Hypercatabolism of IgG, IgA, IgM, and Albumin in the Wiskott-Aldrich Syndrome

A UNIQUE DISORDER OF SERUM PROTEIN METABOLISM

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ABSTRACT The Wiskott-Aldrich syndrome is an immune deficiency disorder with an impairment of both humoral and cellular immune responses. Metabolic turnover studies of IgG, IgA, IgM, and albumin were conducted in seven patients with the Wiskott-Aldrich syndrome using purified radioiodinated proteins. The survival of each of the proteins studied was significantly shortened with a half-time of 7.5 days for IgG (normal 22.9 ± 4 SD), 3.0 days for IgA (normal 5.8 ± 1), 5.0 days for IgM (normal 10.1 ± 2.1), and 8.6 days for albumin (normal 17, range 13–20); the fractional catabolic rates were correspondingly elevated and the distribution of protein among the body compartments was normal. For three of the four proteins, IgG, IgA, and albumin, the steady-state synthetic rates were generally elevated leading to normal or even elevated serum protein levels. Thus, in the case of IgA, the synthetic rate averaged five times normal while the fractional degradative rate was twice normal. The resulting serum concentration was, therefore, significantly elevated. IgM represented an exception to this pattern in that the increased rate of degradation was not counterbalanced by an increased synthetic rate and, therefore, the serum levels were low.

Albumin clearance studies using albumin-68Cr showed gastrointestinal protein loss in these patients to be slightly greater than normal, but this could account for only a small fraction of the hypercatabolism observed. There was no proteinuria or abnormalities of thyroid, adrenal, renal, or liver function. Thus, none of the previously recognized causes of increased serum protein catabolism were present. Patients with the Wiskott-Aldrich syndrome, therefore, have a unique disorder of serum protein metabolism characterized by endogenous hypercatabolism of at least four major serum proteins. This phenomenon may be related to reticuloendothelial hyperfunction since the Wiskott-Aldrich syndrome is associated with reticuloendothelial hyperplasia and accelerated clearance of colloidal materials from the plasma.

INTRODUCTION

In the past few years a number of syndromes characterized by shortened serum protein survival have been discovered. Most commonly, the shortened survival may be accounted for by loss of protein from the body, either into the urine, as in nephrosis or into the lumen of the gastrointestinal tract, as in the protein-losing gastroenteropathies. Shortened serum protein survival without evidence of protein loss, that is, a disorder of endogenous catabolism, is a much less frequent occurrence.

In this report we describe studies of serum protein metabolism in seven patients with the Wiskott-Aldrich syndrome. This is a sex-linked disease characterized by eczema, thrombocytopenia and increased numbers of infections associated with profound cellular and humoral immune deficiency (2–7). Significantly shortened survival of IgG, IgA, IgM, and albumin was found, and this could not be accounted for by any of the recognized causes of shortened serum protein survival. Thus, these patients represent a previously undescribed disorder of serum protein metabolism with endogenous hypercatabolism of at least four major serum proteins.

METHODS

Patients. 14 boys with the Wiskott-Aldrich syndrome were studied. They ranged in age from 5 months to 13 yr
of age and all had the triad of thrombocytopenia, eczema, and increased numbers of infections, as well as the immunologic abnormalities previously reported (4,6). A family history of involved male relatives compatible with a sex-linked mode of inheritance was obtained in eight of the cases including five of the seven undergoing protein turnover studies. Serum concentrations of total protein, transferrin, haptoglobin, ceruloplasmin, and fibrinogen were normal. The patients were free of proteinuria, fever, and diarrhea during the period of metabolic study. 24 hr urinary 17-hydroxy and 17-ketosteroid excretion was normal as were tests of thyroid function including protein-bound iodine (PBI), T3 uptake, T4, by column, free thyroxine, and basal metabolic rate (BMR) in those patients tested.

36 young adult volunteers and patients with various neurologic and malignant diseases served as controls for the turnover studies. Turnover studies in other hospitalized children aged 9 months, 2, 4, and 9 yr showed rates of protein catabolism comparable with adult controls.

Quantitation of immunoglobulin levels. The levels of IgG, IgA, IgM, and IgD in sera from 14 patients, 26 age-matched control children, and adult control patients were determined by radial diffusion in agar (8). IgE levels on 12 patients were determined using a double-antibody radioimmunoassay (9) as described by Gleich, Averbeck, and Swedlund (10).

Preparation and labeling of proteins. IgG was isolated from normal serum by DEAE-cellulose chromatography as previously described (11). IgA was prepared by Geon1-Pevicon2 block electrophoresis (11) of sera from two patients with marked monoclonal elevations of serum IgA. Similarly, albumin was isolated by block electrophoresis of normal serum. IgM was isolated from the serum of a patient with Waldenström's macroglobulinemia by block electrophoresis. The purity of the isolated proteins was assured by immunoelectrophoresis and Ouchterlony analysis, and by radioimmunoelectrophoresis of the labeled proteins.

The purified proteins were labeled with 131I and 125I by the iodine monochloride method of McFarlane (12) and were calculated to contain less than one atom of iodine per molecule of protein. Free radiiodide was removed by dialysis and the final product contained less than 2% nonprecipitable radioactivity. Human albumin was added to each labeled protein preparation to prevent damage due to irradiation. albumin-51Cr was obtained from E. R. Squibb & Sons, New Brunswick, N. J.

Study protocol. Each of the patients was hospitalized at the Clinical Center of the National Institutes of Health during the period of study. Patients received two to eight drops of Lugol's solution three times a day throughout the period of study to prevent thyroid uptake of released isotope. Concentrations of various serum proteins were determined periodically throughout the study to verify that each patient was in the steady state. Turnover studies were done either simultaneously or sequentially and several patients had repeat studies with different preparations of the same protein. Each protein preparation was tested in normal subjects to assure that it had normal metabolic behavior. Patients received from 1 to 15 μCi of labeled protein intravenously from a calibrated syringe, and a serum sample was collected at 10 min and then daily thereafter.

Stool and urine specimens were collected in 24-hr lots where possible, and all patients that received protein labeled with 131I were counted daily in a whole body counter as previously described (13). Several of the repeat studies of a protein were evaluated solely in the whole body counter because of the difficulty in obtaining a sufficient number of serum samples in small children. Serum and urine samples were counted with appropriate standards to within ±3% counting error in an automatic gamma counter. When two isotopes were studied simultaneously, they were differentiated with a pulse height analyzer.

The patients were evaluated for gastrointestinal (GI) protein loss by intravenous injection of 5-15 μCi of albumin-51Cr. 24-hr lot stool samples were brought to constant weight with water, homogenized, and counted with appropriate standards in a gamma ray bulk counter.

Calculation of the protein turnover data. The turnovers of iodinated proteins were analyzed according to modifications of the methods of Berson, Yalow, Schrireher, and Post (14), or Nosslin (15). Time plots of the plasma radioactivity and the radioactivity retained in the body were constructed on semilogarithmic paper and the survival half-times of the labeled proteins determined graphically. Calculations of the metabolic parameters are summarized by the following equations. The fraction of the body protein remaining in the intravascular space = (plasma volume × plasma radioactivity per ml)/radioactivity retained in body determined after equilibration of the labeled protein among the body compartments. Total circulating protein = plasma volume × plasma concentration of the protein. Total exchangeable pool of protein = total circulating pool/fraction of the protein in the intravascular pool. The fraction of the circulating protein catabolized per day (FCR) = radioactivity excreted in each 24 hr period/mean circulating radioactivity during the same period. The absolute catabolic rates (turnover rates) = total circulating protein × fraction of the circulating protein catabolized per day. Since the concentration of the plasma proteins remained constant throughout the period of study, the patients were assumed to be in a steady state and, therefore, the synthetic rates were considered equal to the turnover rates (absolute catabolic rate).

The albumin-51Cr results are expressed either as the per cent of the injected isotope recovered in the feces during the first 4 days after injection, or as the gastrointestinal clearance of albumin-51Cr as previously described (16).

RESULTS

Immunoglobulin levels. Fig. 1 shows the serum concentration of the five classes of immunoglobulin in 14 patients with the Wiskott-Aldrich syndrome. The IgG levels of the patients (10.3 ±3.5 mg/ml) were similar to those observed in 26 age-matched control children (9.1 ±2.6 mg/ml). The IgA levels of the patients were significantly higher, P < 0.001, than in the 26 controls (4.8 ±2.2 vs. 1.7 ±1.1 mg/ml). The serum IgM levels in the patients (0.55 ±0.25 mg/ml) were significantly lower, P < 0.001, than in the controls (1.06 ±0.46 mg/ml). The mean level of IgD in 11 patients was 0.238 ±0.184 mg/ml compared with 0.121 ±0.08 mg/ml in 14

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1 Geon Vinyl Resins, B. F. Goodrich Chemical Co., Niagara Falls, N. Y.

control children. There was wide scatter in the values for both patients and normals, but 5 of the 11 patients had higher concentrations of IgD than any of the control children. The mean level of IgE in 12 patients was significantly elevated to 11,700 ng/ml (geometric mean 2625 ng/ml), compared with a control geometric mean of 76 ng/ml with a ±2 s.d. log-normal range of 6–912 ng/ml.

The pattern of immunoglobulins observed in our patients with the Wiskott-Aldrich syndrome is generally similar to those reported by several other investigators (5, 17–20). The serum immunoglobulin levels of our patients as a group formed a characteristic pattern with significant elevations of IgA, IgD, and IgE and a significantly decreased level of IgM. However, individual patients showed a considerable degree of variability in their immunoglobulin levels when observed over a period of time, and for each of the immunoglobulins, there were several patients with a normal serum concentration. Therefore, the absence of the characteristic immunoglobulin pattern in an individual patient does not necessarily rule out the diagnosis of the Wiskott-Aldrich syndrome.

**Turnover studies, IgG metabolism.** A summary of the results of nine IgG turnover studies in six patients with the Wiskott-Aldrich syndrome is shown in Table I. The most striking finding was a markedly shortened survival of IgG in the patients with the mean t1 of 7.5 days vs. 22.9 ±4.0 days in the controls. The fraction of the circulating IgG catabolized per day, the fractional catabolic rate, was increased almost threefold on the mean to 18.4%/day, compared with 6.7 ±1.5% in the controls. The synthetic rate for IgG in these patients was found to be as high as five times the adult normal. This probably represents an even greater increase over the normal childhood rate of IgG synthesis because children generally have a significantly lower IgG level than adults, and therefore, lower synthetic rates. The control values are those previously established by this laboratory in 23 normal, young adult volunteers (11). The values obtained for each control subject studied during the present investigation fell within this normal range. In addition, IgG survival was normal in two mothers of boys with this disorder.

It is interesting that one patient in this series had an IgG paraprotein. Fig. 2 shows an immunoelectrophoretic pattern of the serum from this patient at age 3. There is a clearly recognizable IgG, type λ-paraprotein which completely disappeared from the patients' serum

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**Table I**

* IgG Metabolism

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum IgG mg/ml</th>
<th>% IV</th>
<th>t1 days</th>
<th>Fractional catabolic rate %/day</th>
<th>Synthetic rate mg/kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. G.</td>
<td>11.4</td>
<td>50</td>
<td>9.6</td>
<td>14.5</td>
<td>84.5</td>
</tr>
<tr>
<td>A. D.</td>
<td>17.4</td>
<td>41</td>
<td>7.2</td>
<td>23.8</td>
<td>157.4</td>
</tr>
<tr>
<td>10/69</td>
<td>17.4</td>
<td>56</td>
<td>5.6</td>
<td>22.0</td>
<td>178.8</td>
</tr>
<tr>
<td>M. M.</td>
<td>13.2</td>
<td>64</td>
<td>7.5</td>
<td>14.4</td>
<td>98.8</td>
</tr>
<tr>
<td>R. M.</td>
<td>6.0</td>
<td>51</td>
<td>9.0</td>
<td>14.9</td>
<td>38.7</td>
</tr>
<tr>
<td>7/67</td>
<td></td>
<td></td>
<td>7.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W. M.</td>
<td>4.5</td>
<td>41</td>
<td>8.0</td>
<td>21.1</td>
<td>50.3</td>
</tr>
<tr>
<td>7/67</td>
<td></td>
<td></td>
<td>5.2*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. H.</td>
<td></td>
<td></td>
<td>7.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>50.5 ±8.0 SD</td>
<td>7.5 ±1.3</td>
<td>18.4 ±3.9</td>
<td>101.4 ±51.6</td>
<td></td>
</tr>
<tr>
<td>Control (adult)</td>
<td>45.3 ±6.1</td>
<td>22.9 ±4.0</td>
<td>6.7 ±1.5</td>
<td>34 ±11</td>
<td></td>
</tr>
</tbody>
</table>

* t1 determined by use of whole body counter.

% IV; percentage of protein in the intravascular space.

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**Serum Protein Hypercatabolism in the Wiskott-Aldrich Syndrome** 2333
several months later. There are two other reports of similar abnormal proteins in patients with the Wiskott-Aldrich syndrome (21, 22).

IgA metabolism. Table II contains the IgA turnover data from eight studies in five patients compared with our previously published normal values (23, 24). Again, the IgA survival in our patients was significantly shortened, with the mean $t_1$ of 3.0 days vs. the control mean of 5.8 days. The fractional catabolic rate was doubled from the control mean of 25.2 ±3.8%/day to 49.9%/day. The average rate of IgA synthesis was five times the adult mean.

IgM metabolism. The IgM turnover data for seven studies in five patients are shown in Table III. As with IgG and IgA, the survival of IgM was also shortened in the patients with a mean $t_1$ of 5.0 days vs. 10.1 days for the controls. The mean fractional catabolic rate was 19.5%/day compared with 8.8%/day in the controls.

In these studies the turnover data in the controls differed significantly from that previously reported from this laboratory for normal IgM survival. A possible explanation of this discrepancy is that the earlier report (25) employed IgM isolated from normal serum while these studies utilized IgM isolated from the serum from a patient with macroglobulinemia of Waldenström. The values for IgM survival in normals obtained in this study agree closely with those reported by Olesen (26) and Birke, Norberg, Olhagen, and Plantin (27) also utilizing proteins isolated from patients with macroglobulinemia of Waldenström.

Albumin metabolism. Table IV lists the results of albumin turnover studies in five patients. As with the other serum proteins studied, albumin also had a shortened mean survival of 8.6 days compared with 17 days in normals (28). Also, the mean fractional catabolic rate was elevated to 18.7% of the circulating albumin pool/day, compared with 10% in normals. The rate of albumin synthesis was elevated in all five patients to approximately two times normal.

Studies of gastrointestinal protein loss. Because of the shortened survival of these four classes of serum proteins, we examined the possibility that gastrointestinal protein loss may have contributed to the shortened survival observed. Each patient studied had a small but significant amount of protein loss into the gastrointestinal tract as measured by albumin-4C excretion in

<table>
<thead>
<tr>
<th>Table II</th>
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<tbody>
<tr>
<td>IgA Metabolism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum IgA</th>
<th>% IV</th>
<th>$t_1$ days</th>
<th>Fractional catabolic rate</th>
<th>Synthetic rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. D.</td>
<td>7.0</td>
<td>46.5</td>
<td>2.9</td>
<td>51.4</td>
<td>172.0</td>
</tr>
<tr>
<td>M. M.</td>
<td>7.6</td>
<td>43</td>
<td>3.4</td>
<td>47.4</td>
<td>167.5</td>
</tr>
<tr>
<td>R. M.</td>
<td>2.6</td>
<td>40</td>
<td>3.4</td>
<td>51.0</td>
<td>62.2</td>
</tr>
<tr>
<td>J. H.</td>
<td>2.8*</td>
<td>2.6*</td>
<td>3.1*</td>
<td>3.3*</td>
<td>2.9*</td>
</tr>
<tr>
<td>Mean</td>
<td>43.2 ±2.6</td>
<td>3.0 ±.3</td>
<td>49.9 ±1.8</td>
<td>133.9 ±50.7</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>42</td>
<td>5.8 ±1</td>
<td>25.2 ±3.8</td>
<td>24 ±15</td>
<td></td>
</tr>
</tbody>
</table>

* $t_1$ determined by use of whole body counter.
Aldrich syndrome.

Calculation of the rate of clearance of injected albumin-\(^{51}\)Cr appearing in the stools during the 4 day period after intravenous injection was 2.14, 1.46, and 2.40% in the three patients studied compared with the range in normals of 0.1–0.7% excreted in 4 days.

Calculation of the actual rate of clearance of \(^{51}\)Cr-labeled albumin into the intestine in the last patient showed clearance of 2.85% of the plasma volume into the bowel daily, compared with a normal mean clearance of 0.64%/day (range 0.2–1.6%/day). Thus, in this patient, gastrointestinal loss of proteins can account for only about 2% of the increase in the fractional catabolic rate observed for his serum proteins.

**DISCUSSION**

This study demonstrates accelerated catabolism of four major serum proteins in patients with the Wiskott-Aldrich syndrome. Shortened survival of IgG, IgA, IgM, and albumin was found to be the result of a significant increase in the fraction of the circulating pool of each protein catabolized each day. In spite of the shortened protein survival, three of the proteins were present in the serum in normal or elevated concentrations because the rate of synthesis of these proteins was increased up to seven times normal.

A variety of physiologic and pathologic processes have been demonstrated to affect the survival of serum proteins. Most clinical conditions associated with shortened protein survival are characterized by loss of protein from the body. The most easily recognized route of such loss is proteinuria. The other site of loss of serum proteins resulting in shortened protein survival is the gastrointestinal tract. In contrast to the relatively selective protein loss that occurs in renal disease (29), gastrointestinal loss tends to be a bulk process with loss of all serum proteins to roughly the same extent (11).

Our patients with the Wiskott-Aldrich syndrome were free of proteinuria throughout these studies, but evaluation with albumin-\(^{51}\)Cr in three patients did demonstrate a small amount of gastrointestinal protein loss in excess of normal in each. Calculation of the amount of

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**TABLE III**

IgM Metabolism

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum IgM</th>
<th>% IV</th>
<th>t(_4) days</th>
<th>Fractional catabolic rate</th>
<th>Synthetic rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. M.</td>
<td>0.50</td>
<td>62</td>
<td>5.6</td>
<td>20.0</td>
<td>4.06</td>
</tr>
<tr>
<td>R. M.</td>
<td>0.55</td>
<td>73</td>
<td>5.8</td>
<td>16.4</td>
<td>4.66</td>
</tr>
<tr>
<td>A. D.</td>
<td>0.45</td>
<td>80</td>
<td>5.2</td>
<td>16.7</td>
<td>3.4</td>
</tr>
<tr>
<td>M. M.</td>
<td>0.22</td>
<td>85</td>
<td>5.5</td>
<td>14.8</td>
<td>1.62</td>
</tr>
<tr>
<td>J. H.</td>
<td>0.60</td>
<td>55</td>
<td>4.9</td>
<td>18.4</td>
<td>7.06</td>
</tr>
<tr>
<td>Mean</td>
<td>0.40</td>
<td>55</td>
<td>5.3</td>
<td>23.8</td>
<td>3.79</td>
</tr>
<tr>
<td>Controls (5)</td>
<td>0.40</td>
<td>55</td>
<td>5.3</td>
<td>23.8</td>
<td>3.79</td>
</tr>
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**TABLE IV**

Albumin Metabolism

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum albumin</th>
<th>% IV</th>
<th>t(_4) days</th>
<th>Fractional catabolic rate</th>
<th>Synthetic rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. D.</td>
<td>4.2</td>
<td>42.0</td>
<td>9.3</td>
<td>17.0</td>
<td>341</td>
</tr>
<tr>
<td>M. M.</td>
<td>4.3</td>
<td>43.1</td>
<td>10.0</td>
<td>16.1</td>
<td>314</td>
</tr>
<tr>
<td>R. M.</td>
<td>4.5</td>
<td>44.3</td>
<td>8.6</td>
<td>18.8</td>
<td>393</td>
</tr>
<tr>
<td>R. G.</td>
<td>4.2</td>
<td>35.8</td>
<td>8.8</td>
<td>22.2</td>
<td>339</td>
</tr>
<tr>
<td>J. G.</td>
<td>3.8</td>
<td>52.0</td>
<td>6.3</td>
<td>19.4</td>
<td>376</td>
</tr>
<tr>
<td>Mean</td>
<td>43.4 ±5.2</td>
<td>8.6 ±1.2</td>
<td>18.7 ±2.1</td>
<td>353</td>
<td></td>
</tr>
<tr>
<td>Control Mean (range)</td>
<td>43.1</td>
<td>17 (13–20)</td>
<td>10 (8.7–13.2)</td>
<td>171 (150–200)</td>
<td></td>
</tr>
</tbody>
</table>
plasma cleared into the stool daily showed that the magnitude of this loss was only 2–3% of the plasma pool/day, and therefore responsible for only a small fraction of the accelerated catabolism observed in our patients. For example, the fraction of circulating IgG catabolized daily by the patients was 18.5% of the intravenous pool compared with 6.7% by the controls. With gastrointestinal loss accounting for the catabolism of only 2–3% of the plasma pool/day, the bulk of the elevated rate of IgG catabolism by our patients remains unaccounted for.

Shortened serum protein survival has been observed in the absence of external loss. The first disease state described with such abnormal endogenous hypercatabolism of a serum protein was myotonic dystrophy (28). The hypogammaglobulinemia observed in many of these patients is the result of accelerated catabolism of IgG, while IgM, IgA, and albumin have normal fractional catabolic rates. IgG isolated from normals had a short survival in patients with myotonic dystrophy, while IgG isolated from the patients had normal survival in control subjects. Thus the error in this disorder is the result of faulty catabolic mechanisms rather than an abnormality in the proteins themselves.

Patients with hypergamma-globulinemia (30) have shortened IgG survival as a result of a normal physiologic mechanism, the concentration-catabolism effect. The survival of IgG is inversely proportional to its serum concentration, with a longer survival time in hypogammaglobulinemia and short survival associated with hypergamma-globulinemia. The fractional catabolic rate is independent of the rate of synthesis, however, as demonstrated by the shortened survival of IgG produced by passive infusion of plasma to cause an elevated IgG concentration (31). This mechanism is unlikely to account for the shortened IgG survival in our patients because their serum IgG levels were not elevated and it would not explain the hypercatabolism of IgA, IgM, or albumin.

Familial hypercatabolic hypoproteinemia (32) is another recently described disorder of endogenous hypercatabolism. Two siblings with an unusual constellation of abnormalities including hypogammaglobulinemia, necrobiosis lipoidica diabeticorum, foreshortened and bowed arms (Madelung's deformity), and diabetic glucose-tolerance tests were observed. Protein turnover studies in these two patients disclosed shortened survival of both IgG and albumin without abnormalities in the distribution of these proteins or evidence of protein loss. Thus, these patients had endogenous hypercatabolism involving at least two major serum proteins.

Another rare cause of shortened protein survival is an abnormal protein-protein interaction. Waldmann, Johnson, and Talal (33) have described a patient with Sjögren's syndrome and macroglobulinemia in whom the monoclonal IgM combined specifically with IgG of subclasses 1, 2, and 4, resulting in shortened IgG survival. Strober, Wochner, Barlow, McFarlin, and Waldmann (23) have demonstrated shortened survival of infused IgA in two IgA-deficient patients. In this instance, the shortened survival was due to an IgG anti-IgA antibody in plasma of these patients. Shortened protein survival has also been observed in the hypermetabolic states accompanying fever (30), thyroid hormone administration (34, 35), and massive corticosteroid treatment (36).

Our patients with the Wiskott-Aldrich syndrome do not resemble those with familial hypercatabolic hypoproteinemia or myotonic dystrophy, and it appears that their protein catabolic defect is a more general one. There is also no evidence that abnormal protein-protein interactions can account for the shortened survival of the four proteins studied. Our patients also fail to demonstrate features of a hypermetabolic state sufficient to explain the accelerated protein catabolism. They were euthyroid, generally afibrile, and had normal values of urinary and plasma corticosteroids. Thus, none of the previously recognized causes of shortened serum protein survival are present in these patients, and the syndrome represents a unique disorder with endogenous hypercatabolism of four major serum proteins.

The Wiskott-Aldrich syndrome is inherited as a sex-linked recessive (3) and is characterized clinically by thrombocytopenia, eczema, and multiple infections with all classes of microorganisms. Recently, a number of reports have defined a severe form of immune deficiency in these patients with defects in both humoral and cellular-immune mechanisms (4-7). The patients exhibit anergy to all classes of antigen, and poor antibody responses, particularly to polysaccharide antigens. Using somewhat different lines of evidence, two groups of investigators (4, 5) have postulated that this disease represents a defect in the afferent limb of immunity; that is, a defect in the proper initiation of a specific immune response.

Most children with the syndrome die in early childhood of either infection or hemorrhage, and only a handful have survived into the second decade. At autopsy, the most characteristic finding has been diffuse reticuloendothelial hyperplasia (5). In fact, in 10–20% of these children, this hyperplastic process has apparently progressed to overt malignancy (37), frequently with distant metastasis. Functionally, the reticuloendothelial hyperplasia has been detected as accelerated clearance of colloidal gold (5) from the blood of these children. In four clearance studies on two of the subjects of the present report, we found that the mean half-time for clearance of 125I-microaggregated human serum albumin
(38) was 6.9 min compared with a normal adult mean of 14.8 ±0.2 se min.

The cause of the abnormal serum protein catabolism in these patients is unknown. Indeed, the normal site and mechanism of catabolism of the immunoglobulins and albumin has not yet been found. Organ perfusion and extirpation studies (25) of the kidneys, spleen, gastrointestinal tract, liver, lungs, and pancreas have failed to identify a single organ as playing the primary role in normal serum protein catabolism, and have suggested diffuse catabolism throughout the body.

The wide distribution and well-known degradative functions of the reticuloendothelial system (RES) has suggested to several workers that this system might be the normal site of serum protein catabolism. It has been shown that intravenously administered antigen-antibody (39) complexes and heat denatured proteins (40, 41) are rapidly cleared by the RES, and the blockade of the RES by carbon particles slowed the elimination of these complexed or denatured proteins. However, it has also been shown that RE blockade with carbon or thorium dioxide decreased rather than increased the survival of undenatured serum proteins (40, 42). Therefore, if the RES is the site of normal serum protein breakdown, the mechanism must be different from that for the catabolism of denatured and colloidal material.

Evidence that certain conditions associated with RE hyperplasia do result in accelerated serum protein catabolism has been presented by Sell (43). Guinea pigs with RE hyperplasia after repeated injections of complete Freund's adjuvant had substantially shortened survival of both IgG and albumin. In this regard, the presence of both histologic and functional evidence of RE hyperplasia in patients with the Wiskott-Aldrich syndrome, together with hypercatabolism of three immunoglobulins and albumin, certainly suggests a possible causal relationship, and demands that a more careful appraisal be given to the role of the reticuloendothelial system in the catabolism of serum proteins.

REFERENCES


Serum Protein Hypercatabolism in the Wiskott-Aldrich Syndrome 2337


