AD NUMBER

AD840476

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

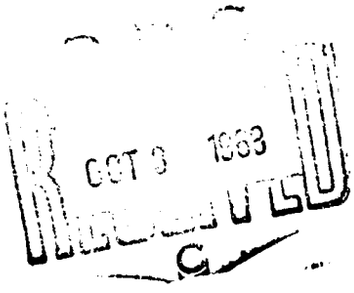
Distribution authorized to U.S. Gov't. agencies and their contractors; Administrative/Operational Use; JAN 1967. Other requests shall be referred to Department of the Army, Fort Detrick, Attn: Technical Release Branch/TID, Frederick, MD 21701.

AUTHORITY

SMUFD, d/a ltr, 15 Feb 1972

TRANSLATION NO. 1948

DATE: 13 jan. 1967



BLOOD PROTEIN DISORDERS IN VARIOUS INTERNAL DISEASES

Münchener Medizinische Wochenschrift
(Munich Medical Weekly)
Vol 107 No 48 pages 2423-2428, 1965

Siegfried Zimmermann

Summary

The author reports on eight γ_2 paraproteinemias observed in various internal diseases without a sure indication at that time of plasmocytoma. 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 γ_2 line, splitting at the cathodic end of the γ_2 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 plasmocytoma 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 lymphosarcomatosis and reticulosarcomatosis [5], and osteomyelosclerosis [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, ulcus ventriculi, cholangitis, etc. [10-13]. Even in clinically healthy blood donors paraproteins have been found [14].

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]. — 0.03 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. Antihuman 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 1c). ([Note] The figures are on page 2435.)
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 33.6%. 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, edemata in the legs, pneumonic 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 6.97 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.S., 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: Hyperregenerative erythropoesis with maturation disorders, hypoplasia of the megacaryocytopoesis without evidence of atypy.

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 esophogeal 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 100/113. 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.)

Name	Age/ Sex	Diagnosis	ESR	Total Protein	Albumin	Globulins α_1	α_2	β	γ	Extra-gradients in Agar	Plasma Cell Symptoms in the Sternal Marrow
K. S.	22/♂	Idiopath. Thrombozytopenie	20/52	6,42	55,5	6,7	10,0	11,0	16,8	‖‖‖ ‖	Plasmazellen nicht vermehrt
A. T.	72/♀	Metastasierendes Hypernephrom	126/146	7,8	43,7	9,5	19,5	14,4	12,9	‖ ‖	nicht durchgeführt
H. K.	48/♂	Erworb. hämolyt. Anämie, Diabetes mell.	25/60	5,11	49,0	10,2	7,4	10,2	23,0	‖ ‖‖ ‖	Plasmazellen nicht vermehrt
M. W.	56/♂	Chron. interstitielle Lungenfibrose, Bronchiektasen, narbenbildende Hepatitis	70/105	8.21	36,8	6,3	6,3	11,2	39,5	‖ ‖	nicht durchgeführt
W. K.	22/♂	Mononucleosis infectiosa	42/72	7,81	50,3	6,1	10,2	10,4	23,0	‖ ‖‖ ‖	nicht durchgeführt
R. H.	51/♂	Komb. Mitralvitium, chron. Polyarthritis	18/24	7,94	48,5	6,2	11,8	12,9	20,6	‖ ‖	nicht durchgeführt
K. S.	57/♂	Bronchialkarzinom, Retentionspneumonie, atrophische Leberzirrhose	118/142	6,20	18,8	11,3	15,2	15,6	39,2	‖ ‖‖‖ ‖	Plasmazellen vermehrt (8%) mit qualitativen Veränderungen
W. O.	69/♂	Bronchialkarzinom, Diabetes mell.	60/100	8,27	41,0	6,4	11,0	11,7	28,9	‖ ‖‖ ‖	Plasmazellen vermehrt (6,5%), ganz vereinzelt atypische Plasmazellen mit kristallinen Einschlüssen
H. G.	64/♂	Ausgeprägte Knochenmetastasierung bei ungeklärtem Primärtumor	148/150	7,62	32,6	11,7	22,7	12,5	21,0	‖ ‖	Plasmazellen stärker vermehrt
D. M.	19/♂	Cholangitis, Pankarditis bei rezidivierender Polyarthritis	71/120	7,91	48,4	5,6	8,1	10,5	27,4	‖ ‖‖ ‖	Plasmazellen vermehrt
O. H.	58/♂	Immunol. bedingte Thrombozytopenie	16/46	7,53	52,9	5,4	9,0	12,4	20,3	‖ ‖	nicht durchgeführt
E. R.	43/♀	Asthma bronch. bei chron. Bronchitis, Pleuritis exsud.	72/101	8,90	42,5	11,8	16,8	11,0	17,9	‖ ‖‖	Plasmazellen vermehrt (9%)

Legend:

[Translation of third and last columns, with first column for index purposes:]

K.S.	idiopathic thrombocytopenia	plasma cells not multiplied
A.T.	metastasizing hypernephroma	not performed
H.K.	acquired hemolytic anemia, diabetes mellitus	plasma cells not multiplied
M.W.	chronic interstitial pulmonary fibrosis, bronchiectases, cicatrizing hepatitis	not performed
W.K.	infectious mononucleosis	not performed
R.H.	combined mitral deficiency, chronic polyarthritis	not performed
K.S.	bronchial carcinoma, retention pneumonia, atrophic cirrhosis of the liver	plasma cells multiplied (8%) with qualitative changes
W.O.	bronchial carcinoma, diabetes mellitus	plasma cells multiplied (6.5%), quite isolated atypical plasma cells with crystalline inclosures
H.G.	well-developed metastases in the bones with unexplained primary tumor	plasma cells rather greatly multiplied
D.M.	cholangitis, pancarditis with recidivant polyarthritis	plasma cells multiplied
O.H.	immunologically conditioned thrombocytopenia	not performed
E.R.	bronchial asthma with chronic bronchitis, exudative pleuritis	plasma cells multiplied (6%)

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. — BSR 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 hepatoportal 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.

For the kind permission to publish specific findings I thank:

Prof.Dr.med. Holle, Director of the Pathological Institute, Leipzig,

Prof.Dr.med. Lohmann, Chief Physician of the Friesenstrasse Municipal Hospital, Leipzig, and

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 Märki and Muhrmann [10] as typical findings in paraproteinemia. The atypy 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 deflection, 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 paraproteinemia 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] the 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 [22] they are observed in gamma 1A and gamma 1M paraproteinemia, 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 Wieme'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. Conversely, in only a few cases in which several extra gradients were visible in the gamma globulin region in agar gel electrophoresis 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 discerned on the paper. There was no correlation with definite clinical pictures, but certain of these diseases make the occurrence 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 paraproteinemias (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 quantitatively or if a loss of the paraprotein occurs through paraproteinuria. A diminution of the paraproteins is also possible through deposit of these proteins in the form of the paramyloid [25].

Inconspicuous serum electrophoreses in plasmocytomata have been described repeatedly [26-28]; according to Wuhrmann and Märki [4] they are to be observed in 2 to 10% of all plasmocytomata. 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 paraproteins, one or more extra gradients were detectable in agar gel electrophoresis. Paraproteins revealed by immuno-electrophoresis 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 plasmocytomata and the Waldenström macroglobulinemias, accompanied by obligatory paraproteinemia, which will not be further described here.

The second group consists of facultative paraproteinemias in neoplastic proliferations of the lymphoreticular system.

A third group is made up of the remaining paraprotein-

emias, 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]. Kürki 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 autoptically. 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, malign tumors are especially noteworthy, in connection with which Waldenström [8], Wieme [15], Ossermann [7], Creyssel [32], Kojecky and Matlocha [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.

Bibliography

1. Spengler, G.A., Roulet, D.L.A., Ricci, C., Schnider, U., Schopp, W., Kappeler, R., and Riva, G., Schweizerische Medizinische Wochenschrift (Swiss Medical Weekly), Vol 91, 1961, pages 984 and 1125.
2. Braunsteiner, H. and Sailer, S., Acta Haematologica (Basel), Vol 23, 1960, page 306.
3. Ossermann, A.F. and Lawlor, D.P., American Journal of Medicine, Vol 18, 1955, page 462.
4. Wuhrmann, F. and Märki, H.H., Dysproteinämie und Paraproteinämien. Grundlagen, Klinik und Therapie (Dysproteinemia and Paraproteinemia. Principles, Diagnosis and Therapy), Benno Schwabe & Co., Basel, 1963.
5. Wagner, K., Wiener Medizinische Wochenschrift (Vienna Medical Weekly), Vol 113, 1963, page 579.
6. Klima, R., Rettenbacher-Däubner, H., and Rieder, H., Wiener Zeitschrift für Innere Medizin (Vienna Journal of Internal Medicine), Vol 43, 1962, page 189.
7. Ossermann, E.F., Radiology, Vol 71, 1958, page 157.
8. Waldenström, J., Acta Medica Scand., Suppl. 367, 1961, page 110.
9. Kojecky, Z. and Matlocha, Z., Clin. Chim. Acta, Vol 8, 1963, page 685.
10. Märki, H.H. and Wuhrmann, F., Klinische Wochenschrift (Clinical Weekly), Vol 43, 1965, page 85.
11. Scheurlen, P.G., Verhandlungen der Deutschen Gesellschaft für Innere Medizin (Transactions of the German Society of Internal Medicine), Vol 69, 1963, page 451.
12. Schobel, B. and Wewalka, F., Deutsches Archiv für Klinische Medizin (German Archives of Clinical Medicine), Vol 207, 1961, page 85.
13. Rádl, J. and Masopust, J., Schweizerische Medizinische Wochenschrift, Vol 94, 1964, page 961.
14. Laurell, C.B., Laurell, M., and Waldenström, J., American Journal of Medicine, Vol 22, 1957, page 24 (cited in no. 11).
15. Wieme, R.J., Studies on Agar Gel Electrophoresis, Verlag Arscia Uitgaven N.V., Brussels, 1959.
16. Lohmann, D., Zeitschrift für die Gesamte Innere Medizin (Journal of General Internal Medicine), Vol 19, 1964, page 145.
17. Grassmann, W. and Hannig, K., Naturwissenschaften (Natural Sciences), Vol 21, 1950, page 496.
18. Scheidegger, J., International Archives of Allergy, Vol 7,

1955, page 103.

19. Knedel, M., lecture presented to the medical faculty in Munich in 1958, cited in Schettler, G. and Neikes, K., Medizinische Klinik, Vol 55, 1960, page 496.

20. Heremans, J.F. and Heremans, M.-Th., Acta Medica Scand., Suppl. 367, 1961, page 27.

21. Oss, C.J. van and Heis, Y.S.L., Zeitschrift für Immunitäts-Forschung (Journal of Immunological Research), Vol 122, 1961, page 44 (cited in no. 21 [sic]).

22. Heremans, J.F., "Die Immunelektrophorese und ihre Klinische Bedeutung" (Immuno-Electrophoresis and its Clinical Significance), in Ergebnisse der Inneren Medizin und Kinderheilkunde (Advances in Internal Medicine and Pediatrics), New Series, 20th Volume, Springer, Berlin-Göttingen-Heidelberg, 1963.

23. Edelmann, G.M., Heremans, J.F., Heremans, M.-Th., and Kunkel, H.G., Journal of Experimental Medicine, Vol 112, 1960, page 203.

24. Hitzig, W.H., Helv. Paediat. Acta, Vol 12, 1957, page 596.

25. Stobbe, H., Schoffke, M., Haase, J., and Herrmann, H., Deutsches Gesundheits-Wesen (German Public Health), Vol 18, 1963, page 1295.

26. Stobbe, H., Wildner, G.P., and Tichter, E., Deutsches Gesundheits-Wesen, Vol 18, 1963, page 1283.

27. Scheiffarth, F.H.G. and Sörgel, K., Klinische Wochenschrift, Vol 36, 1958, page 82.

28. Innes, J. and Newall, J., Lancet I, 1961, page 239.

29. Märki, H.H. and Wuhrmann, F., Schweizerische Medizinische Wochenschrift, Vol 93, 1963, page 1381.

30. Martin, N.H., Lancet I, 1961, page 237.

31. Waldenström, J., Acta Medica Scand., Vol 176, 1964, page 345.

32. Creyssel, R., Granjde, J., Fine, J.M., and Beutel, H., Protides of the Biological Fluids, 11th Colloquium, 1963. Etude Immunochimique de 463 Sérums Contenant une Paraprotéine, Elsevier Publishing Company, Amsterdam-London-New York, 1964.

33. Lohmann, D., "New Findings in the Blood Protein in Carcinomata," 1. Tagung der Sektion Innere Medizin der Deutschen Gesellschaft für Klinische Medizin (First Meeting of the Internal Medicine Section of the German Society for Clinical Medicine), 1963, Leipzig.

Address of the author: Dr.med. S. Zimmermann, Medizinische Universitäts-Klinik, X701 Leipzig, Johannisallee 32.