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SMUFD, d/a ltr, 15 Feb 1972

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BLOOD PROTEIN DISORDERS IN VARIOUS INTERNAL DISEASES

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Summary

The author reports on eight γ2 paraproteinemias observed in various internal diseases without a sure indication at that time of plasmacytoma. In immuno-electrophoresis the changes varied in intensity, but were unequivocally demonstrable. Agar-gel electrophoresis showed one or several extra gradients in all cases. Paper electrophoresis, on the other hand, revealed a narrow-base gradient only four times. The majority of the cases showed a moderate plasmacellular reaction in the sternal punctate. In addition, atypical changes in the γ globulin area (elongated duplication of the γ2 line, splitting at the cathodic end of the γ2 line) could be demonstrated immuno-electrophoretically in thirteen additional patients with various diseases.

Until a few years ago the detection of paraproteins was tantamount to a diagnosis of a plasmacytoma or of Waldenström's macroglobulinemia. Quite recently reports of the occurrence of paraproteins in other diseases as well have appeared repeatedly. Especially in chronic lymphadenosis [1-4], in lymphosarcoma and reticulosarcoma [5], and osteosclerosis [6] and malignant tumors [7-9] paraproteins have been observed in individual cases. Paraproteins have also been found in rare cases in numerous other diseases, such as diabetes mellitus, ulcer ventriculi, cholangitis, etc. [10-13]. Even in clinically healthy blood donors paraproteins have been found [14].

- 1 -
Proof of a paraproteinemia is generally based on changes in the paper electrophoresis and in the immuno-electrophoresis. If the sera are studied simultaneously in paper electrophoresis and agar-gel electrophoresis, extra gradients can be found in a much higher percentage in the agar gel than on the paper [15, 16]. If these sera are tested by immuno-electrophoresis, then in a small percentage changes typical for paraproteins are discernible, although the paper electrophoresis gave no sure indication of them.

Our Own Investigations

Over 200 sera from patients with various diseases (not including plasmocytoma and Waldenström's macroglobulinemia), which in agar gel electrophoresis showed one or more extra gradients.

Methods

Paper electrophoresis by Grassmann and Hannig's method [17]. — 0.05 ml serum, separation time 16 hours, current 110 volts, Michaelis's buffer pH = 8.6, ionic strength 0.1, paper: precipitate "FN3."

Agar gel electrophoresis by Wieme's method [15,16]. — Separation time 45 minutes, agar gel ("Difco" agar) 1% on slide glasses, field strength 23 volts/cm, veronal-acetate buffer pH = 8.2, ionic strength 0.05.

Immuno-electrophoresis by Scheidegger's micromethod [18]. — Separation time 45 minutes, agar gel ("Difco" agar) 2% on slide glasses, field strength 11 v/cm, veronal-acetate buffer pH = 8.2, ionic strength 0.05. Anti-human serum from the horse (Institut Pasteur, Paris), charge no. 2234.

Results

In all the sera studied one or more extra gradients could be found by agar gel electrophoresis. In 200 immuno-electrophoreses changes were found in the gamma globulin area twenty-one times.

The changes may be classified into several forms.

1. Deflection, circumscribed intensification and doubling of the gamma 2 line in the middle or cathodic third of the gamma 2 line (Figure 1a). ([Note] The figures are on page 2453.)
2. Deflection, circumscribed intensification and doubling of the gamma 2 line at the transition from the anodic to the middle third (Figure 2d).
3. Slightly undulating gamma 2 line (Figure 3c).
4. Splitting at the cathodic end of the gamma 2 line (Figure 4c).
5. Doubling of the gamma 2 line (Figure 5c).
Cases

Case 1:

W.K., age 61, male. Became ill with an acute febrile infection of the air passages. An anemia of 58% Hb with 2.3 million erythrocytes was conspicuous and led to his being admitted as a bed patient. Examination showed satisfactory general condition, pale complexion, no pathological findings in the organs of the thorax. Liver and spleen not enlarged. No swellings of the lymphatic glands. X-ray: No destructions in the skeletal system. ESR (erythrocyte sedimentation rate) 26/50; total protein 6.3 g%. 

Paper electrophoresis: 63% albumins, alpha 1 2.7%, alpha 2 3.4%, beta 4.8%, gamma 26.1%. Definite narrow-based gradient in the gamma region.

Agar gel electrophoresis: Strong extra gradient in the middle gamma region.

Immuno-electrophoresis: Deflection, intensification, and duplication of the gamma 2 line in the middle region.

Sternal marrow: Subchronic inflammation constellation with strikingly strong plasmacellular reaction.

Diagnosis: Hyperchromatic anemia, suspicion of incipient gamma 2 plasmocytoma.

Case 2:

E.K., 69, female. Pronounced goiter since age 40; in the last year development of two nodules the size of plums inside the goiter. Following an excision, continuous fistula formation in the region of the operation. Increasing weakness, gain in weight, and lack of appetite. X-ray examination showed well-developed cavity formations throughout the lung. ESR 98/134. Total protein 7.11 g%.

Paper electrophoresis: Albumin 35.8%, alpha 1 9.7%, alpha 2 9.7%, beta 11.2%, gamma 23.6%. Narrow-based gradient in the gamma region.

Agar gel electrophoresis: Strong extra gradient in the middle gamma region.

Immuno-electrophoresis: Deflection and duplication of the gamma 2 line in the middle third.

Sternal marrow: Definite plasmacellular reaction. Slight increase in eosinophiles.

Diagnosis (autopsy): Struma maligna with well-developed metastases in the lymphatic glands and lung as well as metastases in the cortex of the kidney and in the spinal column. General cachexia.
Case 3:

E.A., 60, female. The patient was under treatment as a bed patient at the clinic because of a slight pancreatitis following cholecystectomy. She said her ESR had been high for years.

- ESR 41/80. Total protein 9.9 g%.
- Paper electrophoresis: Albumin 48.3%, alpha 1 3.8%, alpha 2 7.6%, beta 14.8%, gamma 25.5%.
- Agar gel electrophoresis: Definite extra gradient in the gamma region.
- Immuno-electrophoresis: Deflection and doubling of the gamma 2 line in the middle third.

No sternal puncture was made. Bence-Jones protein negative. X-ray: No destructions detectable in the skeletal system.

Case 4:

H.W., 71, female. Admitted as a bed patient because of dyspnea, backache, and loss of weight. At admission, poor general condition with anemia of 60% Hb, edema in the legs, pneumatic infiltrations and pleuritic exudations, arrhythmic heart action; liver enlarged, hard, and with an uneven surface. Resistance as large as a fist in the region of the navel. ESR 85/130. Total protein 6.37 g%.

- Paper electrophoresis: Albumin 18.8%, alpha 1 9.4%, alpha 2 12.2%, beta 15.0%, gamma 44.6%.
- Agar gel electrophoresis: Marked extra gradient in the fast-shifting gamma region, several weaker extra gradients in the rest of the gamma region.
- Immuno-electrophoresis: Deflection and doubling of the gamma 2 line in the middle region.

Sternal marrow: Definite plasmacellular reaction.

Diagnosis (autopsy): Ovarian carcinoma on the left with penetration into the surrounding region, peritoneal carcinosis, metastases in lymphatic glands, liver, and vertebral bodies. Bronchial pneumonia.

Case 5:

R.C., 75, male. Increasing dyspnea and edema of the legs over a period of two years. Admitted because of pronounced anemia of 32% Hb with 1.7 million erythrocytes. Leucocytes were reduced to 1150, thrombocytes to 2000, without detectable clinical symptoms of a hemorrhagic diathesis. ESR 4/11. Total protein 5.72 g%.
Paper electrophoresis: Albumin 64.0%, alpha 1 5.3%, alpha 2 8.0%, beta 10.7%, gamma 12.0%.

Agar gel electrophoresis: Two extra gradients in the gamma globulin region.

Immuno-electrophoresis: Slight deflection of the gamma 2 line in the middle third.

Sternal marrow: Hyporregenerative erythropoiesis with maturation disorders, hypoplasia of the megacaryocytopenosis without evidence of atypia.

Diagnosis: Panmyelopathy.

Case 6:

W.H., 54, male. Jaundice twenty years before; for the last year and a half deterioration of the general health, intolerance of fat, occasional dark coloring of the urine, and gradual increase in bodily circumference. Examination showed reduced general condition, sclerotic icterus, lung and heart clinically normal, ascites. Liver enlarged 2 x, spleen 3 x. Well-developed esophageal varices. Laparoscopy gave a picture of active cirrhosis of the liver with portal hypertonia. ESR 37/60. Total protein 6.8%.

Paper electrophoresis: Albumin 41.9%, alpha 1 4.4%, alpha 2 4.4%, beta 6.5%, gamma 42.8%.

Agar gel electrophoresis: Definite extra gradient in the fast-shifting gamma region.

Immuno-electrophoresis: Deflection and doubling at the transition from the anodic to the middle third of the gamma 2 line (clearly evident when the patient's serum is diluted 1:5).

Sternal marrow: Plasmacellular reaction. X-ray: No destructions in the skeletal system.

Case 7:

D.O., 60, male. Patient became ill with dyspnea, bloody sputum, and loss of weight. Examination showed slight dyspnea in repose, rales and murmurs in all sections of the lungs. Liver enlarged 2 x. X-ray examination showed a slow-growing tumor in the region of the upper lobe of the left lung. Bronchoscopy showed a severe atrophic bronchitis. In the matter drawn off with the catheter were found cells suspected of being tumor cells (small-celled bronchial carcinoma). -- ESR 100/115. Total protein 6.91 g%.

Paper electrophoresis: Albumin 37.8%, alpha 1 7.7%, alpha 2 12.5%, beta 14.0%, gamma 28.0%.

Agar gel electrophoresis: Several slight extra gradients in the gamma globulin region.
Table 1. Extended Duplication of the Gamma 2 Line
(In the schematic representation of the extra gradients only the beta 2 fraction and the extra gradients situated in the gamma globulin region are shown.)

<table>
<thead>
<tr>
<th>Name</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>ESR</th>
<th>Total Protein</th>
<th>Albumin</th>
<th>Globulins</th>
<th>Plasma Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>K.S.</td>
<td>28/6</td>
<td>Idiopathic, Thrombocytopenia</td>
<td>20/22</td>
<td>6.42</td>
<td>55.5</td>
<td>6.7</td>
<td>10.0 11.0</td>
</tr>
<tr>
<td>A.T.</td>
<td>73/6</td>
<td>Metastasierender hypernephrom</td>
<td>128/146</td>
<td>7.8</td>
<td>42.7</td>
<td>9.5</td>
<td>19.5 14.4</td>
</tr>
<tr>
<td>H.K.</td>
<td>40/6</td>
<td>Erworben hminolyt. Anämie, Diabetes mell.</td>
<td>25/60</td>
<td>5.11</td>
<td>49.0</td>
<td>10.2</td>
<td>7.4   10.2</td>
</tr>
<tr>
<td>M.W.</td>
<td>66/6</td>
<td>Chron. interstitielle Lungenfibrose, Bronchiectasen, narbenbildende Hepatitis</td>
<td>70/105</td>
<td>8.31</td>
<td>58.8</td>
<td>6.3</td>
<td>6.3   11.2</td>
</tr>
<tr>
<td>W.K.</td>
<td>28/6</td>
<td>Mononucleosis infectious</td>
<td>42/72</td>
<td>7.81</td>
<td>50.3</td>
<td>6.1</td>
<td>10.2 10.4</td>
</tr>
<tr>
<td>R.H.</td>
<td>81/6</td>
<td>Komb. Mitralvitium, chron. Polyarthritis</td>
<td>18/24</td>
<td>7.94</td>
<td>46.5</td>
<td>6.2</td>
<td>11.8 12.9</td>
</tr>
<tr>
<td>K.S.</td>
<td>77/6</td>
<td>Bronchialkarzinom, Retentionspneumonia, atrophische Leberzirrhose</td>
<td>118/143</td>
<td>6.20</td>
<td>18.8</td>
<td>11.3</td>
<td>15.3 15.6</td>
</tr>
<tr>
<td>W.O.</td>
<td>60/6</td>
<td>Bronchialkarzinom, Diabetes mell.</td>
<td>60/100</td>
<td>8.27</td>
<td>41.0</td>
<td>6.4</td>
<td>11.0 11.7</td>
</tr>
<tr>
<td>H.G.</td>
<td>66/6</td>
<td>Ausgeprägte Knochentastasierung bei ungebärttem Primärtumor</td>
<td>148/130</td>
<td>7.63</td>
<td>32.6</td>
<td>11.7</td>
<td>22.7 12.5</td>
</tr>
<tr>
<td>D.W.</td>
<td>76/6</td>
<td>Cholangitis, Pankarditis bei residivierender Polyarthritis</td>
<td>71/120</td>
<td>7.91</td>
<td>48.4</td>
<td>8.6</td>
<td>8.1 10.5</td>
</tr>
<tr>
<td>O.H.</td>
<td>81/6</td>
<td>Immunol. bedingte Thrombocytopenie</td>
<td>16/48</td>
<td>7.23</td>
<td>43.9</td>
<td>8.4</td>
<td>8.0 12.4</td>
</tr>
<tr>
<td>E.R.</td>
<td>49/6</td>
<td>Asthma bronch. bei chron. Bronchiit, Pleuritis erweit.</td>
<td>72/101</td>
<td>8.90</td>
<td>43.0</td>
<td>11.0</td>
<td>16.0 11.0</td>
</tr>
<tr>
<td>Name</td>
<td>Diagnosis</td>
<td>Description</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K.S.</td>
<td>idiopathic thrombocytopenia</td>
<td>plasma cells not multiplied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.T.</td>
<td>metastasizing hypernephroma</td>
<td>not performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H.K.</td>
<td>acquired hemolytic anemia, diabetes mellitus</td>
<td>plasma cells not multiplied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.W.</td>
<td>chronic interstitial pulmonary fibrosis, bronchiectases, cicatrizing hepatitis</td>
<td>not performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W.K.</td>
<td>infectious mononucleosis</td>
<td>not performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.H.</td>
<td>combined mitral deficiency, chronic polyarthritis</td>
<td>not performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K.S.</td>
<td>bronchial carcinoma, retention pneumonia, atrophic cirrhosis of the liver</td>
<td>plasma cells multiplied (6.5%), quite isolated atypical plasma cells with crystalline inclosures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W.O.</td>
<td>bronchial carcinoma, diabetes mellitus</td>
<td>plasma cells multiplied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H.G.</td>
<td>well-developed metastases in the bones with unexplained primary tumor</td>
<td>plasma cells rather greatly multiplied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.M.</td>
<td>cholangitis, pancarditis with recidivant polyarthritis</td>
<td>plasma cells multiplied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O.H.</td>
<td>immunologically conditioned thrombocytopenia</td>
<td>not performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.R.</td>
<td>bronchial asthma with chronic bronchitis, exudative pleuritis</td>
<td>plasma cells multiplied (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immuno-electrophoresis: Slightly wavy gamma 2 line.

Sternal marrow: Moderate marrow eosinophilia, definite plasmacellular reaction.

Diagnosis: Strong suspicion of bronchial carcinoma in the region of the upper lobe of the left lung. Emphysematous bronchitis.

Case 8:
A.M., 62, female. Received as a bed patient because of increasing weakness, lack of appetite, backaches, and temperatures above 38° C. Examination showed reduced general condition with pronounced anemia of 51% Hb with 2.62 million erythrocytes. Thoracic organs clinically normal, liver not certainly enlarged, spleen enlarged 2 x. Swellings of the lymphatic glands on the head, in the neck region, and in the underarm and groin. — ESR 75/130. Total protein 5.94 g%.

Paper electrophoresis: Albumin 53.3%, alpha 1 6.7%, alpha 2 11.2%, beta 12.2%, gamma 16.6%.

Agar gel electrophoresis: Several extra gradients in the slowly shifting gamma region.

Immuno-electrophoresis: Wavy pattern of the gamma 2 line.

Sternal marrow: Macrolymphoidal reticulosis.

Diagnosis (autopsy): Neoplastic reticulosis with infiltrates in the inguinal, axillary, mediastinal, and hepato-portal lymphatic glands. Infiltration of the spleen.

The casuistics of the elongated duplication of the gamma 2 line has been summarized in Table 1.

Splitting of the cathodic end of the gamma 2 line was observed in one patient with a chronic lymphadenia and in one patient with a bronchial carcinoma.

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Dr. med. Bergmann, Senior Physician of the District Hospitals, Meiningen.

Discussion

The forms discussed in our results under 1 to 3 constitute clear indications of the presence of a paraproteinemia.
Figures 1 and 2 were recently described by Härki and Wührmann [10] as typical findings in paraproteinemias. The atypia of the gamma globulin shown in Figure 2 may be identical with the gamma 1 syndrome published earlier by Knedel [19]. Knedel found among a large number of patients examined thirty with a sharply homogeneous, fast-shifting gamma 1 fraction in paper electrophoresis and with iseflection, intensification, and doubling of the precipitation line at the transition from the anodic to the middle third of the gamma 2 line in immuno-electrophoresis. This finding proved constant in checks at long intervals of time; it was found in patients with the most varied diseases (hypertony, cholecystitis, polyarthritis, tuberculosis, kidney damage, malignant tumors) and in healthy persons.

Attention was called to the wavy shape of the gamma 2 line in paraproteinemias by Heremans [20]. In these cases several narrow-based gradients are often found in paper and agar gel electrophoresis.

On the other hand appraisal of the changes mentioned under 4 and 5 is difficult and not uniform. The splitting at the cathodic end of the gamma 2 line is generally evaluated only with great reservations. In our cases the change was constant when the test was repeated and could be detected even with a serum dilution at 1:5. Among the numerous tests made with the same antiserum this feature could be found in only two cases; this does justify the conclusion that there is a modification of the gamma 2 globulin.

Doubling of the gamma 2 line can be brought about by an antigen excess (the so-called Liesegang effect [21]). According to Heremans [22] this doubling is certainly pathological if it is a broad doubling, visible throughout the gamma 2 region. Such doublings, according to Edelmann's studies [23], are dependent on the antigen composition of the gamma 2 molecule. According to Heremans [27] they are observed in gamma 1A and gamma 1M paraproteinemias, in quantitatively diminished gamma 2 globulin in some cases of antibody-deficiency syndrome, in some cases of Waldenström's purpura, and in various clinical pictures marked by heightened gamma 2 globulin. This longitudinal split in the gamma 2 line stands out more in the serum of newborn infants than in the serum of adults [24], and is found especially frequently in the pathological liquor cerebrospinalis.

This doubling is probably due to selective increase or selective deficiency of a part of the immune globulin, perhaps of certain antibodies. In Wiese's method of high-voltage electrophoresis a discontinuous distribution of the gamma globulines was often found [15].

By agar gel electrophoresis in the serum of our patients
with duplication of the gamma 2 line it was always possible to
detect several extra gradients in the gamma 2 region. Con-
versely, in only a few cases in which several extra gradients
were visible in the gamma globulin region in agar gel electro-
phoresis was there a duplication of the gamma 2 line. Paper
electrophoresis showed an increase in gamma globulins in the
majority, but in three cases the gamma globulin figure was in
the normal range. In no case were extra gradients to be dis-
cerned on the paper. There was no correlation with definite
clinical pictures, but certain of these diseases make the oc-
currence of antibodies appear probable. Attention has already
been called to a connection between extra gradients in agar
gel electrophoresis and autoantibodies in immuno-hematological
clinical pictures by Lohmann [15].

If we compare the results of agar gel electrophoresis
and immuno-electrophoresis with those of paper electrophoresis,
we find that of the immuno-electrophoretically confirmed para-
proteinemias (only the modifications described under 1 to 3
were evaluated as unambiguous signs of a paraproteinemia) an
extra gradient could be detected only four times in paper
electrophoresis, while in the other five cases paper electrophoresis
gave no indication of a paraproteinemia. A characteristic symptom may be lacking in paper electrophoresis if
the paraproteinemia has attained only a small extent quantita-
tively or if a loss of the paraprotein occurs through para-
proteinuria. A diminution of the paraproteins is also possible
through deposit of these proteins in the form of the paramyloid
[25].

Inconspicuous serum electrophoreses in plasmacytoma
ta have been described repeatedly [26-28]; according to Wuhrmann
and Mörki [4] they are to be observed in 2 to 10% of all
plasmacytoma. No large-scale observations of the frequency
of paraproteinemias with inconspicuous paper electrophoreses
in other diseases are yet available. Even in cases where
paper electrophoresis failed as a test reaction for parapro-
teins, one or more extra gradients were detectable in agar gel
electrophoresis. Paraproteins revealed by immuno-electrophore-
sis without extra gradients in agar gel electrophoresis were
not observed by us. The value of routine performance of agar
gel electrophoresis is thereby underscored.

If we compare the paraproteinemias with the clinical
pictures, three groups may be distinguished:

The first group comprises the plasmacytoma and the
Waldenström macrooglobulinemias, accompanied by obligatory
paraproteinemia, which will not be further described here.

The second group consists of facultative paraprotein-
emias in neoplastic proliferations of the lymphoreticular
system.

A third group is made up of the remaining paraprotein-
emia, where diseases of the first two groups could be ruled out at the time of examination. These idiopathic paraproteinemias, also called rudimentary because of their quantitative slightness [29], are still obscure as to their clinical significance. For at least a part of these cases an early form of plasmocytoma is to be considered. Occasional transitions of paraproteinemia observed for years without clinical signs of myeloma into typical plasmocytomata have been observed [30]. Mirki and Wuhrmann [10] also concur in this interpretation for the majority of their published cases, while they regard the frequency of a greater osteoporosis than is accounted for by age and the reduction of the physiological gamma globulin components as further indications. On the other hand Waldenström [31] was able to observe patients for years whose paraprotein level remained constant for years and in whom no plasmocytoma could be detected either clinically or in several cases autopsically. Years ago Waldenström coined for these cases, which are sometimes accompanied by a definite paraproteinemia, the term essential hyperglobulinemia.

Of the multiplicity of diseases in which paraproteins can occasionally be detected, malignant tumors are especially noteworthy, in connection with which Waldenström [8], Wieme [15], Osermann [7], Creggassal [32], Kojecky and Katlocha [9], and others have described paraproteins. Among our patients, too, there were three carcinomata. Apart from these clear cases of paraproteinemia, extra gradients can be detected electrophoretically in a much higher percentage in malignant tumors, while immuno-electrophoresis shows no definite changes in the gamma globulin system. These findings have been reported by Wieme [15] and more especially by Lohmann [16,33]. The nature of these atypical proteins is still largely unexplained.

The group of idiopathic paraproteinemias also includes paraproteinemias in chronic inflammatory processes, the so-called collagen diseases, cirrhosis of the liver, immunohematological diseases, and numerous other clinical pictures, as well as in rare cases in clinically healthy individuals. In view of the variety of the diseases the question arises whether a connection with the diseases which are clinically in the foreground exists at all or whether we have to do here with a coincident and completely independent disturbance of the protein synthesis.

It is interesting that in the majority of the published cases [13] and of our own cases a slight to moderate excess (averaging 5 to 8%) of plasma cells, largely normal under the light microscope, was found in the sternal marrow. This common characteristic points to an intensification of certain immunization processes, while at the same time the question of why the excessive production of certain abnormal proteins only comes about in individual cases of these reactive plasmacellular changes still remains open.
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