IgM paraproteins

J. R. HOBBS, P. M. CARTER, K. B. COOKE, M. FOSTER, AND C.-J. OON

From the Department of Chemical Pathology, Westminster Medical School, London

Our current methods for establishing the presence of an IgM paraprotein will be outlined, after which the clinical presentation of patients bearing such proteins will be considered under three main headings: (1) with symptoms due to the protein; (2) with symptoms due to the tumour; (3) with paraproteinaemia as a chance finding.

IgM paraproteins usually show narrow electrophoretic bands, having a single type of μ chain combined with a single class of light chain (μ -chain disease is discussed separately elsewhere in the Symposium). Some are cryoglobulins or act as cold

agglutinins and these can be completely missed unless serum is separated at 37° (fig 1). The nature of the narrow band can be established by immunoelectrophoresis with antisera containing anti- μ or anti-k or anti- λ respectively. The urine, concentrated up to 300 times if necessary, should be examined for Bence-Jones protein, and with IgM paraproteins it is useful to check for cryoprecipitability, cold agglutinin activity and rheumatoid factor activity, and to measure plasma viscosity.

It is also informative to 'size' IgM paraproteins, eg, by ultracentrifugation (Pedersen, 1945) which has the advantage that the pattern of pentamer IgM (19S) can be readily distinguished from complex aggregates such as 19S rheumatoid factor bound to 7S IgG etc (fig 2). Another method of assessing the size of these proteins is to use thin-layer Sephadex 200 on which chromatography can be directly

Fig 1 Separation of serum at 30° results in a cold agglutinin IgM-paraprotein being removed from the serum on the red blood cells, from which it can be eluted at 37°C. Unless such sera are separated at 37°, the band will be missed.

Fig 2 The value of ultracentrifuge studies. The white arrows indicate the abnormal peaks with 10S, 22S and 27S sedimentation, which occur together with excess 19S when rheumatoid factor activity occurs with an IgM paraprotein. The 10S peak may be due to IgG or IgA rheumatoid factors (or a 7S IgM as in the present case) complexing with target 7S IgG.

Fig 3 Thin-layer chromatography in superfine Sephadex G200, followed by immunodiffusion. By comparison of precipitin arcs with stained parallel runs the protein spots can be identified as indicated.

combined with immunodiffusion (Grant and Everall, 1965; Hobbs, 1966); this is more convenient than combining immunodiffusion with polyacrylamide gel electrophoresis. The Sephadex method more readily identifies 7S IgM, and can distinguish simple 19S IgM from 19S IgG or rheumatoid complexes (Carter and Hobbs, 1971; fig 3). Complexes of $> 21S$ are found to some extent in 85% of all non-rheumatoid IgM paraproteins. However, in our experience this has no special clinical significance as, once 19S is present, the additional viscosity due to higher aggregates is relatively slight and contributes little to the symptoms. In contrast, excess 7S IgM results in less viscosity than expected.

Quantitative estimation of IgM paraprotein is difficult, as immunochemical methods are unreliable (fig 4), probably because of the variability in molecular size together with idiotypic antigenicity.¹ The Mancini method (Cooper and Hobbs, 1970), automated immune precipitation and formylated rockets (Slater, 1975) are all unsuitable for this purpose, and errors of over 100% can occur. Where a distinct narrow band of paraprotein is present after electrophoresis its dye binding (Hobbs, 1965) is measured, preferably by elution, as a percentage of the total dye bound. The total serum protein is measured by the biuret method, corrected by about 12% for the underestimation due to the carbohydrate content of IgM, and from the corrected serum total protein the concentration of IgM is

Fig 4 Results of radial immunodiffusion measurements. While normal serum IgM and cold agglutinin IgM (A.R.) give calibration curves parallel with the standard (pooled purified IgM), lymphomatous IgM (M.I.) is not parallel. This could be due to variation in molecular size (19S + 7S), formation of complex aggregates (rheumatoid factors, etc) or idiotypic antigenicity, and invalidates such measurements.

derived. If the protein band is ill defined it is often better simply to measure the total protein or viscosity. When, as is usually the case, nearly all the IgM is 19S, a refractive index measurement can be made in the ultracentrifuge; estimations by ultracentrifuge and by dye binding usually agree within $\pm 10\%$.

Using such methods IgM paraproteins have been carefully studied in the laboratory and, thanks largely to the teamwork of the macroglobulinaemia trial

¹Idiotypic antigenicity refers to the Fab fragment which, because it contains the variable region, is specific for a particular molecule. For the significance of this in relation to the quantitative estimation of paraproteins, see the contribution by Dr Carter on page 45.

Group	Percentage of Final Diagnoses
I Predominantly because of the Protein	
1 Viscosity syndrome (Waldenström's, excess IgM)	49
2 Haemolytic anaemia (IgM agglutinins)	30
3 Rheumatoid disease (IgM rheumatoid factors)	7
4 'Switch-cell clones' (IgM + IgG, etc)	4
5 Neurological (IgM-anti-nervous tissue)	2
6 'Primary' amyloid (Affinity for connective tissue)	2
7 Cryoglobulinaemia (Above 22°C)	1
8 Xanthomatosis (IgM + lipoprotein)	1
II Predominantly because of the Tumour	
9 Malignant lymphoma (10% have an IgM paraprotein)	44
10 Myelomatosis (0.5% have an IgM paraprotein)	34
	(Typical) 4)
	(Atypical) 1)
11 Soft-tissue plasmacytoma (10% have an IgM paraprotein)	3
12 Chronic lymphatic leukaemia (2% have an IgM paraprotein)	2
	(Typical) 1)
	(Richter's syndrome) 1)
III Incidental Finding (Initially 31%)	
13 Benign (For at least five years, preferably 10)	7
Persistent } Idiopathic	
Transient } Familial	

Table I Clinical presentation with IgM paraproteins

of the Medical Research Council's Working Party on Leukaemia in Adults together with the cooperation of many other doctors, it has been possible to obtain adequate clinical information and follow up of 160 patients with IgM paraproteinaemia. Their diseases covered a wide range from highly malignant lymphosarcoma (miscalled 'reticulosarcoma') through more chronic varieties (Waldenström's macroglobulinaemia; chronic lymphatic leukaemia) to benign conditions, and these are summarized in table I.

I Clinical Presentation with Symptoms due to the Protein

In this major group the patient's symptoms can be largely attributed to the properties of the IgM paraprotein, although manifestations of the tumour are also present in 11%. In the rest, the tumour may not appear until later. This group comprises 34% of all patients in whom we found IgM paraproteins. The presenting syndromes follow in order of frequency (table II).

1 VISCOSITY SYNDROME

This is the term (after Smith, Kochwa, and Wasserman, 1965) which best describes the syndrome characterized by the clinical features set out in table II because, although it is commonest with IgM paraproteins, occurring as a presenting feature in 30% of all such patients and emerging later in another 15%, it also occurs with other proteins especially when they form complexes as listed in table III.

Relative serum viscosity usually 4.00 (normal 1.55-1.83)
Lassitude, confusion, coma, typical optic fundi
Bleeding (associated with coated platelets)
Infection (associated with coated phagocytes)
Anaemia (dilutional; associated with coated RBCs)
Renal failure (due to high concentration in the efferent arteriole)
Can simulate congestive cardiac failure
Can simulate malignant hypertension

Table II Features of the viscosity syndrome

In our experience it is rarely seen with serum levels of IgM paraprotein below 30 g/l (the mean level in 46 patients was 50 g/l) and its occurrence below this level is an indication for seeking complexes of types A or B (table III). Higher aggregates of IgM (21S to 28S), found in 85% of all serum containing IgM paraproteins, do not themselves increase viscosity much more. In measuring the viscosity of body fluids containing IgM paraproteins, Somer (1966) found that measurements on whole blood, plasma or serum all showed the increase of viscosity equally well. Rotary viscometry of whole blood is better than capillary viscometry for showing increased viscosity due to IgA paraproteins. Where symptoms are mainly due to increased viscosity (table II), treatment can be directed against this especially if a continuous-flow cell separator is available for plasmapheresis, for the efficiency of continuous-flow cell separator in plasma exchange can result in a 70% washout of 19S IgM, of which some 80% is in the vascular compartment (Oon and Hobbs, 1975). With 7S IgG, only 40% of which is in the vascular compartment, the plasma level rapidly rises again after plasmapheresis, and more frequently

Monoclonal	Mixed
19S IgM (symptomatic > 30 g/l)	A Monoclonal rheumatoid factor + polyclonal antigen
Higher polymers IgM	IgM - IgG
Polymer IgG ₂ (can be symptomatic < 30 g/l)	IgA - IgG
Polymer IgG ₁ , or IgG ₂ , or IgG ₄	IgG ₁ - IgG ₂
Polymer IgA	B IgA } + lipoprotein
IgE	IgM }
Polymer Bence-Jones protein	IgG }
	C Monoclonal IgA + albumin
	D Others

Table III High molecular weight aggregates causing the viscosity syndrome

Fig 5 Reticulin stain of a section of a lymph node infiltrated with cells of Waldenström's macroglobulinaemia ($\times 60$). Note preservation of normal architecture. With malignant lymphomatous invasion the reticulin pattern shows gross distortion and destruction (by courtesy of Professor V. Harrison).

Fig 6 IgM paraprotein with affinity for nervous tissue. Axons of peripheral nerve showing fluorescence in both longitudinal and cross section after exposure to purified monoclonal IgM and then to fluorescein-labelled anti- μ ; from a patient who presented with peripheral neuropathy (By courtesy of Professor B. W. Lacey.)

plasma exchanges are needed. Manual plasma exchange, even with closed Fenwall packs, carries a higher risk of infection, especially if prednisone is being used therapeutically, and over a period of 16 years we are aware of three deaths from staphylococcal septicaemia out of about 30 patients so treated. If a continuous-flow cell separator is not available it is preferable to use cytotoxic therapy to reduce the IgM paraprotein level, albeit slowly over six to 12 weeks. If plasmapheresis is necessary as a life-saving measure, eg, in patients with renal failure, coma, etc, then manual exchange is justifiable. After plasmapheresis the time taken for the serum paraprotein level to rise again varies. If the rise is slow, eg, one month, then the only treatment recommended is a once-a-month exchange. If it is rapid, then cytotoxic therapy should be used to attack the underlying tumour, which is presumably fast growing, and so reduce the frequency of exchanges. Plasma exchange, even using small pools screened for Australia SH antigen, carries a small but definite risk of transmitted disease. The rapidity with which such treatment can reduce IgM viscosity confirms that the proteins alone are the major cause of the syndrome, as after a four-hour exchange

patients may feel better than for many years. In typical Waldenström's macroglobulinaemia, the underlying tumour is indolent and infiltrates slowly (fig 5), allowing the paraprotein to accumulate and reach viscosity levels. The prognosis is accordingly much better than in more rapidly progressing conditions and we have had patients on exchange therapy alone for up to four years. Since cytotoxic treatments can induce faster growing tumours after five years (Hobbs, 1971) it is best to reserve them until needed, when survival for a full 10 years becomes a possibility.

2 HAEMOLYTIC ANAEMIA (7% OF ALL PATIENTS)

The commonest variety is chronic (primary) cold haemagglutinin disease reviewed in depth elsewhere (Cooper and Hobbs, 1970). This syndrome can be summarized as being the result of the proliferation of an IgM monoclonal producing immunoglobulin with affinity for human red cell antigens, enhanced in the cold whereby agglutination can result in Raynaud's phenomenon and complement may become fixed, resulting in chronic haemolytic anaemia. The commonest antigen is the I antigen, present in adult but not in fetal RBCs; the antibodies are of one μ subclass (Cooper, Chavin, and Franklin, 1970) and largely of one idiotype (Lecomte and Feizi, 1975). Sometimes anti-i, anti-p, and other activities are found. Anti-I from different patients tends to have uniform avidity for red cells if the latter are first papainized but behave irregularly if papain is not used (Cooper and Hobbs, 1970). The average IgM paraprotein level is 4 g/l on clinical presentation. Symptoms of cold agglutination usually occur long before any underlying tumour becomes manifest in 90% of patients with cold haemagglutinin disease. In the 10% of these patients presenting with tumour, the anti-RBC activity is usually less or directed at less susceptible antigens, eg, anti-i. Of the 90% presenting with cold agglutination, one-third remain nearly static as if the monoclonal were benign, one third progress slowly and eventually die of uncontrollable haemolysis, and one third progress more rapidly; in the remaining 10% a frank tumour finally emerges to kill the patient. In general the more malignant clones produce Bence Jones proteins which are detectable in concentrated urine, produce 7S IgM and cause more depression of normal serum IgG, so these can be used as warning signs. In patients in whom haemolysis cannot be controlled by avoiding exposure to cold, prednisone therapy and splenectomy may help, but often only transiently for three to 12 months. Cytotoxic treatment will then produce improvement in about one-third of patients and arrest deterioration in another one-third; the remainder will derive little

benefit (Worlledge, Brain, Cooper, Hobbs, and Dacie, 1968). Some such treated patients showed 'induction' of faster growing tumours, so cytotoxic drugs should be reserved until all else has failed. Many of the cold haemagglutinin-producing cells are in the spleen (Curtain and Baumgarten, 1965) so splenectomy, like plasmapheresis, lowers the serum IgM level but only temporarily (Worlledge *et al*, 1968). Our concept in this subgroup is that because the paraprotein has antibody activity (and offers a special area in which to study the binding site of a human monoclonal antibody) the patient usually presents and dies long before any underlying tumour can be found clinically. Finally, as with those lymphomas which do not produce IgM, an IgG-Coombs-positive haemolytic anaemia can occur, presumably due to immune imbalance (Hobbs, 1968). Two of the present series of 160 patients had this complication.

3 RHEUMATOID FACTOR ACTIVITY IN PARAPROTEINS

This was recognized by Kritzman, Kunkel, McCarthy, and Mellors (1961), and is now well documented (Bonomo, Dammacco, Tursi, and Trizio, 1970). Here again the paraprotein can be of other classes (table III) but here we are concerned only with IgM paraproteins, of which 4% show rheumatoid factor activity with Rose-Waaler titres from 1 in 1024 to 1 in 10^6 and can be recognized by ultracentrifugal analysis (fig 2); these have mostly emerged in patients with a history of rheumatoid disease. Of all patients with rheumatoid arthritis about 2% show an IgM paraprotein with rheumatoid factor activity if the correct tests are performed, eg, adsorption to aggregated IgG (Torrigiani and Roitt, 1969). About 2% of our IgM paraprotein patients have had IgM paraproteins with rheumatoid factor activity even though there was no previous rheumatoid disease. The patients in this subgroup can develop the viscosity syndrome, manifestations of immune complex disease (Carter, 1973), or obvious tumour, eg, parotid (Klein, van Rood, van Furth, and Radema, 1968), or can remain asymptomatic for some years. We believe that for the latter patients a yearly follow up is mandatory, and that others should be treated on their merits. Our overall concept is that subjects with a tendency to form clones making classical IgM rheumatoid factor (8% of the population) run a higher risk than average (0.2% of the population over 50 years of age) of an IgM immunocytoma which may behave in a benign (10%) or malignant (90%) manner.

4 SWITCH-CELL CLONES

Biclonal paraproteinaemia occurs in about 2% of

patients with paraproteinaemia, and in the majority of such cases the two paraproteins have different light chains, eg, IgA-k and IgG-λ, and thus represent two distinct clones. In a few cases the light chains belong to the same class but belong to different subclasses or show different electrophoretic mobilities, which also indicates an origin from distinct clones. However, in some cases the light chains are identical. In some of the latter Wang, Wilson, Hopper, Fudenberg, and Nisonoff (1970) showed that not only do the two paraproteins contain identical light chains, but also identical variable portions (V_H) of their heavy chains. It was postulated that in such cases the two paraproteins are produced by daughters of a B lymphocyte which became neoplastic during a switch from IgM-λ to IgG-λ synthesis,¹ so that about half of the subsequent plasma cells synthesized and released IgM-λ and the other half IgG-λ; simultaneous production of IgG and IgM by the same cell was not observed. Three such patients have been found among the present series (all type λ), and idiotypic light chain antisera have confirmed the identity of their light chains; V_H studies have not been done. These patients have had slowly progressive lymphomas, the 'switch' presumably occurring in a fairly well differentiated cell resident in a lymphoid centre, but are included in group 1 because of the interest aroused at presentation by the protein pattern.

5 IgM-PARAPROTEINS BINDING TO NERVOUS TISSUE
Neurological complications can result from interference with the blood supply (table I, categories 1, 6 and 7), from bony invasion causing local pressure or from infection (table I, group II). Recently Propp (personal communication) observed peripheral neuropathy where all such mechanisms had been excluded but where the IgM was found to bind specifically to the patient's nervous tissue. We have observed three patients with similar peripheral neuropathy without an obvious cause in whom amyloid was not evident on biopsy and where studies inspired by Propp's report have shown that their IgM binds to homologous nervous tissue (fig 6). Such binding has not been found with all IgM paraproteins examined nor in any of over 100 IgG and IgA myeloma proteins tested. In one of our three patients the level of paraprotein was higher in CSF than in plasma but in another it was not. All three patients presented with neuropathy before any IgM-secreting tumour had become evident. It is at present too early to assess the results of cytotoxic therapy with such monoclonal 'autoantibodies' but we have observed improvement

on cytotoxic therapy in a patient who exhibited IgM paraproteinaemia (13 g/l) and a syndrome resembling bulbar motor neurone disease, but whose paraprotein showed no affinity for homologous nervous tissue and was not present in excess in the CSF.

6 'PRIMARY' AMYLOID
In similar fashion, affinity of IgM paraprotein for connective tissue can result in clinical presentation with amyloidosis before any tumour is obvious; as happened in 2% of all patients with IgM paraproteinaemia. In so-called 'primary' amyloidosis an underlying malignant tumour ultimately became manifest clinically or was found by careful postmortem examination in 83% of patients with paraproteinaemia (Hobbs, 1973). We therefore feel it is worth using cytotoxic drugs early in patients with 'primary' amyloidosis where a paraprotein can be detected (Jones, Hilton, Tighe, and Hobbs, 1972), especially as results in advanced cases are discouraging.

7 CRYOGLOBULINAEMIA
Many IgM paraproteins will precipitate at 4° but cause no symptoms referable to cold agglutination. The latter occurs with proteins which, on cooling, start to precipitate or gel at temperatures above 22° and in most cases at a temperature above 29°. The greater the concentration of a cryoprotein, the higher the temperature at which it aggregates, so that stasis in dependent areas is one mechanism for causing lesions, and concentration as a result of renal glomerular filtration is another. In our own series, cryomacroglobulins were usually associated with clinically obvious malignant lymphoma (table IV) and only a few patients presented solely with symptoms of cryoglobulinaemia. As increased plasma viscosity usually occurs as well, the management of such patients has been as for the viscosity syndrome, except that special care has been taken

	1 Due to Protein (Waldenström's)	2 Due to Tumour (Regional Lymphoma)
Onset	Insidious, viscosity syndrome	More rapid, lumps
IgM level (g/l)	All > 31 (average 50)	19% > 31 (average 20)
Possible subclones	8%	42%
7s IgM	20%	50%
Cryoglobulin	3%	15%
Subnormal IgG	8%	64%
Lymph-node architecture	Preserved	Destroyed
Initial treatment	Plasmapheresis	Cytotoxic/radiotherapy
Good response	52%	22%
Survive one year	> 95%	< 45%

Table IV Two predominant presentations with IgM paraproteins

¹There is now much evidence that normal lymphocytes switch at some stage from IgM synthesis to IgG synthesis.

to keep all tubing, etc, at 37-38°. It is important not to exceed 40° as some macroglobulins can also aggregate above normal body temperature, eg, pyroglobulins.

8 IgM-PARAPROTEINS BINDING TO LIPIDS

In 1950 Brehmer and Lübbers observed a patient with xanthomatosis associated with paraprotein-aemia; subsequently Beaumont, Jacotot, Vilain, and Beaumont (1965) clearly showed that in such patients the paraprotein (most often IgA but occasionally IgM) can be an antibody against the apoprotein of β -lipoprotein. Thus after serum electrophoresis the paraprotein band can be stained for lipid. The paraprotein can also be shown in the skin deposits. The serum total cholesterol is often close to or more than 2 standard deviations above the normal mean for age and sex, ie, is clearly raised compared with the often low level found in ordinary IgA-myelomatosis (Seitanidis, Shulman, and Hobbs, 1970) where β lipoprotein may be consumed as a result of the extensive membrane synthesis occurring in plasma cell formation.

We have observed one patient aged 47 years with all the above findings, the paraprotein being of the IgM class at a serum level of 13 g/l; so far the disease has taken an apparently benign course. His fasting serum total cholesterol was 285 mg/100 ml. We are aware of one similar, less well investigated patient (Millard, 1973). Cooper, Cohen, Huntley, Waite, Spees, and Spurr (1974) have recently reviewed IgM paraproteins with antibody activity and described one with specific affinity for phospholipids; their patient was not recorded as having xanthomatosis.

II Clinical Presentation Predominantly because of the Tumour

This occurs in 35% of all patients with IgM paraproteins; a further 15% show clinically obvious tumour at a later date. Of the 35%, some (15% of all IgM) exhibit the viscosity syndrome but are included here because the major symptoms were assigned to the tumour.

The presenting features due primarily to the tumour include malaise, weight loss, backache, girdle pain or pain due to bony involvement elsewhere, noticeable masses in the area of regional lymph nodes or within soft tissue, abdominal swelling, diarrhoea and often malabsorption, headache and cranial nerve involvement. Only rarely is the skin involved.

9 MALIGNANT LYMPHOMA

We found IgM paraproteins in some 10% of more

than 200 sera from patients with biopsy-proven malignant lymphomas, confirming observations of Mackay, Taft, and Woods (1957). The patient usually presented with massive enlargement of a group of lymph nodes, and/or the spleen, and/or the liver. The major findings are listed in table IV. The single most reliable diagnostic feature has been destruction of the reticulin framework of an involved lymph node found at biopsy (fig 5). The history is relatively short so that the serum IgM level on average only achieves 20 g/l. Malaise and weight loss are usually prominent. Cryoglobulinaemia or pyroglobulinaemia occur in about 15% of cases of IgM lymphoma. More than one paraprotein (possibly

Fig 7 Serum and urine results for a patient with malignant lymphoma. The two serum IgM bands are each 19S in size, and the two urine bands are each due to dimer chains. They represent the products of the parent clone and a subclone with a single amino acid difference. Similar findings are common with IgM lymphomata.

due to subclonal mutation) can be demonstrated in 42% of serum and urine samples (fig 7). The incidence of 7S IgM is 50% and it is usual to find a depression of normal IgG (64% < 5 g/l). Fluorescence studies of biopsies may show only a minority of cells with cytoplasmic staining by anti- μ , but lymphocyte suspensions always show IgM surface marker staining. Bone marrow biopsy may initially show no involvement, unlike typical Waldenström's (1944) disease. Lymphangiography may reveal abdominal lymph node involvement, and radiology an overlap with myelomatosis, ie, predominantly soft-tissue involvement but with some bony lesions. In most of our cases, however, the clinical picture has been clearly either predominantly in soft tissue or predominantly skeletal. Overall, it is not difficult to recognize the more malignant forms of IgM paraproteinaemia using the features listed in table IV, and it is important to do so as in these cases fewer than 45% survive one year from presentation despite the use of cytotoxic therapy. This treatment is recommended whenever lymph node biopsy shows invasion and destruction of the architecture. At present, it is not yet known which treatment is best, and the current MRC trial is comparing chlorambucil alone with chlorambucil and prednisone. It is likely, however, that, as better grading of malignancy is achieved, combined regimens will be used for severe forms of lymphoma.

10 IgM MYELOMATOSIS

By 1969 Hobbs had collected 25 known examples of radiological and clinical myelomatosis with IgM as the paraprotein, and this entity accounts for 0.5% of all myelomatosis and some 5% of all IgM paraproteinaemia. At necropsy the tumour has been seen to be largely confined to the bone marrow with little macroscopic involvement of lymphoid tissue; the overall picture has been typical of myelomatosis with Bence-Jones proteinuria (often heavy), very low serum IgA and IgG levels and lytic bone lesions. An occasional patient has been atypical with sclerotic bone lesions, but still with a normal serum alkaline phosphatase, or with a presentation which overlaps types 1, 9, 11 or 12 (table I). The prognosis is worse than that of patients presenting with the viscosity syndrome (group 1) as few survive three years; cytotoxic treatment is usually indicated.

11 SOFT-TISSUE PLASMACYTOMA

Some 3% of IgM paraproteins have been associated with soft-tissue plasmacytomas and account for 10% of all our patients with the latter diagnosis. Usually, the mass has been either in the nasopharynx or the gut but on rare occasions in the skin or muscles. Biopsy has shown a typical plasmacytoma with

cytoplasmic staining of most cells with fluorescent anti- μ . They have been treated on their merits. Where local excision is used it is best followed by local irradiation, a combination which has been followed by long recurrence-free survival. Nevertheless, these patients can relapse with dissemination up to 20 years later, involving certain bones which are not usually affected by plasmacytoma, such as the radius and fibula (Wiltshaw, 1969).

12 CHRONIC LYMPHATIC LEUKAEMIA

Classical chronic lymphatic leukaemia is now known from surface-marker studies to be of B-lymphocyte origin in 98% of cases, allowing for the loss of markers as the disease progresses (McLaughlin, Wetherly-Mein, Pitcher, and Hobbs, 1973). This accords with the finding of Bence-Jones proteinuria in 15% and of serum paraproteins, mostly IgM, in 5% of such patients. It is also in this group that μ -chain disease was proven (see contributions by Dr Franklin). The patients with paraproteins show no obvious differences from the others except in two atypical cases where the rapid development of paraproteinaemia coincided with lymphosarcomatous change, with progressive enlargement of lymph nodes, liver and spleen with fever and with rapid demise (Richter's syndrome).

III IgM-Paraproteinaemia as an Incidental Finding

This was the initial presentation in 31% of all our patients (table I, group 3), in whom after full investigation there was no clear evidence of group 1 or 2 syndromes. As time went by most of this group displayed a syndrome whereby they could be assigned to types 1-12 (table I) and it was not until then that any treatment was given, for the reasons stated in the section on the viscosity syndrome (type 1). Unless there is a suspected mass, a radiological lesion or Bence-Jones proteinuria, it is recommended that follow up should be not more frequent than yearly so as not to cause undue anxiety to the patient.

13 BENIGN IgM-PARAPROTEINAEMIA

This diagnosis really cannot be made until there have been 10 years of observation with no emergence of syndromes 1-12. No rise in the IgM level over five years is a favourable sign, but some of the group 1 syndromes can be so insidious that they can still emerge after this (as they did in six out of 17 patients who reached five years without symptoms). In a few rare patients a further mutation can occur and a previous benign situation can change to a malignant one, so that we recommend a yearly follow up of all patients with 'benign' paraproteins. Seven other

patients (not included in table I) have been incompletely followed up and their fate is unknown. Thus there remain only 11 patients with clearly benign behaviour and they represent only 7% of all IgM paraproteins where a diagnosis has been finally made. These 11 all had serum IgM levels remaining under 14 g/l with normal serum levels of IgA and IgM and no Bence-Jones protein detectable in urine concentrated 300 times.

Benign IgM paraproteins have been recorded in relatives of patients with malignant IgM paraproteinaemia (Seligmann, Danon, Mihaesco, and Fudenberg, 1967), and also in Africans with parasitic infections (Michaux and Heremans, 1969), although a 10-year follow up was rare in those series.

Transient paraproteins (Young, 1969) can be of the IgM class, and we have seen such in the sera of two infants who had successful bone marrow grafts for a severe combined immunodeficiency syndrome, confirming the original observation of Rádl, Dooren, Eijssvoegel, van Went, and Hijmans (1971).

Allowing for age, we have found no more than the random incidence expected (Hobbs, 1968) of IgM paraproteins in association with liver or gut disease or with cancer (Hobbs, 1971).

Histopathology

Histopathological studies of biopsy or postmortem

Histological Appearance ¹		Usually Associated with
9%	NAD	Benign types
13%	Follicular hyperplasia	Haemolysis
31%	Diffuse lymphomas grade 1 (good to intermediate differentiation)	Waldenström's disease or chronic lymphatic leukaemia
12%	Plasma cell	Myeloma
35%	Diffuse lymphomas grade 2 (poorly or undifferentiated)	Plasmacytoma
		Regional lymphoma

Table V Histopathology in 103 patients with IgM-paraproteins

¹Amyloid noted in 10%

Fig 8 Electronmicrograph ($\times 20,000$) of the nucleus of a Waldenström cell which showed a PAS-positive Dutcher body. The content of polyribosomes indicates that this is due to cytoplasm invaginated into the nucleus (by courtesy of Dr Kristin Henry).

specimens are available from 103 patients, and in table V, these have been classified according to Bennett, Farrer-Brown, Henry, and Jelliffe (1974). There is an association of the more benign appearances with group 3 or group 1 syndromes and of the more malignant ones with group 2 syndromes. Overall it is not easy to predict which lymphomas will be associated with paraproteinaemia, although a predominantly plasmacytic picture, positive PAS reaction or cytoplasmic or nuclear inclusions (fig 8) do suggest the possibility. This can be further investigated not only by examining serum and urine but also by immunofluorescence studies of tissues freshly fixed in alcohol. A case has been made for concentrating urine from every patient with suspected lymphoreticular disease (Hobbs, 1975). It is important in assessing the prognosis to obtain the biopsy from the 'heart' of an involved site, eg, a supraclavicular lymph node may be normal and a scalene node show only infiltration when a mediastinal node is clearly malignant.

Origins of IgM Monoclonones

IgM paraproteinaemia can be considered to result from a random event or from a selective event under special circumstances. Hobbs (1968) favours the former as the pathogenesis in most cases, because the IgM class represents 11% of all patients with paraproteinaemia found in large series, and 11% is the expected fraction of the normal adult plasma cells secreting IgM. Furthermore, there is a higher incidence of IgM paraproteinaemia in association with increased IgM secretion, as in the Congo (Michaux and Heremans, 1969), as a result of rheumatoid diseases or multiple blood transfusions (Young, 1969). It must nevertheless be admitted that genetic constitution can play an aetiological role in a minority of patients such as those with familial IgM-paraproteinaemia (Seligmann *et al*, 1967) or inborn immune deficiencies. A preexisting immune deficiency may be due to obvious B or T cell deficiencies or may be a relative deficiency as when most clones are preoccupied with some intercurrent condition which stimulates a widespread immunological response such as systemic lupus erythematosus, rheumatoid disease, malaria, Burkitt's lymphoma or cirrhosis.

Normally, IgG clones have a much higher affinity for antigen than IgM clones and thus deprive the latter of antigen. In the circumstances mentioned above it is conceivable that lack of competition by high affinity IgG clones, or deficient regulation by T cells, may allow the emergence of an IgM monoclonal against weak antigens such as altered IgG (rheumatoid), I and other red cell antigens, eg, cold

haemagglutinins, Coombs-positive haemolysis, or lipids (Cooper *et al*, 1974) etc.

Conclusions

Long-term studies of 160 patients have shown that IgM paraproteinaemia has a malignant outcome in some 90% of cases and occurs with a wide range of overlapping syndromes depicted in figure 9. In one

Fig 9 The spectrum of overlapping syndromes associated with IgM paraproteins. The areas of the circles are proportional to the incidence.

of the largest groups, the patient's symptoms can be mainly attributed to the properties of the IgM paraprotein, and the commonest syndrome is hyperviscosity, where the underlying tumour is so slowly progressive that its product gains a high serum level, which is best managed initially by plasmapheresis. For the second largest group, the underlying tumour is more aggressive and causes most of the symptoms; it should be identified by biopsy whenever possible and treatment should include cytotoxic drugs as the prognosis is so much worse. Between these two poles there are intermediate situations that must be managed on their individual merits; among these, affinity of the IgM for nervous tissue is newly recognized. Benign macroglobulinaemia can only be diagnosed with confidence after 10 years of observation, and even then yearly follow up is advisable.

References

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