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Frequency of Pathological Proteins (M-components) in 6,995 Sera from an Adult Population

By

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Pathological proteins (34) or M-components (25) in the serum were formerly observed mainly in myelomatosis and macroglobulinaemia Waldenström. In recent years such components have been found with increasing frequency also in patients with other diseases (1, 4, 9, 17, 19, 20, 22, 26, 29, 30, 31, 32) and even in apparently healthy persons (10, 14). Knowledge of the frequency of M-components in a random population would help us to understand the significance of the occurrence of such proteins.

A paper electrophoretic analysis of sera from 294 largely healthy subjects above 70 years was described in a previous publication (10). In none of the 9 subjects with M-components did subsequent investigation warrant a diagnosis of myelomatosis or macroglobulinaemia Waldenstrom with certainty. Several of these subjects have since died from cancer of various organs.

A mass-health control of the population of the district of Värmland in Sweden offered an opportunity to study the frequency of pathological proteins in a larger series covering a wider age range.

The subjects in whom paper electrophoresis revealed M-components were studied clinically, roentgenologically, cytologically and immunologically.

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Material and design of investigation

Sera were collected during a 3 month period (April-June 1964) in 4 parishes (Ekshärad, Gustaf Adolf, Rämmen and Norra Råda). All persons above 25 years and living in this area were invited to take part in the mass health control; 79 % accepted. Blood samples were collected from the 7.918 persons. On account of the fact that sera could not be sent to us every day, samples from 6,995 persons were placed at our disposal. These samples, which covered 70 % of the population above 25 years, were on the whole just as representative as the entire number of samples from 79 % of the population. The 6,995 sera derived from 3,400 men with a mean age of 51.3 years and 3,595 women with a mean age of 50.3 years. The age and sex distribution as well as the percentages of persons who

cooperated in the various age classes are given in table I.

The blood samples were collected between 1 p.m. and 8 p.m. During transport to Malmö, which lasted about 10 hours, the sera were kept at − 5° — + 10° C, after which they were stored at — 20° C until analysed.

All sera were studied by paper electrophoresis. The strips were inspected visually for M-components by two independent examiners. M-components were said to be present when a discrete, narrow extra fraction was seen in the paper electrophoretic strip. Sometimes an increased concentration of a normally occurring fraction suggested the possible occurrence of an M-component of equal electrophoretic mobility. An hi-component was then said to be present if immunoelectrophoresis revealed a corresponding bow in any of the precipitation lines of the immunoglobulins.

When M-components were demonstrated, the paper electrophoretic fractions were studiec quantitatively.

The 11-components were also classified immunologically.

Persons with ill-components were requested to present themselves for medical examination (during July — September 1964) by one (U.A.) of us, who was stationed in Värmland. Examination included a detailed history of the patient. general physical examination. ophthalmoscopy and sternal puncture. The laboratory studies included determination of the haemoglobin (Hbj, white blood cell count (W.B.C.), differential count. erythrocyte sedimentation rate (E.S.R. — Westergren) and examination of the urine for protein. In cases with proteinuria paper electrophoresis was done on concentrated urine.

Two marrow smears from each person were examined. The number of plasma cells and lymphocytes per 500 nucleated cells was counted in each smear. The preparations were closely examined for mast cells, and a large number of plasma cells were studied for atypical features and properties known to be common in the presence of myelomatosis with AI-components of γA-type (23). As in the investigation by Drivsholm and Clausen (6) a distinction was made between blue-grey hyaline intranuclear inclusions surrounded by a dark rim and others. Marrow smears from 15 supposedly healthy subjects in Gormsen's series (8) were examined for plasma cells with inclusions. flamin and compartments.

The examination also included roentgenography of the skeleton. For technical reasons the examination included only the skull in 10 cases, but otherwise also the thoracic and lumbar spine, pelvis. proximal parts of the upper arms and the thighs.

Methods

Paper electrophoresis was done according to the method of Laurell et al. (13). With this method the distance between the β_1-globulin fraction and the most cathodal part of the γ-globulin fraction is 5—6 cm. The concentration of the M-components was determined either by elution of the hi-cornponent separately and subsequent subtraction of the estimated concentration of the normal serum proteins with the same paper electrophoretic mobility, or by visual evaluation of the concentration of the M-component compared with that of other protein fractions. particularly of the β_1-globulins. The latter method was used mainly for estimation of the concentration of M-components in low concentration (< 0.5 g/100 ml).

The serum protein concentration was determined by a biuret method (24).

Immunological classification of the M-components was done by the methods used by Bachmann and Laurell (2) and *zone immunodimetric determination* according to Kunkel [1].

Heller's test with nitric acid and heated urine and water in equal parts sensitive down to about 6 mg/100 ml) was used for demonstrating proteinuria.

Concentration of urine was done with the aid of a collodium rube (Membranfilter-Gesellschaft. Göttingen, Germany) according to Mies (15).

Bone marrow smears were stained according to May-Grünwald-Giemsa at pH 7.0

TABLE I. Proportion of population ab and female grouped accordi

	Subjects studied		
	Male		Female
Age	No	% [1]	No
25—29	208	58	287
30—39	617	70	664
40—49	762	70	783
50—59	772	71	859
60—69	662	61	634
70—79	296	56	315
80—89	76	43	48
90—99	7	33	3
Total	3.400	66	3,595

[1] Per cent of total population in eac
[2] Per cent of subjects esamined in ea

Results

Frequency of M-components, age-distribution

M-components were suspected onstrated in 73 of the 6.0 M-components satisfying tht mentioned criteria were dem in 64 sera corresponding to a of 0.9 %. These sera were males (mean age 68 years females (mean age 59 years). T age in this group was 64 yea I). The incidence of the M-co increased significantly ($P < 0$ age and was highest (5.7 % 80—89 years. The increas ed more marked for the men th but this difference wa cally significant only for the 80 age class ($P = 0.042$).

Table I. Proportion of population above 25 years examined and incidence of M-components in male and female grouped according to age

Age	Subjects studied				M-components found					
	Male		Female		Male		Female		Total	
	No	%[1]	No	%[1]	No	%[2]	No	%[2]	No	%[2]
25—29	208	58	287	76	0	0	0	0	0	0
30—39	617	70	664	83	0	0	3	0.5	3	0.2
40—49	762	70	783	83	1	0.1	1	0.1	2	0.1
50—59	772	71	859	80	8	1.0	10	1.2	18	1.1
60—69	662	61	634	69	13	2.0	9	1.4	22	1.7
70—79	296	56	315	55	7	2.4	5	1.6	12	2.0
80—89	76	43	48	31	7	9.2	0	0	7	5.7
90—99	7	33	5	14	0	0	0	0	0	0
Total	3,400	66	3,595	74	36	1.1	28	0.8	64	0.9

[1] Per cent of total population in each age group.
[2] Per cent of subjects examined in each age group.

Results

Frequency of M-components, age- and sex distribution

M-components were suspected or demonstrated in 73 of the 6,995 sera. M-components satisfying the above-mentioned criteria were demonstrated in 64 sera corresponding to a frequency of 0.9 %. These sera were from 36 males (mean age 68 years) and 28 females (mean age 59 years). The mean age in this group was 64 years (table I). The incidence of the M-components increased significantly ($P < 0.001$) with age and was highest (5.7 %) in the age class 80—89 years. The increase appeared more marked for the men than for the women, but this difference was statistically significant only for the 80—89 year age class ($P = 0.042$).

Paper electrophoresis of the 64 sera with M-components

The mobility of the SI-components varied between that of β_1 and that of γ_3. Their concentrations are given in fig. 1 (for sera with two SI-components the values given indicate the sum of the concentrations of both). In most (84%) of the sera the concentration of the M-components was $\leqslant$ 1.0 g/100 ml. The highest was 2.4 g/100 ml.

The concentration of the paper electrophoretic gammaglobulin fraction (excluding M-components with the same electrophoretic mobility) is given in fig. 2, together with the concentration of the M-components. In most of the sera the values crowded around the lower border of the normal range. In 15 sera

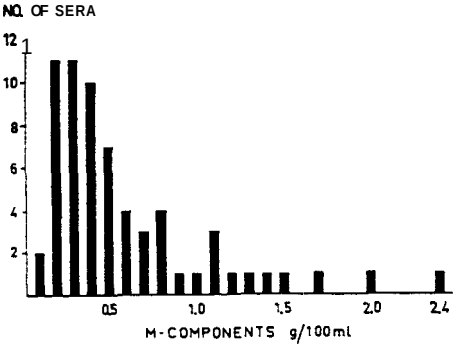


Fig. 1. Concentration of M-components **in 64** sera.

the concentration was clearly low ($\leqslant$ 0.5 g/100 mlj. In no instance was it clearly increased ($>$ 1.3 g/100 ml).

The albumin concentration was never decreased ($<$4.2 g/100 ml). The α_2-fraction was increased ($>$ 0.66 g/100 ml, in **3** sera.

Immunological classification. In 39 sera (61 %) the M-components were of type γG, in 17 (**27** %) of type γA and in 5 (8 %) of type γM. Three (5%) sera contained **2** components, namely γG + γM in 2 and γA + γG in 1. In the former **2** the γG-M-component wa the larger fraction and in the latter cas the γA-M-component.

Paper electrophoresis of the urine was done in the **5** cases in which proteinuria was demonstrated. No M-component of the type light chain protein could be detected.

E.S.R. In fig. 3 the E.S.R. is presented together with the concentration of the M-components. In 11 (18 %) cases the E.S.R. was normal (males $<$ S. females $<$ 12 mm/1 hour) and in 27 43 %, including *2* with increased α_2-fraction, it was over 20 mm/1 hour. In several cases with M-components in relatively high concentration the E.S.R. was only slightly raised.

Zinc turbidimetric determination. The values were normal in 39 cases (γG:30, γA:6, γM:2, γG + γM:1 case), decreased in 19 (γG:5, γA:11, γM:2, γA + γG:1 case) and increased in 6 (γG:4, γM:2, γG + γM:1 case).

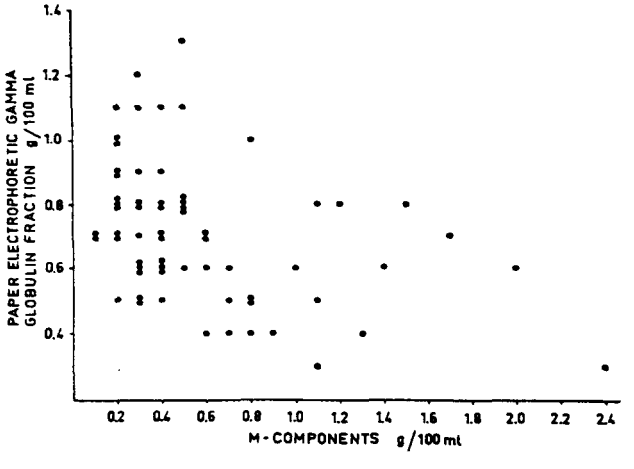


Fig. 2. Paper electrophoreti gammaglobulin fractio cluding any M-compone same mobility) and M-compo nents in 64 sera.

Fig. 3. E.S.R. and concentration of M-components in 62 subjects.

Bone marrow. Sternal p done in 63 cases (one refu case the yield was very differential count was mad the number of bone marro smears was somewhat low other cases the yield of the good-

. The mean number of (excluding one case of l kaemia) was 15.9 %, stand 4.9 % and the error of the 1,000 counted cells 1.3 %, sponding figures for plasm 27 %, 3.4 % and 0.4 %.

Fig. 4 shows that 23 % had more than 3 % Nine had between 3 % a 6 %, 6 %, 7 %, 9 %,

In the 2 smears with number of plasma cells (ca 7006) the nuclei and ti varied in form and size. there plasmocytic reticul were seen. In one smea plasma cells of homogenou

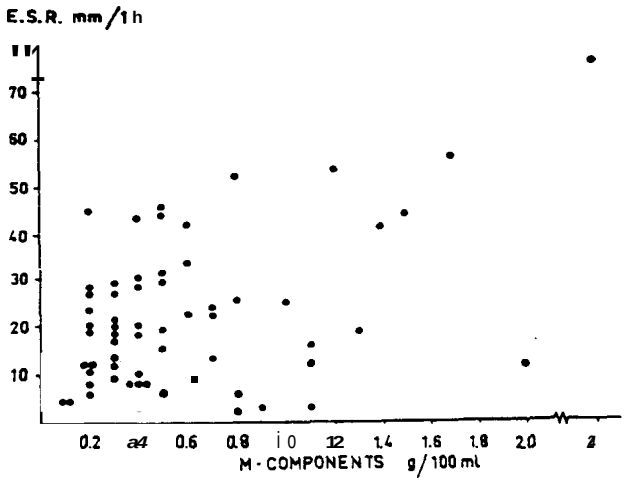


Fig. 3. **E.S.R. and concentration of M-components in 62 subjects.**

Bone marrow. Sternal puncture was done in 63 cases **(one** refused). In one case the yield was very poor, and no differential count was made. In 6 cases the number of bone marrow cells in the smears was somewhat low, but in the other cases the yield of the puncture was good.

The mean number of lymphocytes excluding one case of lymphatic leukacmia, was 15.9 %, standard deviation 4.9 % and the error of the method per 1,000 counted cells 1.3 %. The corresponding figures for plasma cells were 2.7 %, 3.4 % and 0.4 %.

Fig. 4 shows that 23 % of the cases had more than **3** % plasma cells. Sine had between 3 % and 5 % and 6 had 6 %, *6* %, 7 %, 9 %, 18 %, 19 %.

In the *2* smears with the largest number of plasma cells (cases 6884 and 7006) the nuclei and the cytoplasm varied in form and size, and here and there plasmocytic reticulum cells (27) were seen. In one smear with *2* % plasma cells of homogenous appearance, some were seen in clusters which did not **happen** to be included in the differential count.

Of 1,500 plasma cells in bone marrow smears from 15 supposedly healthy persons a pink, intranuclear inclusion was seen in one, flaming in none, and compartments in 8, including 2 discovered among 100 plasma cells in one and

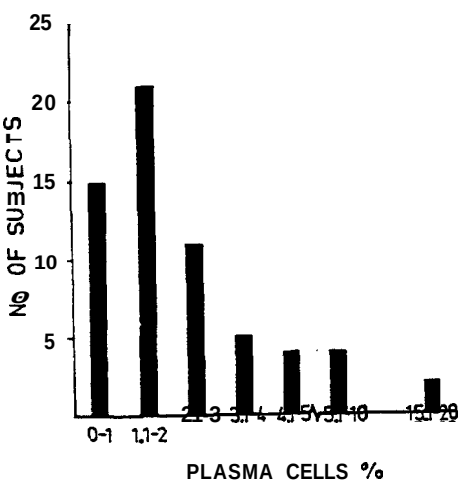


Fig. 4. Plasma cells in bone marrow in 62 **subjects with** M-components.

TABLE II. Subjects with special types of bone marrow plasma cells

Type of plasma cell	Of 18 subjects with γA-M-components	Of 35 subjects with γG-M-components
1	2	3
2	2	0
3	2	0
4	3	0

Type 1: with blue-grey, hyaline, intranuclear inclusion body surrounded by a dark rim. Type 2 with other types of intranuclear inclusion bodies. Type 3: with flaming. Type 4: with compartments.

rhe same smear. A hundred plasma cells were studied for these properties in each case of our series with M-components except in 4 cases in which the cell density of the smear and the percentage of plasma cells were too low. These 4 cases are not included in what follows. Table II shows the results of this part of the investigation. In view of the findings in the controls, only cases with more than 2 cells with compartments or one inclusion body per 100 cells will be accounted for. The number of cells with blue-grey inclusion bodies with surrounding rims was 2/100 and 33/100 in 2 cases in the γA-group and 2/100, 10/100 and 20/100 and 3 cases in the γG-group. The number of cells with inclusion bodies of the other type was 2/100 and 4/100, the number of flaming cells was 3/100 and 9/100 and cells with compartments 3,3,4,9 and 15/100; all these cells were found on counting 100 plasma cells in smears from the γA-group. In several cases more than 100 plasma cells were seen and then in 2 preparations from cases with γ G-M-component one respectively two flaming cells were observed. The incidence of these features did not vary with the number of plasma cells or the concentration of the M-component: 4 cells with compartments and one with a pale inclusion body were seen. for example, in one case with 1 % plasma cells and an M-component (γA in a concentration of 0.2 g/100 ml. while in 2 cases with 19 % and 18 % plasma cells and M-components γA in concentrations of 1.0 respectively 2.4 g/100 ml the plasma cells showed nothing remarkable apart from marked polymorphism.

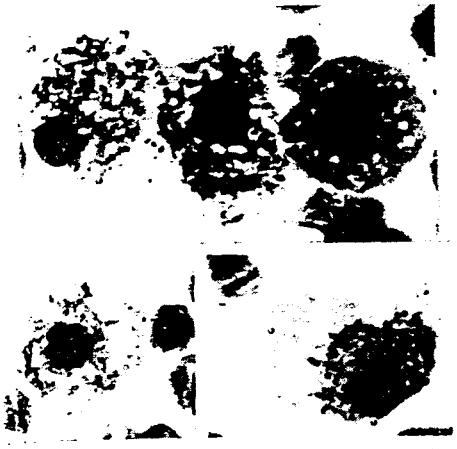
In one case (apparently healthy 50-year-old woman with 4 % plasma cells. M-component (γA) in a concentration of 1.6 g/100 ml, E.S.R. now 56 mm. and E.S.R.-increase to 20—30 mm known for about 10 years) 95 % of the plasma cells showed vacuolated cytoplasm, which in some cells was divided into compartments. In several cells the cytoplasm showed patches of eosinophilic material especially in the vacuoles (fig. 5, case 7848).

In 7 cases with M-components of type γM, the number of plasma cells was not more than 1.5 % except in one



Fig. 5. Case 78-18: vacuolated p eosinophilic patches and compar

case with 4 %, .and sho morphologically remarkab the last mentioned case w them were small lymphoid from a man with lymphat and γG-M-component th tive number of lymphoc marrow, namely 29 %, w 76-year old woman (case γM-M-component (0.2 g these lymphocytes several ha shaped nuclei with loose ch nucleoli-like areas and irr lined cytoplasm (fig. 6). 1 who had a long history anaemia felt well, the peri contained 26 % normal (W.B.C.:7,000/mm³) and showed an increased num cells (3—4 per smearj. Suc of mast cells were seen als cases with M-components γG, γG + γM; in the last t ed, however, the prepar very rich in cells.



Case 7848: vacuolated plasma cells with eosinophilic patches and compartments.

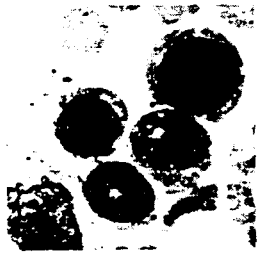


Fig. 6. Case 7677; two lymphoid cells, low right.

case with 4 %, and showed nothing morphologically remarkable except in the last mentioned case where most of them were small lymphoid cells. Apart from a man with lymphatic leukaemia and γG-M-component the largest relative number of lymphocytes in the marrow, namely 29 %, was seen in a 76-year old woman (case 7677) with γM-M-component (0.2 g/100 ml). Of these lymphocytes several had irregularly shaped nuclei with loose chromatin and nucleoli-like areas and irregularly outlined cytoplasm (fig. 6). This woman, who had a long history of moderate anaemia felt well, the peripheral blood contained 26 % normal lymphocytes (W.B.C.:7,000/mm³) and the marrow showed an increased number of mast cells (3—4 per smear). Such a number of mast cells were seen also in 3 other cases with M-components of type γA, γG, γG + γM; in the last two mentioned, however, the preparations were very rich in cells.

Roentgenography. One woman (Case 8420) had myeloma-like changes in the skull (see case reports). Two women (75 and 60 years) had slight and one woman (76 years) marked osteoporosis. In the latter case the concentration of the M-component was 0.5 g/100 ml and the number of plasma cells in the marrow was 4 %. Apart from degenerative joint lesions nothing remarkable was seen in the series except an obscure change in the cavitas glenoidalis scapula dst. in one case. The nature of this change could not be cleared up. It was seen in an apparently healthy woman with moderate brachialgia, the serum electrophoretic pattern was normal apart from an M-component of 0.2 g 100 ml, the E.S.R. 6 mm and the Hb was 14.2 g/100 ml.

State of health. Fifty-nine of the 64 persons presented themselves for medical examination. Three had been admitted to hospitals from which we obtained information, and one had emigrated to U.S.A. and was examined there. A feeble-minded woman (6359) did not come for examination, but information about her was obtained from the records of a hospital where she had been admitted in February 1963 because

TABLE III. Data concerning the 7 cases described in detail

Case	Sex	Age	Hb (g/100 ml)	W.B.C.	Bone marrow plasma cells (%)	E.S.R.	Gammaglobulin[1] (g/100 ml)	M-component (g/100 ml)	M-component (type)	Skeletal X-ray appearance
6140	M	61	13.3	7,600	3	19	0.4	1.3	γG	Normal
8416	M	56	16.5	15,200	9	19	0.9	0.5	γA	Normal
6497	M	75	16.0	7.200	7	55	0.6	0.4	γG	Normal
6350	M	87	13.6	20.500	1	12	0.3	1.1	γG	Normal
6844	M	73	12.4	6,300	18	76	0.3	2.4	γA	Normal
7006	M	67	14.7	10,000	19	25	0.6	1.0	γA	Normal
8420	F	76	13.9	11,900	4	54	0.8	0.9 ÷ 0.3	γA—γG	Abnorma

[1] Paper electrophoretic gammaglobulin fraction excluding any M-components of same mobility

of an attack of hypoglycaemia following medication with chlorpropamide.

Analysis of the history, general physical examination or laboratory studies revealed nothing remarkable in 21, who were classified as healthy. Abnormalities were found in 36, but in only few of these cases was their normal activity impaired. To this group belonged: 22 persons with cardiovascular and/or cerebrovascular diseases including 8 with substantial symptoms. In addition some subjects had diabetes, gallbladder symptoms, peptic ulcer, pyelonephritis, spondylosis, severe psychasthenia, intestinal cancer (2 healthy men had been operated upon 6 and 8 years previously), severe infection with actinomyces 18 years previously, and a well-controlled pernicious anaemia. Anaemia (Hb < 12 g/100 ml) was noted in 3 women. Two had 11.8 g/100 ml; one of them had had a low value for several years. One, who had 9.8 g/100 ml, was studied further and found to have sideropenia but no demonstrable source of bleeding. In an apparently healthy 78-year-old man the Hb was 11.5 g 100 ml. Two persons had unexplained leucocytosis (16.000 and 14,000) with normal differential count respectively 77 % neutrophilic granulocytes.

In 7 cases presented below more noteworthy findings were made. Data on them are given in table III.

Case 6140 (*K.S.*). A 61-year-old man whose father had died from prostatic cancer, and whose brother had died from leukaemia. For the last 20 years he had bruised readily. In 1962, after an infection of the upper respiratory tract, he had had pain in the region of the right shoulder and weakness of his arms, symptoms which, however, had more or less disappeared. Examination revealed suggillations of the arms and legs as well as muscular atrophy of moderate degree of the arms and some muscular fasciculation. Two months later he was referred to the department of internal medicine in Malmö for investigation. Then he had suggillations and comprehensive coagu-

tion studies (18) showed
The diagnosis is obscure,

Case 8416 (*A.H.*). A 56-
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Case 6497 (*K.P.*). A
75-year-old man was ad
in September 1964 beca
history of obsripation. a
anorexia, loss of weight an
slightly jaundiced and asc
Roentgen examination of
colon, skull, ribs, spine and
to explain this condition.
rubin was slightly increasec.
ml) and the alkaline phor
kedly increased (45—70 U
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patient deteriorated rapi
weeks later. Post mortem
not done. Diagnosis: neopl
ment of the liver (?).

Case 6350 (G.S.) An 87-
had always felt well. Palp.
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or of the liver, and genc
ination showed nothing
W.B.C. was 20,500. Th
contained 64 % normal
abundant ghost cells. The
which were poor in cells.
lymphocytes. Diagnosis:
kaemia.

Case 6844 (*E.E.*). A 73-y
had felt well until 1962.

mponent

(type)	Skeletal X-ray appearance
γ G	Normal
γA	Normal
γG	Normal
γG	Normal
γA	Normal
γA	Normal
γA+γG	Abnorma

ients of same mobility.

ole source of bleeding
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A 61-year-old man, whos
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ion studies (18) showed nothing abnormal. The diagnosis is obscure.

Case 8416 (A.H.). A 56-year-old man, who had for the previous 2 years been disabled by low back pain. Apart from this he felt well and physical examination revealed nothing remarkable. On two occasions, however, the white blood count was 15,200 and 15.700 with 51 % morphologically normal lymphocytes. The bone marrow contained 9 % plasma cells and 10 % lymphocytes. and roentgen examination showed pronounced spondylosis. The diagnosis is obscure: lymphatic leukaemia is suspected but the increased number of plasma cells in the bone marrow remains unexplained.

Case 6497 K.P.). A previously healthy 75-year-old man was admitted to hospital in September 1964 because of 6 months' history of obstipation. abdominal tension. anorexia. loss of weight and fatigue. He was slightly jaundiced and ascites was suspecred. Roentgen esamination of the chest, stomach, colon, skull. ribs. spine and pelvis was unable to explain this condition. The serum bilirubin was slightly increased (1.3—2.6 mg/100 ml and the alkaline phosphatase was markedly increased (45—70 U. Buch & Buch; normal laboratory range 2—8 U). The patient deteriorated rapidly and died 3 weeks later. Post mortem examination was not done. Diagnosis: neoplasia with involvement of the liver (?).

Case 6350 G.S.). .In 87-year-old man who had always felt well. Palpation revealed no enlargement of the lymph nodes, of the spleen or of the liver. and general physical examination showed nothing remarkable. The W.B.C. was 20.500. The blood smears contained 64 % normal lymphocytes and abundant ghost cells. The marrow smears. which were poor in cells. contained 53 % lymphocytes. Diagnosis: lymphatic leukaemia.

Case 6844 E.E.,. A 73-year-old man who had felt well until 1962. when he was subjected *to* prostatectomy. In the spring of 1964 he had been found *to* have diabetes, for which he was treated with chlorpropamide. The E.S.R. was then 100 mm. At examination in July 1964 he had no symptoms. The sternal marrow contained 18 % polymorphous plasma cells. and the concentration of the 11-component (γA) was 2.4 g/100 ml. Roentgen examination of the skeleton revealed no abnormalities. Diagnosis : myelomatosis.

Case 7006 (*F.J.*). A 67-year-old man who after symptoms of biliary disease for some years had been subjected to cholecystectomy in Slay 1964. He had for some years had chest pain on physical exertion and a few weeks before the present examination he had noticed a rash.. Status: slight dyspnoea, B.P. 200/125 mm Hg, pityriasis rosea-like efflorescences on the trunk. E.C.G. showed signs of coronary insufficiency. The sternal marrow contained 19 % polymorphous plasma cells and the concentration of the M-component (γA) was 1.0 g/100 ml. Roentgen examination of the skeleton revealed no abnormalities. Diagnosis: myelomatosis.

Case 8420 (K.O.). A 76-year-old woman who had for **3—4** years been known to have slight diabetes and who had always felt well and now appeared healthy. Roentqen examination showed a few rarefactions suggestive of myelomatosis, the bone marrow contained 4 % plasma cells and the concentration of the AI-components (γA − γG was 1.2 g/100 ml. Diagnosis: myelomatosis ?

None of the 64 subjects had symptoms or pain suggesting osteolytic lesions. None had an increased bleeding tendency of the type seen in macroglobulinaemia Waldenstrom or myelomatosis. Sone of the subjects had any enlargement of the lymph nodes, spleen or liver, and examination of the eyes had not revealed so-called "fundus paraproteinaemicus" (3). Xone had increased

tendency to infection, which is common in pronounced immunoglobulin deficiency.

Discussion

Material. It is difficult to find out th reasons why some persons fail to attend mass health controls. In the present control some of the men in active age were probably prevented by their work, even though the department was open until 8 p.m. As to the youngest groups, the lack of cooperation was probably due to the fact that they felt well. The absences among the aged could probably be esplained largely by their poor general condition and a nihilistic attitude. Some sick persons surely failed to attend because they were disabled by their diseases and thought control examination unnecessary because they were under medical observation or had been admitted to hospital. Persons with myelomatosis probably failed to cooperate for such reasons. Inquiry at local hospitals and interviews with doctors who knew the population revealed that two persons with myelomatosis were known; a 57-year-old man and a 53-year-old woman who had had symptoms for 2 years and 1 year, respectively. Seither of them attended the mass health control.

Judging from the composition of the material (table I) it may be regarded as largely representative of the population above 25 years in the 4 parishes with reservation for the low percentage of men in thelowest age classes and of persons above 70 years.

The frequency of M-components was found to be about 1 %. M-components in low concentration (< 0.4 g/100 ml) and with a paper electrophoretic mobility corresponding to that of α_2, β_1 or γ-fractions or to the maximum concentration of the gamma globulin fraction of normal or increased concentration may remain undetected by the method used. It is therefore probable that the frequency of M-components in low concentration was somewhat higher than that found by us. The frequency of 54-components increased with decreasing concentration of the M-components but only down to a concentration of 0.3 g/100 ml. This may be esplained by the above mentioned remarks.

M-components with the same mobility as the a,-fraction are rare (12). Apart from such components there is no reason to assume that M-components in a concentration of 0.4 g/100 ml or more have been missed. The frequency of M-components in this range of concentration in our material was 0.6 %.

The frequency of M-components increased with age. The increase appeared to be more pronounced for men than for women, but the difference was not statistically significant except in the highest age class.

Unlike the distribution of M-components according to immunological type in hospital series, that in the present investigation was not dependent on the conventional indications for paper electrophoresis. But as far as the three main types of immunoglobulins are concerned, the distribution did not differ substantially from that in large hospital series (2, 5, 16, 21, 28), though the frequency

of γM-M-component observed.

The results of th determination and E.S. methods cannot be re screening tests for M-concentration.

Bone marrow finding (23) showed that cer the plasma cells in th patients with myeloma number of cases with γA-type. Flaming. cor tion or intranuclear however, not observe with γG-M-componen myelomatosis series Di sen (6) made similar in a few cases with they observed plasm above-mentioned prc series the blue-grey surrounding dark ri common in patients wi nent as in those with Apart from these inclu ties under discussion Pronounced in 39 % γA-M-component anc among 100 plasma ce other cases. An inc. of plasma cells with inclusions, flaming d

thus occurred also in sui component but probab matosis, and the pr appear to be correlated tration of the M-com number of plasma cells

Skeletal X-ray. In the rarefactions of the sku

of γM-M-components was the lowest observed.

The results of the *zinc turbidimetric determination and E.S.R.* show that these methods cannot be regarded as sensitive screening tests for SI-components in low concentration.

Bone marrow findings. Paraskevas et al. (23) showed that certain properties of the plasma cells in the bone marrow in patients with myelomatosis occurred in a number of cases with SI-components of γA-type. Flaming, compartment formation or intranuclear inclusions were, however, not observed among patients with γG-M-components. In a later large myelomatosis series Drivsholm and Clausen (6) made similar findings and also in a few cases with γG-M-component they observed plasma cells with the above-mentioned properties, In our series the blue-grey inclusions with surrounding dark rim were equally common in patients with γG-M-component as in those with γA-M-component. Apart from these inclusions, the properties under discussion were abnormally pronounced in 39 % of the cases with γA-M-component and were not seen among 100 plasma cells in any of the other cases. An increased frequency of plasma cells with pale intranuclear inclusions, flaming or compartments thus occurred also insubjects with γA-M-component but probably without myelomatosis, and the properties do not appear to be correlated with the concentration of the M-components or the number of plasma cells.

Skeletal X-ray. In the only case with rarefactions of the skull the suspicion of myelomatosis was suported to some extent by the concentration of the M-component and by slight increase in the number of plasma cells. The finding of osteoporosis among the elderly women was not surprising and does not by itself suggest myelomatosis. In the subject with a dubious picture of the glenoid cavity other findings argued against destruction of neoplastic origin.

The state of health was largely normal for age (64 years). The commonest diseases were those of aging such as cardiovascular diseases and spondylosis deformans. M-components have been described in patients with cancer (*e.g.* 20) and in patients with lymphatic leukaemia (*e.g.* 1). The material included 2 men operated upon for cancer 6 and 8 years previously, one man who died shortly after collection of rhe samples, probably from malignant neoplasm of the abdomen, and one man with clearcut lymphatic leukaemia in a quiescent stage.

None of the 7 with γM-M-components had clinical symptoms or signs of the type seen in macroglobulinaemia Waldenstrom. Some of these symptoms and signs, however, seem *(7)* to be dependent on a concentration of the M-component, which is much higher than those (0.1—0.6 g/100 ml) found in this series. No definite diagnosis could be made in the 73-year-old woman who had for many years had mild anaemia, was found to have an M-component (γM) in low concentration, several atypical lymphoid cells and a slightly increased number of mast cells in the bone marrow. Early

macroglobulinaemia Waldenstrom was, however, suspected.

Myelomatosis was strongly suspected in 3 cases. Estimation of the true frequency of myelomatosis in this series requires further observation.

Judging from figures for the town of Malmö (33), the incidence of living patients with myelomatosis in a population above 25 years of age is 1—2 per 10,000: which agrees with the frequency (2 cases) in the district studied. In this district there must be about 80 cases with 51-components of the type γG and γA. It appears very unlikely that all of these persons will develop myelomatosis.

Summary

In a population of 6,995 persons above 25 years paper electrophoresis of the serum revealed ill-components in 64 cases. 13-components were more common in the higher age classes.

The concentration of M-components was usually low and in only 10 sera did it exceed 1 g/100 ml.

The distribution of M-components from an immunological point of view was: γG 61 %, γA 27 % and γM 8 %. In 3 sera two 1.1-components of different immunological types were seen.

The number of plasma cells in the bone marrow was more than 3 % in 23 % of the cases studied.

Plasma cells with flaming, compartment formation or intranuclear inclusions (excluding blue-grey hyaline surrounded by a dark rim) were more common in patients with M-components of type γA than in patients with other types of M-components.

The X-ray appearance was suggestive of myelomatosis in one case.

The state of health of the 64 persons was fairly normal for age (64 yea ,. The diagnosis of myelomatosis was strongly suspected in 3 cases. Sone of the patients had symptoms of macroglobulinaemia Waldenstrom. Three persons had or had had neoplasms and one had lymphatic leukaemia.

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