The Behavior of Immunoglobulin in Monoclonal Gammopathies and Their Classification and Pathogenesis

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KANOH, T. The Behavior of Immunoglobulin in Monoclonal Gammopathies and Their Classification and Pathogenesis. Tohoku J. exp. Med., 1970, 102 (4), 369-401 — Quantitative measurements of immunoglobulins were made in sera from 203 patients with monoclonal gammopathies. In IgG myeloma the serum IgG concentration averaged six times the normal level, in IgA myeloma 15 times, and in IgD myeloma 370 times the normal values of respective proteins. In primary macroglobulinemia the average serum level of IgM was 38 times higher than normal. The serum levels of the normal immunoglobulin classes were markedly decreased in these diseases, including Bence-Jones myeloma and biclonal myeloma. Various mechanisms were proposed to account for the reduction of normal immunoglobulins. On the other hand, in benign monoclonal gammopathy there was usually no reduction of normal immunoglobulins. However, in patients with cancer and IgG- or IgA-M-components IgM levels were decreased. The reason for lowered IgM value remains obscure. It was of special interest that one of the patients with a potentially malignant type appeared to be developing myeloma. A marked reduction of the normal immunoglobulin classes seems to be a poor prognostic sign in patients with M-components in the absence of myeloma. Since patients with lymphoma have a marked tendency to hypogammaglobulinemia and closely resemble a primary-malignant group, immunoglobulin changes in patients with lymphomas and M-components are more complicated. A classification of monoclonal gammopathies was proposed on the basis of their pathogenesis after the consideration of our data as well as those from the literature. The concept of the pathogenesis of monoclonal gammopathies presented herein is based on the view that lymphomas, immunologic deficiency diseases, and autoimmune diseases form a 'trinity' pathogenetically and etiologically.

In the preceding paper¹ the author reported a study of the clinical significance of M-components. Some criteria for the differentiation between benign and malignant monoclonal gammopathy were clarified. However, such criteria could never be absolute. In order to obtain a further guide to the differentiation, it seems useful to compare quantitatively the changes in each class of immunoglobulin during various disease states with M-components, for the immunoglobulins are closely related to one another with regard to origin,

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structure and metabolism.\textsuperscript{2,3}

It is the aim of this paper to observe the patterns of immunoglobulin changes in patients with M-components. The diagnostic and prognostic value of these determinations will be investigated. Furthermore, the author will propose a classification of monoclonal gammapathies, comparing our data with those from the literature, and will discuss their pathogeneses briefly.

**Materials and Methods**

The materials studied were taken from 203 patients with M-components. The cases were collected from our hospital and its affiliated hospitals during the years 1964–1969.

The classification of the 203 patients is based on the diagnostic criteria described in the preceding paper.\textsuperscript{1} These include 128 patients with plasma cell myeloma, 3 with extramedullary plasmacytoma, 7 with primary macroglobulinemia, 10 with potentially malignant type, 9 with malignant lymphomas and M-components, and 46 patients with benign monoclonal gammapathies.

The materials were stored at $-10^\circ$ to $-20^\circ$C until use. Serum or urine electrophoresis, immunoelectrophoresis, analytical ultracentrifugation, and examinations of Bence-Jones proteins in urine were performed according to the procedures described in the preceding paper.\textsuperscript{1}

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**Fig. 1.** The standard monospecific antisera used in this study. 1. Anti-$\gamma$, 3. Anti-$\alpha$, 5. Anti-$\mu$, 7. Anti-$\delta$, 2, 4, 6, and 8. Anti-whole human serum.
The anti-sera used were anti-whole human serum, monospecific anti-IgG, anti-IgA, anti-IgM, anti-IgD, anti-K, and anti-L, prepared in our laboratory according to the methods reported in the preceding paper¹ (Fig. 1). The antisera were pooled so as to be sufficient to complete this study.

Serum immunoglobulins were quantitated by a modification of the single radial immunodiffusion method of Mancini et al.⁴ (antibody agar plate technique⁶). Each monospecific antiserum was mixed with the veronal buffer (pH 8.6, μ=0.075) in varying proportions, namely 1:4, 1:7 and 1:9 for monospecific anti-IgG, anti-IgA, and anti-IgM, respectively. The immunodiffusion plates, containing each monospecific antiserum, were prepared from a mixture of equal volumes of diluted antiserum and 3% molten agar (Special Agar-Noble, Difco Inc., Detroit). Circular wells 2.2 mm in diameter were punched out in the antibody-containing agar gel. Into each well was placed a suitable volume of antigen solution: 2μl for determinations of IgG and IgA, and 6μl for IgM. The immunodiffusion plates were incubated in a humid chamber at room temperature. The precipitin rings which developed around the antigen wells were recorded at 72 hours, when the final size of precipitate was attained. From the photographic enlargements the precipitate rings were measured to the nearest 0.1 millimeter (Fig. 2). Standardization curves were prepared for the correlation of the concentration of each immunoglobulin and the ring diameter. At least ten points were used to establish a curve, with multiple determinations per point. The standard sera used to prepare the standardization curves were the dilutions of a mixture of the equal volume of sera from 45 normal adults. The logarithm of the concentrations of the specific antigens measured were proportional to the diameters of the precipitates. Normal levels of these major immunoglobulins were determined in our laboratory by testing sera from 45 normal adults (23 males and 22 females, aged 18 to 42 years). The IgG, IgA, and IgM levels were expressed as percentages of the mean normal level (100%) for each immunoglobulin class. The arithmetic means, standard deviations, and ranges of normal value are shown in Table 1. These values were compared with those obtained when a pooled normal human standard serum from Hoechst Pharmaceuticals (Batch No. 166) was used instead of our standard serum and were found to agree well with those reported by other investigators.⁴⁻⁸

Fig. 2. Representative precipitate rings in an immunodiffusion plate. The agar contained rabbit antiserum against human serum IgG. This picture was photographed after 72 hours of the experiment, when diffusion had ceased.

1. Mancini et al. (1957)
2. Special Agar-Noble, Difco Inc., Detroit
3. IgG, IgA, and IgM levels expressed as percentages of mean normal level (100%) for each immunoglobulin class.
4. Hoechst Pharmaceuticals (Batch No. 166)
5. Mancini et al. (1957)
6. Special Agar-Noble, Difco Inc., Detroit
TABLE 1. Normal serum immunoglobulin levels determined by the single radial immunodiffusion method

(1) % normal

<table>
<thead>
<tr>
<th>Authors</th>
<th>No.</th>
<th>IgG Mean</th>
<th>Range</th>
<th>S.D.</th>
<th>IgA Mean</th>
<th>Range</th>
<th>S.D.</th>
<th>IgM Mean</th>
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<td>100</td>
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<td>15.5</td>
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<td>124-394</td>
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<td>107</td>
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<td>280</td>
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<td>61</td>
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(2) mg/100 ml

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<th>No.</th>
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<th>Range</th>
<th>S.D.</th>
<th>IgA Mean</th>
<th>Range</th>
<th>S.D.</th>
<th>IgM Mean</th>
<th>Range</th>
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<td>47-147</td>
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RESULTS

1) IgG-type monoclonal gammopathy (Figs. 3 and 4)

In plasma cell myeloma, the average serum IgG concentration was approximately six times higher than normal, regardless of whether Bence-Jones proteins were present or not. In five out of 88 cases the value for serum IgG was within the normal range; two of these patients had a solitary myeloma. The serum IgA and IgM averaged 22% of normal. The serum levels of the normal immunoglobulins in the patients with solitary myeloma were within the normal range or slightly decreased.

Two patients with extramedullary plasmacytoma showed a considerable increase in IgG (about 300%), normal IgA, and a moderate decrease in IgM, (about 40%).

In the potentially malignant type, the marked reduction of normal immunoglobulins (IgA, 21%; IgM, 24%) which reached the same degree as in plasma cell myeloma constituted more distinct characteristic than the increase in serum IgG (about 400%). The separation of the potentially malignant type from benign monoclonal gammopathy, proposed by the author, is based primarily on such an immunoglobulin pattern.$^9$

In the malignant lymphoma group, the serum IgG levels exceeded the normal range in six of seven cases and the mean concentration was 228% of normal. Either the IgA or IgM levels were below the normal range in four of seven cases. In all cases of lymphosarcoma and reticulum cell sarcoma there was a marked deficiency of serum IgA and IgM, with minimal amounts of the M-components. In Case 150 (lymphosarcoma) the M-component (IgG) was recognized ultimately in the terminal stage of the disease, while in Case 155 (lymphatic leukemia) and in Case 156 (reticulum cell sarcoma) the M-component (IgG or IgM, respectively) seemed to be present throughout the course of the disease.

As a rule, in patients with chronic infections or prolonged sensitizations...
Fig. 3. Serum immunoglobulin changes in patients with IgG-type monoclonal gammopathy. Note the maintenance of normal immunoglobulin levels in benign monoclonal gammopathy, compared with a marked reduction of normal immunoglobulins in plasma cell myeloma or potentially malignant type.
(e.g., syphilis, tuberculosis, cholelithiasis) the serum IgA and IgM levels were slightly elevated or within the normal range, and the increases in IgG (M-component) were not great. The cases which were separated from this category and classified as being the potentially malignant type in view of a marked reduction of normal immunoglobulins were: two patients with cholelithiasis, one with chronic pyelonephritis, and one with pulmonary tuberculosis.

Patients with liver cirrhosis showed markedly elevated serum IgG and IgA levels and normal serum IgM levels. In general, such an immunoglobulin pattern seems to be characteristic of liver cirrhosis. Particularly in Case 169 the serum IgA level was very high and attained 455% of the normal, while the serum also contained a considerable amount of IgG-M-component.

In autoimmune diseases where polyclonal hyperglobulinemia was usually noted, quantitative analysis of five sera revealed high levels of IgG in four patients and a normal level in one patient. The average of the normal immunoglobulin levels were within the normal range.

In monoclonal immunoglobulin disorders other than those we have seen, the increases in serum IgG (M-component) were slight and the serum IgA concentration was almost normal in an average. IgM levels were somewhat low, but the decrease was small compared with that in plasma cell myeloma. Thus, in plasma cell myeloma or in the potentially malignant type a marked reduction of normal immunoglobulins was recognized, whereas in benign monoclonal gammopathy the average serum levels of normal immunoglobulins were within the normal range (Fig. 3).

We further studied the correlation between IgG-M-component plus normal IgG and normal immunoglobulin levels (Fig. 4). In plasma cell myeloma the increase in IgG (mostly composed of M-component), except for a few cases with the greatest increase, did not always run parallel with the decrease in normal immunoglobulins; that is, there were several cases where normal or slightly elevated IgG levels were associated with marked depression of normal immunoglobulins, or there were other cases where considerably increased IgG levels were associated with normal values or slight reductions of normal immunoglobulins. On the other hand, in benign monoclonal gammopathy there was a high statistical correlation between IgG and IgA levels ($r=0.65$) and some relationship between IgG and IgM levels ($r=0.32$). These results are in agreement with the observation that, as mentioned above, a reduction of normal immunoglobulins was usually not found in IgG-type benign monoclonal gammopathy.

2) IgA-type monoclonal gammopathy (Figs. 5 and 6).

In multiple myeloma, irrespective of the presence or absence of Bence-Jones proteins, the average serum levels of IgA were about 15 times higher than normal. The depression of IgG (about 60% decrease) was less marked than that of IgM (about 80% decrease). Sera from 25 patients revealed normal levels of IgG in four and IgM in one.
In plasma cell myeloma, there was no parallelism between the increase in IgG and the decrease in normal immunoglobulins. In benign monoclonal gammopathy, there was a high statistical correlation between IgG and IgA levels ($r=0.65$) and some relation between IgG and IgM levels ($r=0.32$).
Fig. 5. Serum immunoglobulin changes in patients with IgA-type monoclonal gammopathy. In plasma cell myeloma or potentially malignant type a marked reduction of normal immunoglobulins was found, whereas, as a general rule, in benign monoclonal gammopathy the average of normal immunoglobulins was within the normal range.
In the IgA-type potentially malignant type, similar to the IgG-type, a marked elevation of IgA and reduction of normal immunoglobulins were characteristic.

As a general rule, in benign monoclonal gammopathy the increase in IgA was less pronounced than in myeloma and not associated with a decrease in normal immunoglobulins. However, in patients with cancer, as in patients with cancer with IgG-type M-component, IgM values were rather low. The basis for the low value of IgM remains uncertain (Figs. 3 and 5). One patient with cholelithiasis (Case 148) was classified as belonging to the potentially malignant type because of a marked reduction of normal immunoglobulins.

Also in IgA myeloma, there was no parallelism between the increase in IgA-M-component plus normal IgA and the decrease in normal immunoglobulins; that is, the degree of the decrease in normal immunoglobulins was independent of the IgA concentration (mostly composed of M-component). In benign monoclonal gammopathy, there was a high statistical correlation between IgA and IgG (r=0.74) as well as between IgA and IgM (r=0.59) (Fig. 6).

3) IgM-type monoclonal gammopathy (Fig. 7)

The greatest increase over normal levels with the exception of IgD myeloma was observed with primary macroglobulinemia where the average serum level of IgM was about 38 times higher than normal, whereas in benign monoclonal gammopathy of type IgM the average serum IgM was at most several times greater than normal. In primary macroglobulinemia the serum levels of normal immunoglobulins were decreased in the same manner as in myeloma, but less pronounced. On such a serum immunoglobulin pattern primary macroglobulinemia could be differentiated from malignant lymphomas with monoclonal IgM, where slightly elevated IgM levels and approximately normal levels of IgG and IgA were found. All patients with primary macroglobulinemia showed considerable reduction of the normal immunoglobulins. However, the number (9 to 21%) of neoplastic cells, so-called transitional cells, did not always parallel the degree of reduction of normal immunoglobulins. In general, there was no reduction of normal immunoglobulins in IgM-type benign monoclonal gammopathy. As an exception, a patient with nephrotic syndrome (Case 177), however, showed a marked decrease in IgG and IgA. The decrease was probably due to urinary protein loss, not the suppression of production of the immunoglobulins.

4) Bence-Jones-type and IgD-type monoclonal gammopathy and biclonal gammopathy (Figs. 8 and 9)

This group consists only of cases of plasma cell myeloma. The average serum levels of IgD in IgD myeloma were about 370 times as high as normal. In Bence-Jones-type as well as IgD-type myeloma there were decreases in IgG, IgA, and IgM, while in Bence-Jones-type extramedullary plasmacytoma IgG and IgA levels were normal and the IgM level was slightly decreased. Biclonal myeloma (IgG+IgA) showed a marked reduction of IgM.
In multiple myeloma, there was no parallelism between the increase in IgA and the decrease in normal immunoglobulins. In benign monoclonal gammopathy, there was a high statistical correlation between IgA and IgG ($r=0.74$) as well as between IgA and IgM ($r=0.59$).

Fig. 6. Correlation between IgA and IgG levels or IgA and IgM levels in patients with M-components of type IgA.
Fig. 7. Serum immunoglobulin changes in patients with IgM-type monoclonal gammopathy.

In primary macroglobulinemia a marked increase in IgM and a moderate decrease in normal immunoglobulins were observed. Such a serum immunoglobulin pattern distinguished primary macroglobulinemia from other known diseases with monoclonal IgM.

In Bence-Jones-type myeloma normal immunoglobulin levels were inversely proportional to the number of plasma cells. This correlation was further clarified in the same patient (Case 127). The coefficients of correlation of the number of plasma cells to IgG, IgA, and IgM levels were -0.79, -0.69, and -0.75, respectively.

**DISCUSSION**

*Serum immunoglobulin changes*

The serum level of immunoglobulins depends on a balance between their production (synthesis) and removal (catabolism). In immunologically competent persons, the environmental antigenic stimulation plus the metabolic factors in the host determines the level of each serum immunoglobulin. In immunologically incompetent persons, the capabilities of central lymphoid organs,11 such as the bursa of Fabricius of birds and its mammalian equivalent, gut-associated lymphoid tissue, will of course come to the front.

According to Fahey and Robinson,12 the rate of immunoglobulin synthesis
seems to be the primary factor determining the level of serum immunoglobulins. Elevated immunoglobulin synthesis occurs following increased antigenic stimulation or development of tumors of immunoglobulin-producing cells. Impaired synthesis of immunoglobulins results in agammaglobulinemia or dysgammaglobulinemia. With IgG, the fractional catabolic rate varies in direct proportion to the concentration of IgG in the serum. Marked serum increases of other immunoglobulin classes do not accelerate IgG catabolism. With IgA and IgM, the catabolic rate is independent of their serum concentration. Excessive catabolism or excessive loss of immunoglobulins causes a reduction in all or selected immunoglobulins.

We have observed that in plasma cell myeloma of any type and primary macroglobulinemia almost all patients have a reduction of the normal immunoglobulins. This is true also in heavy chain disease, alpha chain disease, and 7S-macroglobulinemia (Table 2). In these plasmacytic and lymphocytic malignancies the lowered serum immunoglobulin levels appear to be based upon the reduced synthesis. However, the mechanism by which these disorders (malignancies of immunoglobulin-producing cells) reduce normal immunoglobulin synthesis is poorly understood. On the basis of our present data and on the review of literatures, it seems that the reduction of normal immunoglobulins is probably caused by the following mechanisms:
Fig. 9. Correlation between relative number of plasma cells in bone marrow smears and normal immunoglobulin levels in patients with Bence-Jones-type myeloma. The coefficients of correlation of the number of plasma cells to IgG, IgA, and IgM levels are -0.79, -0.67, and -0.75, respectively. Solid circles signify the different individuals. Open circles signify the different stages of the disease in the same patient (Case 127).

**TABLE 2. Serum immunoglobulin changes in monoclonal gammopathies**

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<th>M-components</th>
<th>Immunoglobulin levels*</th>
<th>Proliferating cells</th>
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<tr>
<td>G-Myeloma</td>
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<td></td>
</tr>
<tr>
<td>A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BJ.</td>
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<tr>
<td>Primary macroglobulinemia</td>
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<tr>
<td>7S-Macroglobulinemia</td>
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<tr>
<td>Heavy chain disease</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>K</td>
<td>L</td>
</tr>
<tr>
<td>$(\gamma_{\alpha_2})$</td>
<td>$\gamma_{\lambda_2}$</td>
<td>↑↑(M)</td>
</tr>
<tr>
<td>$(\alpha_{\alpha_2})$</td>
<td>$\alpha_{\lambda_2}$</td>
<td>↓↓</td>
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</tr>
<tr>
<td>Fc-fragment</td>
<td>↓↓</td>
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</tr>
</tbody>
</table>

* ↑↑↑ or ↓↓↓ markedly increased or decreased; ↑↑ or ↓↓ moderately increased or decreased; ↓ slightly decreased; → normal. (M) indicates M-component.
(1) Crowding out of the normal immunoglobulin-producing cells by the tumor cells. Early in the course of the disease or in localized plasmacytoma (solitary, extramedullary), there is often no reduction of normal immunoglobulins, but sooner or later it eventually develops. Furthermore, normal immunoglobulins increase towards normal levels, when the M-components are decreased during successful treatment. In Bence-Jones myeloma an inverse relationship was observed between the number of plasma cells and normal immunoglobulin levels (Fig. 9). The reduction of normal immunoglobulins may be based partly upon crowding out of the normal immunoglobulin-producing cells by the neoplastic cells synthesizing Bence-Jones proteins.

(2) Decreased production of normal immunoglobulins due to unknown extracellular factors associated with neoplastic proliferation: The decrease in normal immunoglobulins did not always parallel the concentration of M-components indicating the numbers of neoplastic cells within the body (Figs. 4 and 6). Furthermore, it may occur in advance of extensive tumor cell infiltrations (Case 26).

(3) Increased catabolism of normal immunoglobulins: In IgG myeloma a shortened maintenance of normal IgG has been observed. While the catabolic rate of IgA and IgM is independent of their serum concentration, the fractional rate of catabolism of IgG varies in direct proportion to the concentration of serum IgG.

(4) Humoral suppression of normal immunoglobulin-producing cells related to a feedback mechanism in protein synthesis: High serum IgG levels in primary macroglobulinemia were, in rare instances, considered to be due to the failure of the feedback mechanism.

(5) Caggiano et al. speculated that genes related to M-components might suppress the production of normal immunoglobulins without structural changes. Depression of normal immunoglobulin synthesis in myeloma may be analogous to the case of thalassemia in which the net production of hemoglobin polypeptide chains is reduced.

(6) Immunologic deficiency may precede the neoplasm. Konda and Takiguchi reported that M-components occurred in x-irradiated, thymectomized, and appendectomized rabbits. Furthermore, M-components are observed in patients with primary immunologic deficiency diseases, such as ataxia telangiectasia, Wiskott-Aldrich’s syndrome, familial metabolic disorder of unknown etiology in the plasma cell system, primary acquired hypogammaglobulinemia, and immunologic amnesia. In addition, myeloma associated with thymoma has been reported. In these patients and animals the impaired immunologic defence against a mutant monoclonal cell is expected. As a result, this monoclonal might proliferate invasively.

(7) Influence of genetic factors involved in control of immunoglobulin synthesis: Genetic factors seem to be involved in the synthesis of immunoglobulins. It has been clearly demonstrated that relatives of patients
with lupoid hepatitis have a higher incidence of hypergammaglobulinemia than the general population. Furthermore, families have been reported in which polyclonal hypergammaglobulinemia, monoclonal gammapathy, and hypogammaglobulinemia have a high incidence. Plasma cell tumors can be induced only in a specific strain (BALB/c) of mice by the peritoneal instillation of mineral oil. Also in man, familial occurrence of monoclonal gammapathies has been described. From all these considerations, it seems that there might be genetically-determined, profound immunologic disturbances in patients with myeloma or primary macroglobulinemia.

Presumably these mechanisms would be simultaneously involved in the reduction of normal immunoglobulins in a complicated manner.

As a rule, in benign monoclonal gammapathy there was no reduction of normal immunoglobulins. Moreover, a high positive correlation was found between the amount of M-components plus normal immunoglobulins of the same class and normal immunoglobulin levels (Figs. 4 and 6). Reduction of normal immunoglobulins found in a few cases of this group would be explained by the basic diseases. Lowered IgM levels in patients with epithelial neoplasms and M-components of type IgG or type IgA were noteworthy. However, the number of cases is too small to draw definite conclusions. These results indicate that the immunologic homeostasis in the immunoglobulin-producing system was not severely disturbed.

As stated earlier, an outstanding characteristic of the potentially malignant type was a marked reduction of normal immunoglobulins. It is conceivable that the above-mentioned mechanisms assumed in myeloma or in primary macroglobulinemia might be involved in the decrease in normal immunoglobulins. Thus, the condition may not be wholly benign and should be regarded as being potentially malignant. In these patients a severe reduction of normal immunoglobulins would probably be detected several years before the malignant proliferations become large enough to produce detectable lesions or M-components. Moreover, it is noteworthy that some characteristic features common in myeloma are also recognized in this group.

Patterns of normal immunoglobulins in patients with lymphomas and M-components are more complicated. Lowered normal immunoglobulin levels occasionally seen in these patients can be explained not only on the basis of the production of M-components, but also on the basis of an inherent tendency to hypogammaglobulinemia in these disorders. The prognostic aspects of M-components have been discussed in the preceding paper.

Elevated concentrations of M-components may be due primarily to their rapid synthesis. On the assumption that all the immunoglobulin-producing cells produce immunoglobulin at a fixed rate, the concentration of M-components reflects the total number of immunoglobulin-producing cells. The higher the concentration of M-components, the greater the number of cells. Consequently, successful treatment usually leads to a reduction of M-components.
However, an unusual case of primary macroglobulinemia has been reported in which the M-component decreased significantly and lymphosarcoma developed later in the course of a previously typical primary macroglobulinemia. In this case, it seems that tumor cells forming lymphosarcoma were less mature, rapidly growing, and did not produce an immunoglobulin. Therefore, it is clear that reduction of M-components is not always a good prognostic sign.

As we have seen, it is extremely important in the differentiation between benign and malignant proliferations of immunoglobulin-producing cells to determine quantitatively the changes observed among M-components and normal immunoglobulins.

**Classification of monoclonal gammopathies**

Since M-components are found in a variety of diseases, it is important to classify monoclonal gammopathies. Besides an all-inclusive classification, several workers have proposed various classifications based on the pathogenetic relationship between primary diseases and M-components. In view of our data including the recent results concerning the pathogenesis of monoclonal gammopathy, we propose the following classification (Table 3).

Primary (obligatory)-malignant (I, 1-7): This group includes myeloma, extramedullary plasmacytoma, primary macroglobulinemia, 7S-macroglobulinemia, heavy chain disease, alpha chain disease, and potentially malignant type.

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**Table 3. Classification of monoclonal gammopathies**

<table>
<thead>
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<th>I. Primary (obligatory)</th>
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<td>Malignant</td>
</tr>
<tr>
<td>1) Plasma cell myeloma</td>
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<td>2) Extramedullary plasmacytoma</td>
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<tr>
<td>3) Primary macroglobulinemia</td>
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<td>4) 7S-macroglobulinemia</td>
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<td>5) Heavy chain disease</td>
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<td>6) Alpha chain disease</td>
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<td>7) Potentially malignant type</td>
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<tr>
<td>Benign</td>
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<tr>
<td>8) Genetically-determined type</td>
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<tr>
<th>II. Secondary (facultative): Associated with specific diseases</th>
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<tbody>
<tr>
<td>Malignant</td>
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<tr>
<td>1) Lymphoreticular tumors</td>
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<tr>
<td>Benign</td>
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<tr>
<td>2) Infectious diseases or prolonged sensitization</td>
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<td>3) Liver cirrhosis</td>
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<td>4) Autoimmune diseases</td>
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<td>5) Cancer</td>
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<td>6) Myeloproliferative diseases</td>
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<td>7) Tissue proteinoses</td>
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<td>8) Immunologic deficiency diseases</td>
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<td>9) Lipidoses or hyperlipemia</td>
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<th>III. Idiopathic (no specific diseases apparent)</th>
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<tr>
<td>1) Aging</td>
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<td>2) Miscellaneous diseases</td>
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In these diseases M-components are the products of the proliferating cells ('primary') and are constantly, with few exceptions, demonstrable ('obligatory'). The clinical features common to this group are those of malignancy of varying degrees: weight loss, anemia, leukopenia, and other symptoms and signs which are usually present during neoplastic proliferation. Furthermore, it is important that in this group a marked reduction of normal immunoglobulins is more characteristic than a concentration of M-components above 1.0 to 2.0 g/100 ml (Figs. 3, 5, 7 and 8).

Primary (obligatory)-benign; genetically-determined type (I, 8): Although we have not yet observed this type, many reports describing familial incidences of myeloma\textsuperscript{37} and primary macroglobulinemia\textsuperscript{36} as well as malignant lymphomas\textsuperscript{42-44} are rapidly accumulating in recent years. Likewise, a familial feature has also been observed in patients with benign monoclonal gammopathy.\textsuperscript{35,37} Such findings suggest a genetic factor in these conditions. The author has termed familial cases with no evidence of progression a genetically-determined type, as proposed by Michaux and Heremans.\textsuperscript{42} Also in this type, M-components are primarily produced under genetic influence. It is conceivable that this type would be related to various familial immune disorders, such as malignant lymphoma, autoimmune diseases, and immunologic deficiency diseases.

Secondary (facultative)-malignant; lymphoreticular tumors (II, 1): M-components are found increasingly frequently in patients with lymphomas and related disorders,\textsuperscript{41,42,44-48} such as lymphosarcoma (Cases 149 and 150), lymphatic leukemia (Case 155), reticulum cell sarcoma (Cases 152, 153, 156 and 157), Hodgkin’s disease, Brill-Symmer’s disease, reticulosis, thymoma, and Kaposi’s sarcoma. Furthermore, the association of some of these diseases with myeloma or primary macroglobulinemia in the same patients has been reported.\textsuperscript{31,49,50} It is clear that lymphomas with M-components are closely related to the primary-malignant group. Since in lymphomas M-components are not always demonstrated ('facultative'), their appearance could be considered to be 'secondary' to the lymphoma processes. Therefore, it seems advisable in a clinical sense to divide lymphomas with M-components into ‘primary-malignant’ and ‘secondary-malignant’ groups.

Infectious diseases or prolonged sensitization (II, 2): The occurrence of M-components has been reported in patients with bacterial and viral infections usually characterized by a polyclonal hypergammaglobulinemia.\textsuperscript{42,47,51-53} These diseases include tuberculosis (Cases 160 and 165), infectious mononucleosis, viral hepatitis (Cases 158, 161 and 164), and other viral infections (Case 167), syphilis (Case 159), and nonspecific infections of the gallbladder with gall stones (Cases 142, 162, 163 and 166), renal pelvis (Cases 139 and 174), respiratory tract, peritoneum (Case 165), and bones, as well as malaria and parasitic diseases. These long-standing, protracted chronic inflammatory conditions probably induce repetitive antigenic stimulation of the immune tissues,
which might be responsible for their ultimate neoplastic transformation\textsuperscript{10,54-57} (Cases 108 and 129). However, there is no definite evidence that M-components in these diseases are true antibodies against known antigens. It is of interest that BALB/c mice develop plasma cell tumors after intraperitoneal injections with mineral oil or incomplete Freund’s adjuvant.\textsuperscript{34} Also in Aleutian disease in minks a remarkable transition from initial polyclonal hypergammaglobulinemia to monoclonal gammopathy has been documented.\textsuperscript{58,59} One should pay attention to the striking analogy between clinical and experimental data.

Liver cirrhosis (II, 3): The serum of patients with liver cirrhosis contains M-components not infrequently.\textsuperscript{10,52,53,60} We have observed two cases of liver cirrhosis with M-components (Cases 169 and 170) and one case of Banti’s syndrome (Case 171). In addition, M-components have been found in the serum of patients with other liver diseases such as acute and chronic hepatitis, hepatoma\textsuperscript{42} and lupoid hepatitis (Case 176).

Autoimmune diseases (II, 4): M-components have been found in various autoimmune diseases also.\textsuperscript{42,47,61-65} These include rheumatoid arthritis, Sjögren’s syndrome (Case 173), systemic lupus erythematosus, periarteritis nodosa, scleroderma, myasthenia gravis, pulseless disease, atypical glomerulonephritis (Case 177), lupoid hepatitis (Case 176), Hashimoto’s thyroiditis (Case 187), and autoimmune hemolytic anemia. Purpura hyperglobulinemica,\textsuperscript{66} pyoderma gangraenosum\textsuperscript{67}, and drug hypersensitivity\textsuperscript{57} should be added to this category. Porush \textit{et al}.\textsuperscript{65} reported the possibility that M-component possessing antibody-like activity might form antigen-antibody complexes which might be responsible for atypical glomerulonephritis. However, there is little evidence that M-components \textit{per se} are unequivocally autoantibodies responsible for these autoimmune diseases.

In our opinion, in most of autoimmune diseases the intensive stimulation of the immune system with initial polyclonal hypergammaglobulinemia may lead to the ultimate exhaustion of immune tissues on one hand and to increased tendency to malignant or monoclonal transformation on the other hand. It seems especially important to assume the possibility that the latter phenomenon may be based on the former.\textsuperscript{68} In fact, there have been many reports of lymphoid tumors developing during the course of autoimmune diseases.\textsuperscript{62,63,66,69}

Cancer (II, 5): The appearance of M-components in association with malignant neoplasms of epithelial cell origin is well recognized.\textsuperscript{42,44,70,71} Such an association is not infrequent. The primary sites of the associated neoplasms have been in almost all parts of the body. Six patients from our series are in this group. Their neoplasms were in the stomach (Case 178), the larynx (Case 180), the uterus (Cases 179 and 183), and the prostate (Cases 181 and 182). In another patient (Case 17) the coexistence of gastric cancer and IgG myeloma was observed. It remains to be determined whether the association of M-components with epithelial neoplasms implies a causal relationship\textsuperscript{44,70} or it is
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only fortuitous. It Reports that striking infiltrations of plasma cells have sometimes been observed in or around primary neoplasms are noteworthy. It may be that antigenic components in carcinomas are capable of inducing plasmacytic responses with M-components. At present there is no evidence that epithelial cancer cells can produce M-components. Weitzel reported that second primary carcinomas were found in 19.3% of autopsied cases of myeloma. Presumably the immunologic deficiency due to myeloma would facilitate the occurrence of the second primary carcinomas. Inversely, it is possible that benign monoclonal gammopathy associated with carcinomas can develop into myeloma.

Myeloproliferative diseases (II, 6): Also in association with myeloproliferative diseases, such as polycythemia vera, myelocytic leukemia, myelofibrosis, monocytic leukemia, and erythroleukemia, the appearance of M-components or the occurrence of myeloma has been described. Heile et al. proposed the view that a common cell origin (a pluripotential stem cell) should be sought for these diseases. Burkett et al. observed the sequential development of bone marrow plasmacytosis with Bence-Jones proteinuria and spontaneous remission in leukemia. They suggested that the plasmacytosis and Bence-Jones proteins in this case might have been due to an immune reaction induced by the malignancy and responsible for its remission.

Tissue proteinoses (II, 7): The combined occurrence of various tissue proteinoses and monoclonal gammopathy has been described. Primary amyloidosis, lichen myxedematosus, and pulmonary alveolar proteinosis may be in this category. The relationship between primary amyloidosis and monoclonal gammopathy is a much-disputed problem. At present it is considered that the relationship between amyloid substance and immunoglobulins is not direct. Aly et al. have stated that the association of primary amyloidosis with M-components may be due to the abnormal proliferation of a cell line capable of producing both amyloid substance and "monoclonal" globulins. Barth considers that the M-components in primary amyloidosis may be of limited nature (benign) and that the type, duration, or intensity of the stimulus at the stem cell level, precursors of plasma cells and related reticuloendothelial cells, may determine whether the outcome will be amyloidosis, M-components of limited nature or myeloma, either alone or in various combinations. Furthermore, Muckle has suggested that a certain impaired cellular or humoral immunity usually accompanies, not infrequently precedes, and sometimes plays an important role in the development of amyloidosis. Further studies in the interrelation among amyloidosis, monoclonal gammopathy and immunologic deficiency diseases will be of great interest.

In almost all patients with lichen myxedematosus, M-components in the serum have been demonstrated in the slowest γ-globulin region. The fact that a patient with lichen myxedematosus presented by Feldman et al. showed a dramatic response to melphalan with the return to normal of decreased normal
immunoglobulins suggests that lichen myxedematosus may sometimes transform itself into myeloma. Although the combination of pulmonary alveolar proteinosis and M-component is extremely rare, Mork et al.\textsuperscript{85} suggested the possible etiological relationship of these two entities.

Immunologic deficiency diseases (II, 8): As stated earlier, M-components have been observed\textsuperscript{26–31} in a variety of primary or secondary immunologic deficiency diseases in both man and animal models. Judging from this fact, immunologic deficiency states may precede or follow monoclonal gammopathy, or the two conditions may occur simultaneously.

Lipidoses and hyperlipemia (II, 9): The association of various disorders of lipid metabolism with benign or malignant monoclonal gammopathy has been reported. These conditions include xanthomatosis,\textsuperscript{87} hyperlipidemia,\textsuperscript{87} Gaucher's disease,\textsuperscript{88} and Hand-Schüller-Christian's disease.\textsuperscript{89} Diabetes mellitus, hypothyroidism, and cholecystopathies, which are usually associated with hypercholesteremia, may be added to the list. Osserman and Takatsuki\textsuperscript{44} assumed the possibility that disturbances in lipid metabolism may be the basis for the plasmacytic dyscrasia on the analogy of the plasma cell tumors produced in BALB/c mice by the intraperitoneal injection of mineral oil.\textsuperscript{34} In addition, it is interesting to speculate the possibility that a direct metabolic relationship may exist between \(\gamma\)-globulins and lipids, as seen in the nephrotic syndrome.

Idiopathic; aging and miscellaneous diseases (III, 1–2): M-components in this category are of idiopathic nature; that is, no specific diseases related to the appearance of M-components are apparent. A population survey\textsuperscript{90} revealed that 64 out of 6,995 persons above 25 years of age had M-components (0.9\%) and 19 of the 747 persons above 70 years of age (2.5\%). Hallen\textsuperscript{47} reported similar data: M-components were discovered in 18 out of 571 subjects above 70 years of age (3.2\%). In our series there were six cases (3\% of the total). Although there is a large body of evidence indicating that the aging process is accompanied by an increasing incidence of benign monoclonal gammopathy, the exact relationship between these two conditions remains obscure. Impaired immunity in the aged\textsuperscript{91,92} and genetic abnormalities may also be responsible for the appearance of M-components.

M-components were also observed in this study in patients with diabetes mellitus, essential hypertension, cerebral apoplexy, gastric ulcer and poly and prostatic hypertrophy and in a healthy middle-aged man.

The significance of these M-components is completely unknown. Important underlying diseases involved in the appearance of M-components may be concealed.

The broad group of 'benign monoclonal gammopathy' proposed here consists of primary- and secondary-benign groups (I, 8; II, 2–9) and an idiopathic group (III, 1–2). The following features appear to constitute a common denominator in benign monoclonal gammopathy:
(1) The monoclonal proliferations of plasma cells or related cells seem to be self-limited and not-aggressive.

(2) As a rule, in benign monoclonal gammopathy other than the primary-benign group, M-components seem to be 'secondary' to the underlying ('primary') diseases and are usually associated with a polyclonal hypergammaglobulinemia.

(3) In some cases the M-component disappears as the patient recovers (Case 167). 42, 57

(4) As a rule, anemia or a decrease in albumin is absent or only very slight.

(5) Though overt myeloma sometimes develops rapidly from a rudimentary monoclonal gammopathy, 93 the concentration of M-components is below 2 g/100 ml and remains constant for years.

(6) Serum normal immunoglobulin levels are increased rather than decreased. 42

(7) The number of plasma cells in the bone marrow is usually less than 10%. Cytological abnormalities are absent or few.

However, the monoclone, initially benign in these conditions, may ultimately be neoplastic. In fact, cases have been reported which progressed to overt myeloma 94-96 or primary macroglobulinemia 97 many years after the initial detection of M-components. Consequently, most benign monoclonal gammopathies must be followed up for a long time before a final diagnosis can be made. Particularly in the almost asymptomatic potentially malignant type careful observation for a long period of time is required.

Pathogenetic concept in monoclonal gammopathies

Prior to the establishment of the pathogenetic concept of monoclonal gammopathies, the author would like to assume that lymphoreticular malignancies, immunologic deficiency diseases, and autoimmune diseases form a 'trinity' in a pathogenetic and etiological sense (Fig. 10). The combined occurrence of lymphoreticular malignancies and immunologic deficiency diseases within the same family as well as in the same patient has been reported repeatedly. 6, 96-100 Likewise, such a combination has been described between lymphoreticular malignancies and autoimmune diseases 62, 66, 69, 100-103 and between immunologic deficiency diseases and autoimmune diseases. 100, 104-106 Of course, the simultaneous occurrence of these three conditions in the same patient has also been recognized. 107, 108

It is clear that disorders of the immune tissues may form a common background for these three groups of diseases. The phenomenon of 'lymphoid chimerism (runt disease)' can be introduced as a concept to integrate the pathogeneses and etiologies common in the three. 6, 109, 109-111 The following mechanisms may be responsible for the occurrence of 'lymphoid chimerism', namely, for the coexistence of abnormally oriented lymphoid cells and normal lymphoid cells.

(1) Somatic mutation of lymphoid cells. The mutant cells are usually
destroyed by normal immunologic mechanisms. In patients with immunologic
deficiency diseases, however, they would form a graft and proliferate invasively.
The so-called ‘forbidden clone’ producing autoantibodies, proposed by Burnet,
may be derived from such mutant cells. Neoplastic proliferations of the
forbidden clones might explain the association of lymphomas and autoimmune
diseases. Abrupt onset of high fever, rapid deterioration of the general
condition, marked weight loss, hepatosplenomegaly, leukopenia, lymphopenia and
death after only six weeks of illness were observed by Tornyos et al.112 in the later
course of chronic lymphatic leukemia. Autopsy revealed complete replacement
of lymphoid tissues by Hodgkin’s granuloma. These findings bear a considera-
ble resemblance to ‘runt disease’ or ‘graft-versus-host reaction’.110,113,114 Since
the mutant clones could not be destroyed by the impotent immunologic
apparatus of chronic lymphatic leukemia, they would constitute a graft and
react immunologically against the host lymphoid tissues (autoimmune
phenomenon). We have reported similar findings developing in the later course
of reticulosis, which were suggestive of the graft-versus-host reaction seen in
animals.115,116

(2) Maternofetal transplantation of lymphoid cells. Desai and Creger117
have demonstrated the transplacental passage of lymphocytes from mother to
fetus. The possibility of human lymphoid chimerism based on the maternofetal
transplacental passage has been suggested and the relation of this concept to
lymphomas or autoimmune diseases has been discussed.117,118 However, there
is no evidence for permanent colonization of such transplanted lymphoid cells
and their immunologic function. Such transplanted cells seem to be rejected
by normal fetuses, while they would probably form a graft in infants with
immunologic deficiency disease,119 or under certain other circumstances. Of

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**Fig. 10. Trinity theory (hypothesis).** Lymphoreticular malignancies, immunologic deficiency
diseases, and autoimmune diseases could have a common pathogenesis (lymphoid
chimerism).
importance in this regard are the animal models presented by Schwartz and Beldotti. About one third of the F1 hybrid mice which survived the graft-versus-host reaction produced by transplantation of parental lymphoid cells developed lymphoma, in which the histopathology was similar to that of Hodgkin's disease in man.

(3) Blood transfusion and bone marrow transplantation. When competent lymphoid cells have been transferred into the patients in immunologic deficiency states by these procedures, severe bone marrow aplasia, lymphoid tissue depletion, and generalized histiocytosis with marked erythrophagocytosis have been observed. These findings are suggestive of graft-versus-host reaction. Waller et al. reported that some patients with renal transplants had evidence of autoimmune disease. This phenomenon might be due to the graft-versus-host reaction produced by renal transplants with foreign lymphoid tissues. Furthermore, the occurrence of reticulum cell sarcoma after repeated injections of gamma globulins and the development of reticulum cell sarcoma at the site of antilymphatic globulin injection could be understood as a result of the immunologic reaction of the injected immune globulins (graft) to the host.

(4) X-irradiation and immunosuppressive agents. These known oncogenic agents produce chromosomal aberrations on one hand and immunologic deficiency states on the other hand. Such chromosomal aberrations could lead to cell death and to accelerated proliferation of the surviving cells. These surviving cells would have increased susceptibility to somatic mutation and might form a graft on the basis of immunologic deficiency. Furthermore, immunologic deficiency states produced by these agents would facilitate the establishment of naturally occurring mutant clones, which are usually rejected by the normal immune apparatus.

(5) Viral infections. There are indications that the virus could have an effect on the immunologic competence of the lymphoid cells and trigger abnormal immune responses and immunologic diseases. In recent years, possible roles of viruses in the pathogenesis of immunologic diseases, such as lymphomas, autoimmune diseases, and immunologic deficiency diseases have been noticed in man as well as in animal models. These clinical and experimental data could be explained on the assumption that a virus infection might produce 'foreign'-type lymphoid cells and the virus-transformed ('foreign') cells could react against the host cells in such a way as to lead either to autoimmune disease or to neoplasm. This view would help explain virus-induced forms of homologous disease.

(6) Chronic infections and prolonged sensitization. Repeated benign stimulation of immune tissues probably causes rapid multiplication of lymphoid cells with increased susceptibility to somatic mutation. On the other hand, the excessive proliferation of lymphoid cells might lead to the ultimate exhaustion of immune tissues (immunologic deficiency states).
Some of these mechanisms might be often cooperative simultaneously, not always one by one, in the pathogeneses or etiologies of such immunologic diseases in a complicated manner under genetic factors. All these considerations suggest that lymphoreticular malignancies, immunologic deficiency diseases, and autoimmune diseases form a 'trinity' and must be considered as a whole rather than individually.

Further support for this concept ('trinity theory') can be sought in the association of such immunologic diseases with monoclonal gammopathy. The monoclonal, neoplastic, reactive, or genetically-determined, can be understood as a graft; that is, the occurrence of the monoclonal represents the establishment of 'lymphoid chimerism' (Fig. 11). Consequently, the above-mentioned mechanisms responsible for 'lymphoid chimerism' may underlie the pathogeneses or etiologies of monoclonal gammopathies. This concept affords a sound basis for the classification of monoclonal gammapathies presented here (Table 3.)

![Diagram](image)

**Fig. 11.** Pathogenetic concept in monoclonal gammapathies. A close relationship of monoclonal gammapathies to lymphoreticular malignancies, immunologic deficiency diseases, and autoimmune diseases is pointed out.

**Acknowledgment**

I wish to express my heartfelt thanks to Professor Gyoichi Wakisaka, Kyoto University, for his interest and encouragement, Dr. Kiyoshi Takatsuki, Department of Internal Medicine, Kyoto University Hospital, for his guidance and advice, and Miss Yoko Kojima for her cooperation. Grateful acknowledgment is made to many physicians who kindly gave specimens and clinical data to our laboratory.

**Appendix**

Case 7. A 75-year-old man was admitted with a four-month history of hemorrhagic tendency. Blood studies showed severe anemia and thrombocytopenia. Although well circumscribed osteolytic lesions were present in the skull and 4th and 5th lumbar vertebrae, sternal marrow aspiration disclosed 3.8% relatively mature plasma cells. Besides the
electrophoretic pattern of the serum (a prominent $\gamma$-spike, IgG), a marked reduction of normal immunoglobulins was found.

Case 17. A 57-year-old woman. Autopsy revealed the association of gastric cancer and typical myeloma, type IgG.

Case 26. A 55-year-old man was found to have a solitary plasmacytoma of the first thoracic vertebra in February 1965. Treatment with $^{60}$Co-irradiation after surgical excision was followed by disappearance of the M-component (IgG, 0.53 g/100 ml) concurrently with a remarkable decrease in normal immunoglobulins. With reappearance of the circulatory monoclonal immunoglobulin (0.66 g/100 ml) in November 1966, progression from solitary to multiple myeloma occurred.

Case 101. This 49-year-old woman was hospitalized for hemorrhagic tendency. She was diagnosed as having IgA myeloma and hyperviscosity syndrome. The bone marrow aspirate showed 41% plasma cells and their young forms. Routine serum electrophoresis showed a fast $\gamma$-spike (IgA, 6.3 g/100 ml). Ultracentrifugal analysis revealed 17S component consisting of polymers of IgA. Direct removal of IgA polymers by plasmaapheresis and reduction of disulphide bonds of IgA polymers by sulphhydryl-reducing compound (GSH) were effective in reducing serum viscosity.

Case 108. A 59-year-old man had typical symptoms of myeloma. It is of special interest that the patient had showed an unexplained elevation of the erythrocyte sedimentation rate (about 60 mm per hour) for about thirty years. The patient died six months after the onset of major symptoms.

Case 127. This 56-year-old woman had Bence-Jones myeloma. Two months after the institution of an alkylating agent (cyclophosphamide) a decrease in the concentration of Bence-Jones proteins and a diminution of marrow plasma cells could be demonstrated concurrently with the recovery of normal immunoglobulins toward normal levels.

Case 128. This 77-year-old woman was admitted to Iwakuni Hospital because of low back pain and febrile episodes. The diagnosis was myeloma. Bone marrow aspirate showed 6.0% plasma cells, including flaming cells. Serum electrophoresis showed a $\beta$-spike (IgA, 1.2 g/100 ml) and a $\gamma$-spike (IgG, 2.1 g/100 ml). Serum IgG was 160% of normal, serum IgA 600%, and serum IgM 17%.

Case 129. A 65-year-old man had extramedullary plasmacytoma originating in the thyroid gland and IgG-M-component. He had had a firm, egg-sized mass in the region of the left lobe of the thyroid gland for more than thirty years before admission which had recently begun to grow rapidly. Skeletal x-rays disclosed nothing abnormal. Bone marrow aspirate showed 5% plasma cells. The presence of the mass for many years indicates the possibility of late progression of chronic thyroiditis to plasmacytoma.

Case 139. This 55-year-old woman had IgG-M-component (6.4 g/100 ml) associated with chronic pyelonephritis. Bone marrow aspirate showed 16% plasma cells with morphologic abnormalities. She was classified as potentially malignant type.

Case 141. This 43-year-old woman was admitted to the hospital in March 1966 for unexplained anemia. Five years previously, she had entered another hospital because of pallor, where anemia and an abnormal $\beta$-spike (3.6 to 2.7 g/100 ml) on serum electrophoresis were first noted. She was suspected of myeloma. However, a skeletal x-ray survey showed nothing abnormal. Sternal marrow aspirate showed 6% plasma cells. Thereafter she remained asymptomatic until August 1965 when pneumonia developed. During this admission, Bence-Jones proteins could not be demonstrated even by combining the boiling test and immunoelectrophoresis of concentrated urine. Paper electrophoresis revealed a prominent $\beta$-spike (IgG, 3.0 g/100 ml). Quantitative measurements of serum immunoglobulins revealed a marked reduction of unaffected immunoglobulins. Sternal marrow aspirate showed 10.5% plasma cells with cytological abnormalities. She was
classified as potentially malignant type. She was discharged from the hospital in July 1966 without any specific therapy.

In September 1969 she was examined by the author because of anemia and low back pain. Sternal marrow aspirate showed 27.2% plasma cells. Skeletal x-ray showed probable osteolytic lesions of the skull. At present this case appears to be evolving into typical myeloma.

Case 142. This 62-year-old woman had had recurrent cholelithiasis for many years. Routine serum electrophoresis initially disclosed a prominent γ-spike in the absence of myeloma in October 1962. In March 1968, the M-component of type IgG reached 4.0 g/100 ml, with a marked reduction of normal immunoglobulins. Serum IgG was 660% of normal, serum IgA 17%, and serum IgM 12%. The case belongs to potentially malignant type.

Case 148. This 73-year-old man complained of headache which had persisted for several years. Physical examination was unremarkable. Besides the electrophoretic pattern of the serum (IgA-M-component) and a slight marrow plasmacytosis a marked reduction of unaffected immunoglobulins and suspected osteolytic lesions of the skull were the most remarkable findings. The case was classified as potentially malignant type.

Case 149. This 44-year-old man had lymphosarcoma and IgG-M-component. Bone marrow aspirate revealed 48.6% lymphocytes and 0.4% plasma cells.

Case 150. This woman was 23 years old when she was first examined in September 1964. At that time biopsy of a mass in the right tonsil revealed lymphosarcoma. She received x-irradiation to this area with good response. She remained well until August 1965 when she complained of general malaise. Her hemoglobin was 11.8 g/100 ml, and white blood cell count 1,800/mm². Serum electrophoresis revealed a slight increase in γ-globulin, but no M-component. In December 1965, IgG-M-component was demonstrated in the terminal stage, when abnormal blast cells were up to 70% in the peripheral blood. Skeletal x-ray showed nothing abnormal.

Case 151. This 63-year-old man was suspected of having abdominal lymphoma with IgG-M-component (3.5 g/100 ml). Bone marrow aspirate showed 8.6% plasma cells. Skeletal x-ray was negative.

Case 152. This 49-year-old woman had reticulum cell sarcoma and IgG-M-component.

Case 153. This 74-year-old man had reticulum cell sarcoma and IgG-M-component.

Case 155. This 59-year-old man was found to have chronic lymphatic leukemia in March 1968 when blood studies showed a white cell count of 13,000/mm², with 80% lymphocytes and lymphoblasts. Bone marrow aspirate disclosed 66% lymphocytes, 27% lymphoblasts, 5.5% granulocytes and 1.5% monocytes. No marrow plasma cells were demonstrated in 500 leukocytes and leukocyte precursors. Serum electrophoresis revealed a remarkable γ-spike (IgG, 1.9 g/100 ml). There was neither lymphadenopathy nor hepatosplenomegaly. In October 1969 an x-ray series of the skeletal system disclosed two osteolytic lesions of the distal part of the right tibia and fibula, whose nature remained obscure. The cytology of the abnormal cells, a good response to corticosteroid therapy and other clinical features suggest acute rather than chronic lymphatic leukemia. The existence of M-component throughout the course may be related to a more benign course.

Case 156. This 64-year-old woman had reticulum cell sarcoma with IgM-M-component. The concentration of serum IgM paralleled the size of the adenopathy. This patient might have had the M-component from the beginning of the disease.

Case 157. The patient's age and sex are unknown; reticulum cell sarcoma with IgM-component.
Case 158. This 47-year-old man presented with chronic hepatitis with IgG-M-component.

Case 159. This 70-year-old man had syphilis with IgG-M-component.

Case 160. This 61-year-old man had advanced pulmonary tuberculosis with IgG-M-component.

Case 161. This 48-year-old man had serum hepatitis with a small spike on cellulose acetate membrane electrophoresis which was identified as IgG by immunoelectrophoresis.

Case 162. This 46-year-old man had cholelithiasis with IgG-M-component.

Case 163. This 43-year-old woman had cholelithiasis and IgG-M-component.

Case 164. This 58-year-old man was found to have IgG-M-component associated with chronic hepatitis.

Case 165. This 57-year-old man was found to have pulmonary tuberculosis and tuberculous peritonitis with associated IgA monoclonal immunoglobulin disorder.

Case 166. This 51-year-old woman was suspected of having intrahepatic cholelithiasis with IgA-M-component.

Case 167. This 75-year-old woman was admitted in January 1965 with a four-week history of fever and generalized lymphadenopathy. Physical examination on admission disclosed hepatosplenoemegaly. Paper electrophoresis showed a $\beta$-spike (IgM, 0.6 g/100 ml). Soon after admission, without any specific treatment she improved rapidly with disappearance of the M-component. Thereafter, generalized adenopathy and enlargement of the spleen developed again in August 1965 when a polyclonal increase in IgM was found. Her clinical picture was consistent with viral infection. There was no evidence to suggest malignant lymphoma.

Case 169. This 40-year-old man presented with jaundice. His history and biologic data were consistent with the diagnosis of liver cirrhosis. Serum electrophoresis showed a $\gamma$-spike (IgG, 1.2 g/100 ml) superimposed on polyclonal hypergammaglobulinemia.

Case 171. This 45-year-old woman had Banti’s syndrome with associated IgA-M-component.

Case 173. This 55-year-old woman had Sjögren’s syndrome with associated IgG monoclonal gammopathy. Extracts from the salivary gland contained the same M-component as seen in the serum.

Case 174. This 42-year-old woman had chronic nephritis with associated IgG monoclonal gammopathy.

Case 175. This 14-year-old boy had a hemorrhagic tendency. Cellulose acetate membrane electrophoresis revealed a small $\gamma$-spike which was of IgG nature. Quantitative measurements of immunoglobulins were normal.

Case 176. This 43-year-old woman was suspected of having lupoid hepatitis. There was a prominent spike (IgG, 2.1 g/100 ml) in the electrophoretic pattern, superimposed on polyclonal hypergammaglobulinemia.

Case 177. This 17-year-old girl had nephrotic syndrome (membranous glomerulonephritis) with a $\gamma$-spike on agar gel electrophoresis.

Case 178. This 69-year-old man had the serum IgG-M-component associated with gastric cancer.

Case 179. This 50-year-old woman had uterine cancer with IgA-M-component.
Case 180. This 69-year-old man had laryngeal cancer with associated IgA monoclonal gammopathy.

Case 181. This 67-year-old man had prostatic cancer and IgA-M-component.

Case 182. This 72-year-old man was suspected of having prostatic cancer. Serum electrophoresis showed a $\beta$-spike (IgA).

Case 183. This 59-year-old woman was suffering from uterine cancer with associated IgM monoclonal gammopathy.

Case 187. This 65-year-old woman was diagnosed as having Hashimoto’s thyroiditis and hypercholesteremia with associated IgG monoclonal gammopathy. In addition, there was a history of gall stones at the age of 37. Serum electrophoresis revealed a $\gamma$-spike (IgG, 0.7 g/100 ml).

References


15) McKelvey, E.M. & Fahey, J.L. Immunoglobulin changes in disease: Quantitation on the basis of heavy polypeptide chains, IgG ($\gamma$G), IgA ($\gamma$A), and IgM ($\gamma$M), and of light polypeptide chains, type K (I) and type L (II). J. clin. Invest., 1965, 44, 1778–1787.


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