat prolongation (Fig. 3), attributable both to "feedback," i.e. the return of tracer amino acid to the body pool owing to degradation of labeled tissue proteins, and to protein exchange between vascular and extravascular compartments. Since the curves for the S and P proteins are so similar, no further distinction between the two products will be made.

Transit Time—From Fig. 2 the "transit time" is seen to be about 40

---

1 The electrophoretic pattern of the urine at 36 hours was very similar to that of a saline extract of the patient's tumor. All of the urine protein had an $s_{0.5}$ of 3.4 S or lower; i.e., serum proteins were not excreted in ultracentrifugally detectable amounts.
minutes for both the S and P fractions of Bence-Jones protein, as well as for the myeloma globulin. In all three cases this delay is followed by a nearly linear rise period of about 2 hours, which is interpreted as resulting from a constant rate of isotope incorporation. About the same lag period was found for all the serum protein fractions isolated by starch zone electrophoresis. Similar initial rate curves were first observed by Green and Anker (12) for serum proteins of the rabbit and turtle and the hemocyanin of the horseshoe crab. Dalgliesh (13) has reviewed other evidence for the existence of a delay in protein synthesis.

In the case of Bence-Jones protein the time for renal excretion must be added to the above process. In an earlier experiment (7) the transit time for Bence-Jones protein was found to be not less than 30 minutes.

![Image](http://www.jbc.org/)

**Fig. 2.** Specific activity of Bence-Jones protein Fractions S and P and of the myeloma globulin during the first 6 hours after administration of $\text{L-}$glutamic acid-$1$-$\text{C}^{14}$. Note the 10-fold difference in the two ordinate scales.

From the identity in transit times of the two abnormal proteins (Fig. 2) it would appear that the limiting factor for urinary appearance of labeled Bence-Jones protein is not the time required for renal excretion but rather some function of the synthetic process. Further evidence for rapid renal clearance was found in later experiments. For example, when a pooled sample of the same labeled protein was injected intravenously into the donor patient at a later period, the activity of the first urinary sample excreted (at 2 hours) was almost maximal even though he was then uremic (urea clearance of 2.0 as calculated by the square root method). When labeled Bence-Jones protein is injected into the ear vein of a rabbit, the greatest decline in serum activity occurs in the 1st half-hour, most of the

---

2 The transit period has been defined as "the time required for an amino acid residue to pass from the free amino acid pool to the circulating serum protein" and is reported to be practically independent of experimental conditions (12).
protein being excreted in the urine within the first few hours. The normal human kidney, given an overload of 60 gm. of dextran of 34,000 average molecular weight, which is comparable in size to Bence-Jones protein, excretes about one-third in the 1st hour (14). It is significant that a diuresis occurred during the transit time. All this does not disprove that there is a kidney transit time of 15 to 30 minutes for Bence-Jones protein. However, if such is the case, the activity curve for circulating Bence-Jones protein would be displaced towards the left compared to Fig. 2 for urinary protein.

Excretion Curve—Except for the displacement towards a shorter time axis, the excretion curve of Fig. 3 resembles those previously obtained (5-8) and exhibits the remarkable similarity to the excretion curve for urinary urea radioactivity already noted (6, 8, 10). The surprising feature is the rapidity of excretion despite serious renal damage. The cumulative urinary excretion of labeled Bence-Jones protein was estimated by averaging the specific activity (c.p.m. per mg.) of S and P in each sample and multiplying by the total weight of protein present. Unlike the curve for cumulative urinary excretion of dextran of comparable molecular weight (14), the analogous curve for the Bence-Jones protein does not level off

\[676\]

PROTEINS IN MULTIPLE MYELOMA

---

after 12 hours (Fig. 3). The failure to do so may be attributed to the length of the period of isotope incorporation, to tissue redistribution, and to the feedback phenomenon. For comparative purposes note that 6000 c.p.m. were excreted via protein in the 1st hour, 54,000 in the 4th hour, and 4000 in the 50th hour.

Recycling Phenomenon—Unlike the turnover curves of serum or tissue proteins with half life times of a week or more, the rapidly declining activity curve for Bence-Jones protein is little affected during its major phase by the feedback phenomenon. Hence, the decline in activity of the P protein was strictly exponential during the first 24 hours, during which time the activity fell to one-seventh of the maximum. The half time was 7.5 hours. There followed an intermediate phase having a half time of about 21 hours, which may well reflect the distribution process between vascular and extravascular tissues, and subsequently there was an even slower decline, probably owing to feedback. After 234 hours the specific activity was 1 to 2 c.p.m. per mg. The S protein followed a similar but more erratic course.

Serum Radioactivity—Whereas the initial uptake of Cl4 by the myeloma globulin follows a course similar to that for Bence-Jones protein (Fig. 2), the maximum for the globulin apparently occurs later and is certainly much lower and broader (Fig. 4). These results, in keeping with earlier experiments (5, 6, 8, 9), emphasize that the turnover of myeloma globulin parallels that of normal serum globulins; such differences in half life as may exist cannot be evaluated from the present data. The transit time is slightly longer than for the total serum proteins of the rabbit (12), but in other respects the character of the initial part of the curve is similar in the two species.

The activity of serum L-glutamic acid shows a precipitous decline during the transit period for both abnormal proteins (Fig. 4). Indeed, for the first 2 hours, the decline in activity of the amino acid is exponential with a half time of 45 minutes; thereafter a departure from logarithmic behavior occurs. Since the transport and cellular distribution of the amino acid require only 1 to 2 minutes (12), the transit period may reflect an absolute time requirement for protein synthesis de novo from amino acids, the intervention of intermediate synthetic reactions, physical processes such as the diffusion of the newly formed protein into the circulation, or the sum of several of these steps.

The data for serum proteins isolated by starch zone electrophoresis

4 Note that the specific activities of the myeloma globulin and the Bence-Jones protein are plotted on different ordinate scales in Fig. 2 to illustrate the similarity of the uptake curves but are given to the same ordinate scale in Fig. 4 to emphasize their different magnitudes.
were less consistent than those plotted in Fig. 4 for the myeloma globulin purified by salt precipitation, probably because much less radioactive protein was made available for counting in the case of the zone method, and possibly because of the effect of freezing on the properties of the lipoproteins. However, the results for the myeloma globulin prepared by the zone method were not systematically different from those depicted in Fig. 4; i.e., no activity was detectable until after 40 minutes, a broad delayed maximum was found, and except for two erratic points the activity was

![Graph showing specific activity over time](http://www.jbc.org/)  
**Fig. 4.** Specific activity of Bence-Jones protein Fraction P, the myeloma globulin, and of serum L-glutamic acid in the first 20 hours after administration of DL-glutamic acid-1-C\(^{14}\). Note that the activity of the amino acid is expressed in different units from the activities of the proteins, but that the latter are plotted to the same ordinate scale.

within 2 to 4 c.p.m. of the values obtained for the salt-purified specimens. All the serum proteins showed a transit period, but within the first 24 hours no fraction had a specific activity more than one-quarter that of the urinary Bence-Jones protein at the same time interval. In every sample the \(\alpha\) and \(\beta\) fractions were more active than the myeloma globulin.

**DISCUSSION**

In choice of amino acid,\(^5\) isotope, position of label, route of administration, and method of sample collection, this investigation was designed to

\(^5\) Other experimental reasons for choice of glutamic acid-1-C\(^{14}\) are the susceptibility
approximate as closely as possible the optimal conditions for a single dose tracer experiment (15). Thus, glutamic acid, by virtue of the lability of its amino group and the key role of α-ketoglutarate in the citric acid cycle, is about the most active metabolically of the amino acids. Unlike previous studies of the biosynthesis of Bence-Jones protein with N15-labeled amino acids (6, 8), this experiment suffers little from the retention and redistribution of the tracer atom. The α-carboxyl-C14 is rapidly lost via expiratory CO2 or urea (Table I) and undergoes minimal incorporation into other amino acids (10). The extent to which optimal single dose tracer conditions were fulfilled is illustrated by the data summarized in Table I. It can be seen that all major changes in radioactivity occurred within the first 24 hours except in serum proteins (and presumably in tissue proteins). Indeed, the primary change in the non-protein metabolites reached a maximum by 2.5 hours and was complete within 10 hours.

In confirming the above, the excretion curve for labeled Bence-Jones protein was the most rapid yet recorded (2). The sharp peak of Fig. 3 results from rapid removal of the labeled molecules by urinary excretion. It signifies a body pool that is small compared to the rate of synthesis and excretion. On the other hand, the broad maximum for the γ-globulin stems from the dilution of labeled molecules by a large body pool that is subject to reduction only by the comparatively slow process of turnover. Thus, the divergence in the declining rate curves of Fig. 4 is mainly an effect of the different routes for removal of these proteins from the circulation. Without allowance for these effects it is impossible to deduce from the time-course of the activity curves a likely precursor-product relationship among the various substances listed in Table I by use of the Zilversmit-Reiner criteria (15).

In the rate analysis important qualitative and quantitative differences must be recognized. At the time of greatest activity of the myeloma globulin, the total body C14 content in this protein was 1.4 × 10⁸ c.p.m. (17 c.p.m. per mg. X 2.4 gm. per cent γ-globulin X 3500 ml. of serum), whereas up to this point only about 3 × 10⁵ c.p.m. had been excreted via urinary protein (Fig. 3). Indeed, the C14 content of the myeloma globulin at its

of the α-carboxyl to release by glutamic acid decarboxylase (L antipode) and by ninhydrin (p and L). This permits direct C14 measurement with use of the hydrolyzed proteins without isolation of the amino acid. Moreover, the p form is apparently not metabolized by man (10). The increased sensitivity gained by enzymatic release of the C14 from the hydrolyzed proteins enabled a study of the rate of excretion and the fate of biosynthetically labeled protein reinjected into the donor patient (see footnote 3).

6 By contrast, when N15-aspartic acid was administered to another patient, the glutamic acid of the urinary protein had a higher N15 abundance than did the aspartic acid of the protein, and most of the other amino acids of the excreted protein were highly labeled (8).
time of maximal activity was about 3 times the total C\(^{14}\) excreted via Bence-Jones protein during the term of the experiment. Thus, despite its lower specific activity in the first 24 hours, much more myeloma globulin than Bence-Jones protein was synthesized in this period.\(^7\)

The relative rates of synthesis of the two types of abnormal proteins can best be estimated from data for the constant period, during which most of the labeled protein was formed. Throughout this period the specific activity of the excreted Bence-Jones protein was about 10 times that of the circulating globulin (note the ordinates of Fig. 2). Nonetheless, about \(12 \times 10^6\) c.p.m. were incorporated into the myeloma globulin in the first 5 hours compared to only \(2 \times 10^5\) into the Bence-Jones protein. In other words, although the glutamic acid content of the two abnormal proteins is comparable (2), this amino acid was being used for the synthesis of the globulin 6 times as much as for the synthesis of the Bence-Jones protein. That is, the globulin was made from a more active precursor than the Bence-Jones protein, or was being made more rapidly, or both. This suggests that the myeloma globulin entering the blood stream in the first few hours may have been more radioactive than the Bence-Jones protein, which was diluted much less by its serum pool.

Various possibilities for the synthesis and metabolic fate of myeloma globulin and of Bence-Jones proteins are outlined schematically in Fig. 5. It cannot be presumed \textit{a priori} that any particular one of the pathways indicated by unblocked arrows does exist or is the sole pathway. At present, measurement of the activities of most of the pools indicated in the diagram is not feasible. Consequently, we must interpret on the basis of the radioactivity time curve for myeloma globulin in the serum and the Bence-Jones protein in the urine. Present evidence, both circumstantial and experimental (2), implicates the plasma cell tumor as the site of syn-

\(^7\) Because of the similarity in glutamic acid content of the two types of abnormal proteins (2) and because most of the radioactivity of the proteins was in this amino acid (10), the biosynthesis of the myeloma globulin and of the Bence-Jones protein can be compared in terms of their C\(^{14}\) content. The calculations of the magnitude of synthesis of the two abnormal proteins depend on the assumption that all of the Bence-Jones protein synthesized appears in the urine as such. However, after intravenous injection of the labeled Bence-Jones protein into the donor patient (H.H.), the specific activity of the excreted protein was much less than could be explained by the dilution calculated from the daily output. Moreover, whether the heterogeneous labeled protein from this patient (H.H.) or the much more homogeneous protein from another patient (?) was injected into rabbits, the excretion was rapid, but only a fraction of the injected protein appeared in the urine. All the organs investigated, the serum fractions, and the urinary urea showed radioactivity, thus demonstrating that a portion of the Bence-Jones protein was metabolized by the animal (Meyer, F., and Putnam, F. W., unpublished experiments). These criticisms of the calculations based on total activity do not apply to those given later, which are based on the specific activity of the abnormal proteins (see footnote 8).
thesis of the abnormal proteins, and C\textsuperscript{14}-lysine incorporation into Bence-Jones protein by cultures of myeloma bone marrow has been demonstrated (16). Previous tracer work has conclusively shown (5–9) that neither the Bence-Jones protein nor the myeloma globulin is derived from the serum pool of the other. Because the kidney pools, as well as other extravascular pools, must be of similar activity to that of the serum, the processes indicated as pathways 5, 5', 6, and 6', as well as other processes taking place outside the plasma cells, can be excluded. This conclusion is further confirmed by the rate curves of Figs. 2 and 4.

Within the plasma cell the C\textsuperscript{14}-glutamic acid is rapidly incorporated into both proteins. This could occur whether both proteins were synthesized via a common intermediate (X in Pathways 2 and 2'), were formed independently from the intracellular amino acid pool as in Pathways 1 and 1', or if one protein were the precursor of the other as in Pathways 3 and 3' and 4 and 4'. However, since the period in which highly active protein was being synthesized is short compared to the time of degradation of the myeloma globulin or to the time of urinary excretion of labeled protein, some information about the intracellular precursors may be gained by

![Diagram of possible precursor-product relationships of Bence-Jones protein (BJ) and myeloma globulin (MM):](image-url)
study of the time-course of the extracellular activity curves. Such an analysis of the time derivatives of the activity curves revealed that the "precursor" activity for both abnormal proteins was temporally similar in that it was low for the 1st half-hour, rose to a maximum at 1.5 to 2 hours, and then fell sharply. This temporal similarity (like the one in Fig. 2) could occur whether the two proteins were synthesized independently from free amino acids or whether they were made via a common intermediate X. However, it suggests that in neither case does the glutamic acid-C\textsuperscript{14} pass through a large pool available for synthesis of one protein but not for the other. The calculations indicate that throughout the period the activity of the intracellular precursor of the globulin was substantially higher than that of the Bence-Jones protein. This suggests that Bence-Jones protein might be formed intracellularly by breakdown in situ of the globulin or, alternatively, that Bence-Jones protein is formed by addition of free amino acids to some preformed precursor. Clearly, in the absence of further data on processes within the plasma cell, any of the intracellular pathways depicted in Fig. 5 remains possible.

The above conclusions are largely based on analysis of the rising parts of the activity-time curves. When the time relationships of the declining portions of the curves are considered, the later appearance of maximal activity in the globulin, despite the identity in transit periods, seems consonant with a precursor role of Bence-Jones protein for the globulin. Indeed, since the transit period for the urinary protein includes the time required for renal excretion, the first activity of the circulating Bence-Jones protein may well have preceded that of the myeloma globulin. Although the possibility that Bence-Jones protein is a precursor of the globulin has been proposed (17), the present analysis has shown that the time relationships of Fig. 4 could also occur simply because the globulin is accumulating radioactivity whereas the urinary protein is not. It should be noted that the immunological relationships of myeloma globulins and Bence-Jones proteins (18) can be explained as well by virtue of their synthesis via a common high molecular weight precursor as by postulating direct conversion of one protein to the other.

From other considerations the Bence-Jones proteins can best be re-

8 We made these calculations at the suggestion of Dr. Arthur L. Koch, using the equation $P = MM + 1/k(d/MM)/dt$, where $P$ is the specific activity of the "precursor," $MM$ that of the myeloma protein, and $k$, the turnover time. This equation follows from the assumption of a steady state for the formation of $MM$ from a sole precursor $P$. The curves obtained are similar in form to the time derivatives of the curves of Fig. 2, but are weighted by the effect of the turnover time. For Bence-Jones protein, $k$ was taken as 8.5 hours and for myeloma globulin as 14 days. The calculated curves almost coincide if 21 hours is taken for $k$ for the Bence-Jones protein and 7 days for the globulin.
garded as abortive products of a perverted and enhanced serum globulin synthesis. Both pathological proteins are formed in the plasma cell (2, 16) and possess antigenic groupings in common with normal γ-globulin (18). The Bence-Jones proteins are readily excreted because of their lower molecular weight and are often heterogeneous. They are deficient in antigenic activity despite their size and their wide amino acid content. They possess a thermosolubility at 100° lacking in other proteins and suggestive of a disorganized or incomplete structure. Indeed, preliminary work in our laboratory indicates Bence-Jones proteins may be modified by heating more readily than other proteins. All this evidence speaks for a role of Bence-Jones proteins as by-products of the proliferating tumor cells or as intermediates that accumulate because of a misdirected or forced protein synthesis.

SUMMARY

The biosynthesis of proteins in a patient with multiple myeloma was investigated by measuring the change in specific activity with time of the abnormal serum globulin and the urinary Bence-Jones protein after intravenous injection of DL-glutamic acid-1-C\(^{14}\). In both cases the C\(^{14}\) incorporation was slight in the first 40 minutes, during which time the serum glutamic acid activity declined abruptly and the expiratory C\(^{14}\)O\(_2\) increased sharply. The specific activity of the Bence-Jones protein attained an earlier, sharper, and higher maximum than did that of the myeloma globulin and also declined more rapidly. Yet, in the first 24 hours more C\(^{14}\) was incorporated into the circulating globulin than was excreted via urinary protein. An analysis of the specific activity-time curves suggests that the descending portion is a function of the metabolic fate of the protein and that neither protein is the sole direct precursor of the other, at least not in the extracellular space. From the data it cannot be determined whether the two immunologically related, abnormal proteins are formed independently from the amino acids of serum, or share a common intermediate, or whether one is converted to the other in the plasma cell. From other considerations, the Bence-Jones protein appears to be an abortive product of globulin synthesis.

BIBLIOGRAPHY

PROTEINS IN MULTIPLE MYELOMA: VIII. BIOSYNTHESIS OF ABNORMAL PROTEINS

Frank W. Putnam and Aiko Miyake


Access the most updated version of this article at http://www.jbc.org/content/231/2/671.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC’s e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/231/2/671.citation.full.html#ref-list-1