The immunoglobulins: A review

N. H. MARTIN

From St George's Hospital, London

In 1959 Heremans proposed the embracing term 'immunoglobulins' for those globulins primarily associated with the lymphoreticular system. The term 'lymphoreticular system' includes specific and nonspecific proliferations of the plasma cell series. This review deals with disease characterized by a primary proliferation of one of the cellular elements of the lymphoreticular system, in which there is associated an excessive production of a specific immunoglobulin or fragment of a specific immunoglobulin and its release into the vascular space. The classical examples are myelomatosis and essential macroglobulinaemia. The normal immunological mechanisms of defence are frequently associated with production and release of immunoglobulins, but it is not the intention of this review to cover this much wider field. Nevertheless, unusual antigenic stimuli, or the pattern of response of an 'unsalted' population can produce a bizarre immunological response which may be confused by the unwary with the primary lymphoreticular dysplasias.

Porter's elucidation (1962) of the structure of γ G, with the dissection of the molecule into a pair of light chains and a pair of heavy chains, enabled those interested to look with much greater precision at the globulins produced in excess in the primary lymphoreticular dyscrasias, particularly myelomatosis. Thus, it was soon evident that 'Bence Jones protein' was in fact free light chain or a protein very like it. It was also clear that whereas γ G globulin extracted from normal serum consisted of a variety of species, the composition of whose light and heavy chains varied one from another in their sequential pattern, in myelomatosis the species produced was restricted. It was on this basis that the concept developed that myelomata represented the proliferation of a single clone of cells producing a single species of protein. If, and it was clear that they did, these malignant clones displaced the normal cell species, the disease myelomatosis would be associated with varying degrees of immunological paralysis. This indeed turned out to be the case.

The macroglobulinaemias are still in some state of confusion. The structures of the large molecule γ M is being clarified and it is clear that the essential difference from its smaller cousin, γ G, lies in the

detailed structure of its heavy chain. The light chains are to all intents and purposes identical.

Once an understanding of the structure of the molecules had been acquired, workers were able to forecast further protein dyscrasias such as Fc and μ monomer disease on a rational basis, akin to Fisher's forecasting of genetic defects using his statistical skills.

More recently the use of immunochemical techniques, particularly the Mancini application of immunodiffusion to quantitative assay, has contributed to further advances in the identification of patients suffering from myelomatosis and allied conditions. Recent series have regularly included substantial groups of patients whose serum protein pattern suggested a monoclonal dyscrasia, but whose clinical picture did not tally with the classical picture of myelomatosis (Osserman and Takatsuki, 1964; Bachmann, 1965; Hobbs, 1967a). Notable is a detailed analysis by Hällén (1966) of 150 such patients.

THE NOMENCLATURE OF THE IMMUNOGLOBULINS

A memorandum issued by WHO (1964) on the nomenclature of immunoglobulins made certain basic suggestions which have been universally adopted.

Individual chains should be referred to by Greek letters. Thus, the two principal groups of light chains are referred to as κ and λ . The five groups of heavy chains so far identified are referred to as γ , α , μ , δ , and ϵ . The whole molecule is defined by a capital letter G, A, M, D or E, supplemented by a capital K or L where the nature of the light chain has been identified.

The whole molecule may be referred to in one of two ways thus:

γ G or IgG, subgroups γ GK γ GL
or IgGK IgGL
 γ M or IgM, subgroups γ MK γ ML
or IgMK IgML

The molecular formula of the molecule is presented in Greek lettering thus: γ AK or IgAK is written $\alpha_2\kappa_2$, implying that the molecule IgA is made up of two α heavy chains and two κ light chains.

Similarly IgM will be written $(\mu_2\kappa_2)_5$ or $(\mu_2\lambda_2)_5$, depending on which light chain is incorporated in the molecule and the assumption that the macroglobulin circulating in the serum is a pentamer.

As genetic loci are identified on individual chains these may be appended as a suffix to the individual notation in the molecular formulae.

γ G or IgG replaces the old terminology γ , 7S γ , γ_2 , γ_5 ; γ A or IgA replaces the old terminology β_2 A, γ_1 A; γ M or IgM replaces the old terminology γ_1 M, β_2 M.

CHEMICAL CHARACTERISTICS OF THE IMMUNOGLOBULINS

igG Normal serum concentrations are 800 to 1,600 mg/100 ml, and the rate of synthesis is 20 to 40 mg/kg/day.

In 1962 Porter made the tentative suggestion that IgG consisted of four peptide chains, two large and two small, linked together by disulphide bridges. The smaller chains are of two main groups, κ and λ , and have a molecular weight of the order of 20,000, while the larger chains have a molecular weight of the order of 50,000. In general, one disulphide bond links each heavy chain to its respective light chain, the linkage being at or near the carboxy terminal grouping of the light chain. The heavy chains are linked to each other by a disulphide bond which lies on the carboxy terminal side of the point of cleavage of the whole molecule by the enzyme papain.

If we consider the breakdown of the molecule by papain, it appears to consist of three fragments: the two Fab fragments, which are made up of the amino terminal half of the heavy chain still attached to the light chain, and one fragment, the Fc fragment, which consists of the residual carboxy terminal portions of the two heavy chains linked together by a disulphide bond. The amino terminal portion of the heavy chain is referred to in isolation as the Fd fragment.

THE FAB FRAGMENT Enzymic degradation of specific antibodies shows that the antibody activity of a particular globulin is concentrated in the Fab fragment. It was for this reason that the symbol was adopted. The actual site of activity is no more than 3 to 4% of the total Fab fragment, that is, approximately 10 to 12 amino acid residues. Full activity requires the association of a portion of the Fd fragment and the light chain operating together. Each antibody molecule of the IgG series contains two combining sites which correspond neatly to the two Fab fragments known to exist in the individual IgG molecules.

The Fc fragment This fragment represents the

FIG. 1a. A simplified basic structural formula of the immunoglobulins.

FIG. 1b. The pentameric formula of the macroglobulin IgM, together with the fragments occasionally identified in the blood stream of patients suffering from macroglobulinaemia.

'exposed' portion of the heavy chain on the diagram. It is readily crystallized (hence the adoption of the symbol Fc). It does not carry the antibody activity of the molecule. It is the fragment to which the carbohydrate is attached.

It is the Fc fragment that contains the sequential arrangement responsible for the cytophilic properties of the intact IgG molecule. It is as if the carboxy terminal portion of the whole molecule acted as an anchor where anchorage is necessary. Sequential analysis suggests that the pattern of this anchor differs very little from one mammal to the next. Though the Fc fragment contains no antibody activity as such, it has other important biological activities such as the capacity to fix complement and to combine with the rheumatoid factor.

The light chains Reference has already been made to the 'light chains' as an integral portion of the Fab fragment responsible for antibody activity. These are now classified into two main serological groups, the κ and the λ chains, and the complete sequential analysis of the 143 amino acid residues of

which individual chains are composed has been completed (Milstein, 1966a and b). Seventy per cent of normal human immunoglobulins carry the κ chain, while 30% carry the λ chain. It has been claimed that the IgD globulins are predominantly λ and the cold agglutinins predominantly κ chain carriers.

When the light chains separated from immunoglobulin IgG are examined by starch gel electrophoresis 10 components are identifiable (Cohen, 1966), and even the individual chains separated by this technique may be further differentiated by their antigenic behaviour. This antigenic differentiation appears to be under genetic control and is identifiable on the chain as the Inv. locus. Within the two main groups of κ and λ light chains there is a considerable degree of detailed heterogeneity mainly concentrated in the amino terminal portion of the molecule. The whole chain appears to fall naturally into two sections analogous to the Fd and Fc fraction of the heavy chain.

These light chains are common to all the principal groups of immunoglobulins. No worker to date has found κ and λ chains side by side on the same molecule. It is the characteristics of the heavy chain containing the Fd and Fc fragments which differentiate IgG, IgA, IgD, and IgE one from the other.

The heavy chains The heavy chain of IgG has now been analysed in some detail. There are 34 prolines in a total of 422 amino acid residues. These proline residues are not uniformly distributed. Thus, in the first 84 amino acid residues from the amino terminal end there are only four proline residues, whereas in the first 29 amino acid residues in the carboxy terminal fragment adjoining the point of papain cleavage there are nine proline residues. Structurally this implies that the Fd fragment, which contributes to antibody specificity, is a relatively flexible structure and that the Fc fragment is relatively rigid in the area next to the point of papain cleavage.

IgA The normal serum levels lie between 140 and 420 mg/100 ml, and the normal rate of synthesis between 3 and 50 mg/kg/day.

The monomer of normal IgA has a molecular weight of the order of 160,000, but it may sediment in a heterogeneous fashion producing components of 7S, 11S, 13S, and on occasion, 15S.

In the myelomas associated with excess production of IgA, ultracentrifugal analysis may show similar heterogeneity (Kekwick, 1940), or a single unit with a sedimentation coefficient of about 9 (patient C in a series studied by McConnell and Martin, 1958).

The light chains of the two molecules IgG and

IgA are similar, but the heavy chains differ both in their antigenic behaviour and in their carbohydrate content, the α chains of IgA containing four times as much hexose as the γ chain of IgG, being much richer in neuraminic acid.

Clamp, Dawson, and Hough (1966) have analysed the α chain in some detail and found evidence to suggest that the carbohydrate is not concentrated in one area of the chain but that there are several points of attachment.

IgA is of special biological interest because it is the principal protein in human colostrum; it is excreted in the saliva, in the lachrymal glands, and in the mucous glands of the intestine.

In its exocrine form it is attached to an immunochemically identifiable polypeptide, the 'secretory piece' of Hanson and Johansson (1967), referred to by Tomasi, Tan, Solomon, and Prendergast (1965) as the 'transport piece'.

A comparison of specific purified IgA (exocrine) and normal IgA (serum) from the data of Tomasi and Hanson show that the S coefficient is of the order of 11 compared with 7. Treatment with β mercapthanol does not alter the S value of either $I\gamma A^{ex}$ or $I\gamma A^s$ as compared with $I\gamma M$.

The total carbohydrate is somewhat higher in exocrine IgA than serum IgA, but the neuraminic acid content is 0.1 to 1.0% in the excretion compared with 1.7 to 1.8% in the serum IgA. This is in keeping with the slightly slower electrophoretic mobility.

The IgG/IgA ratio in saliva is less than 1 compared with an IgG/IgA ratio 0/over 6 in serum.

Immunofluorescent studies using specific anti α chain sera indicate that the IgA immunoglobulins are concentrated in the plasma cells of the lamina propria of the stomach, duodenum, jejunum, colon, appendix, and rectum (Crabbé and Heremans, 1966).

When antiserum to the 'secretory piece' is used it is noted that the 'exocrine' form of IgA appears to occur principally in the goblet cells excreting mucus. Such antisera did not produce fluorescence in the subepithelial plasma cells in contrast to a preparation using α chain antiserum.

In newborn infants, unlike adults, there are few, if any, subepithelial plasma cells, though the infants have normal quantities of 'secretory piece' in their external secretions. The evidence suggests, therefore, that the secretory piece is manufactured separately and subsequently coupled to IgA.

IgM The normal serum concentration ranges between 50 and 190 mg/100 ml, and the rate of synthesis lies between three and 17 mg/kg/day.

The IgM immunoglobulin was first identified by ultracentrifugal analysis. It stands out as a well

defined peak with a sedimentation velocity of approximately 19 compared with 7 for normal IgG. A detailed analysis of the ultracentrifugal behaviour of the serum protein of normal persons shows that the 19S component is composed of two proteins, an α globulin and a γ globulin. These are almost certainly different in their detailed architecture and biological function. The macroglobulinaemia of Waldenström is regularly associated with increases in the γ macroglobulin. Estimates of the molecular weight of this molecule range from 890,000 to 970,000. It is a pentamer consisting of five monomers linked by covalent bonds. These are probably :S:S: bonds. Estimates of the monomer size range from 160,000 to 170,000. The light chains are similar to, if not identical with, those in IgG. The heavy chains have a molecular weight of between 65,000 and 67,000 and are some five times richer in carbohydrate and in neuraminic acid content than the heavy chains of IgG (Martin, 1968).

Detailed antigenic studies (Seligman and Mihaesco, 1967) indicated that the IgM molecules are as diverse in their individual characters as IgG molecules. Recalculation of physicochemical data (Martin, 1968), as a result of a critical essay by Creeth and Knight (1965) on the assessment of macromolecular symmetry, indicates that IgM is not markedly more asymmetrical than IgG. These calculations, taken together with the electron microscope studies of Svehag, Chesebero, and Bloth (1967), suggest that of the various configurations discussed by Miller and Metzger (1965 and 1966) the 'rosette' is the most likely. Three theoretical possibilities arise from the acceptance of such a structure: first, that up to half of the 10 antibody sites may normally be buried and unavailable within the rosette; second, that a condition exists, 'monomer' disease, in which the error is in the final condensation of the individual monomers to form the pentamer; third, that the 'tails' of the rosette may be synthesized independently as fragments analogous to the Fc fragments of γ G described by Franklin, Lowenstein, Bigelow, and Meltzer (1964). If these do exist *in vivo* in serum they should be demonstrable as having immunological characteristics related to the μ chain, but no reaction to κ or λ sera.

igd The normal serum concentrations lie between 0.5 and 40 mg/100 ml and the normal rate of synthesis is between 0.03 and 1.4 mg/kg/day.

Immunoglobulin D has a sedimentation constant similar to IgG, 6.5 to 7.0. It contains two light and two heavy chains. Its site in the electrophoretic analysis of the serum proteins suggests that it has a slightly higher mobility than IgG. Moreover, Rowe and Fahey (1965), carrying out degradation studies with

papain, noted that the Fc fragment had a higher mobility than that of IgG, indicating that it may be richer in sialic acid though no figures are given.

The light chains resemble those in IgG and are predominantly of the λ species. The heavy chains are antigenically distinct. Hobbs, Slot, Campbell, Clein, Scott, Crowther, and Swan (1966) have described six patients suffering from myelomatosis in whose sera the myeloma cell protein reacted with IgD antisera. The clinical picture was not significantly different from patients suffering from IgG. But in only one patient was the total serum protein level raised significantly. Since the normal levels of IgD are only 0.5 to 40 mg/100 ml, it is evident that production could be enhanced five to tenfold without gross disturbance of the protein pattern. Bence Jones protein was being excreted in large amounts in three of the patients described by Hobbs *et al* (1966) and was detectable in the urine of all following concentrations. Its very low normal serum concentration and its relatively high metabolic turnover suggest that unequivocally abnormal serum levels may be attained without demonstrable gross distortion of the serum protein pattern by the usual techniques employed in routine laboratories.

ige The normal serum concentrations lie between 10 and 140 nanogram/100 ml. The synthesis rate is not known.

In 1968 Johansson and Bennich described a new protein in the serum of a patient suffering from myelomatosis which they designated IgND. It appears that this protein is of the family normally designated IgE. By reason of its dimensions and its carbohydrate content it may be grouped with IgA, though it does not appear to have the same tendency to form polymers.

Its sedimentation value was 7.29. The total carbohydrate content was 10.71 and the neuraminic acid content about 1%. According to Bennich and Johansson (1967) the carbohydrate is attached to at least six prosthetic groups in the heavy chain. One carbohydrate pairing lies to the N terminal side of the point of papain cleavage that is in the Fab fragment. The Fd fragment is rich in methionine. Johansson, Bennich, and Wide (1968) showed that the Fc fragment of IgE is twice the size of the Fc fragment of IgD.

THE PHYSIOLOGY OF THE IMMUNOGLOBULINS

The immunoglobulins are produced in the cells of the lymphoreticular system. In the normal ebb and flow of response to antigenic stimulus, their production and release into the vascular space is associated with an increase in the plasma cell population

of the bone marrow and/or the lymphatic glands. It is strikingly illustrated in the hypergammaglobulinaemias associated with chronic progressive hepatitis and may be observed in a variety of chronic infections, in diffuse lupus, rheumatoid arthritis, sarcoidosis, chronic beryllium poisoning, certain 'hypersensitivity diseases' such as serum sickness, and acquired haemolytic anaemia. Analysis of this type of immunoglobulin production indicates that though there is an increase in specific antibody produced, there is also associated a generalized production of IgG giving a diffuse band on electrophoresis and a demonstrable increase in the 7S component on ultracentrifugal analysis.

Proliferation of other cells of the lymphoreticular series, such as the reticulum cell and the precursors of the lymphocyte are sometimes, but not regularly, associated with extracellular release of excessive quantities of immunoglobulins. This is the situation in the primary macroglobulinaemia of Waldenström where an excessive amount of IgM released is associated with a proliferation of cells resembling lymphocytes, and in the 'heavy chain' syndrome of Franklin in which excessive production and release into the vascular space of Fc fragments is often associated with lymphomata, and, in certain instances, enlarged glands having a histological picture suggestive of Hodgkin's disease (Ellman and Bloch, 1968).

In the normal adult, 50% of the free IgG is concentrated in the vascular space, about 5% of this being catabolized daily.

IgA is distributed in approximately the same proportions, but the loss from the vascular space is about three times greater than that of IgG. IgA is peculiar in that, coupled to a polypeptide the 'secretory piece', it is excreted against the concentration gradient into the saliva, bronchial secretions, and intestinal juice. In these it exists in much higher concentrations than it does in the blood.

IgM is localized almost entirely in the vascular space, its rate of loss from that space being about the same as that of IgA. Humphreys (see Holborrow, 1967) has shown that IgM is 100 times more efficient at lysing red cells than IgG. It is a particularly efficient agglutinator, suggesting that it is specially adapted to handling bacteria and other particulate

antigens. IgG may be more effective in neutralizing antigen in solutions at a molecular level. Table I summarizes these findings.

The work of Fink, Miller, Dorward, and Lo-Spalluto (1962) suggests that the primary response to extrinsic stimulation is associated with an increase in IgM globulins.

Swedlund, Gleich, and Chodirker (1968), investigating a patient with dysgammaglobulinaemia in whose serum there was a deficiency of both IgG and IgA, showed that the IgM response to bacteriophage $\psi \times 174$ was both marked and prolonged, lasting 13 days. In the normal adult the IgM response would have been short lived and overshadowed both in extent and duration by the IgG response. Thus, it is clear that the stimulus responsible for active production of the individual immunoglobulins may be independent and complementary.

SPECIFIC GLOBULIN DYSCRASIAS

Gutman (1948) coined the phrase 'M protein' for the discrete excess of protein strikingly demonstrated by classical electrophoresis in the sera of patients suffering from myelomatosis. Riva (1957) used the term for a discrete, tightly packed band seen when serum proteins are analysed by electrophoresis on a discontinuous medium. Vast numbers of patients showing this serum protein anomaly have been examined in different parts of the world. While it is evident that the majority of such patients are suffering from myelomatosis and macroglobulinaemia or an allied lymphoreticular dyscrasia, a significant percentage are not. Indeed, by the relatively crude techniques used, 'M' bonds could be observed in a percentage of patients with malignant growths such as prostatic carcinoma. Quantitative analysis indicates that the concentrations are rarely as high as those commonly seen in myelomatosis. The protein observed may resemble IgG, IgA, or IgM immunologically.

More refined techniques have indicated that these sera show multiple banding with one zone predominating, as if there were polyclonal stimulation, but that one clone was more sensitive to the specific stimulant than others.

The term 'paraprotein' has been used by some

TABLE I

DISTRIBUTION, SERUM CONCENTRATION, RATES OF SYNTHESIS AND CATABOLISM, AND APPROXIMATE TOTAL OF INDIVIDUAL GLOBULINS

	IgA	IgD	IgG	IgM
Distribution (% in IV pool)	40	63-86	48-62	65-100
Serum concentration	140-420	0.3-4.0	800-1860	50-190
Rate of synthesis (mg/kg/day)	207-55	0.3-1.49	20-40	3.2-16.9
Catabolic rate (% of IV pool)	14-34	18-60	4-7	14-25
Approximate total globulin (g/kg in 70 kiloman)	0.1-0.25	0.01-0.05	0.75-19	0.05-0.19

workers to refer to proteins which do not occur normally in the serum. There seem to be few syndromes in which such a claim can be made with confidence. It would seem reasonable to abandon the use of the term and, as exemplified by Franklin's description of heavy chain disease, to refer specifically to any rogue protein as and when it is identified precisely, together with the clinical circumstances in which it occurs.

CLINICAL FEATURES OF MONOCLONAL PROLIFERATION

In the following sections the clinical and clinicopathological features of monoclonal proliferation are discussed against the background of experience of 225 patients investigated in the past 15 years, because clinical colleagues suspected for one reason or another that the primary disease process from which they suffered might be associated with an unregulated production of one or other of the immunoglobulins. Thus, the information obtained is from a preselected group of the total population. Moreover, because the majority, though not all, of our collaborators have been consultants themselves, there has been in a sense a double process of selection. This experience is tempered by examination of data from equivalent series published in the literature, though it seems clear that the majority of such series are also the subject of selection if only that they are patients in hospital clinics. A notable exception is the Värmland survey by Axelsson, Bachmann, and Hällén (1966). In this survey electrophoretic analysis of the serum proteins was made on 6,995 persons representing 70% of the total population above the age of 25. 'M' component was identified in 64 of these, but in only 10 was the level above 100 mg/100 ml serum. Immunochemical analysis indicated that in 61% the discrete protein excess was IgG, in 27% IgA, and in 8% IgM, but two of the persons showed excess of both IgG and IgM and of IgG and IgA. Fifty-nine of the 64 persons were examined clinically and 36 were found to have an abnormality which did not impair activity. Seven of the 64 persons were over 80.

Detailed investigation of the immunoglobulins isolated from patients suffering from myelomatosis

and allied conditions suggest a homogeneity of the circulating immunoglobulin that is not present when the immunoglobulins from normal healthy individuals are examined by similar techniques. Instead of the 10 or so bands demonstrable on starch gel analysis of the separated light chains, only one or perhaps two are seen. A similar homogeneity is present in the heavy chains though these are technically more difficult to handle. This observation, coupled with the assumption that an individual immunocyte produces only one type of immunoglobulin, has led to the concept of monoclonal proliferation associated with the massive production of immunoglobulins of limited structural range. The principal conditions in which this peculiar type of proliferation occurs are the myelomatoses, the essential macroglobulinaemias of Waldenström, the so-called idiopathic hyperglobulinaemias, and the H chain disease of Franklin. Occasionally, an individual immunoglobulin is produced in excess complicating lymphomata and even totally unrelated neoplasms such as bronchial carcinoma or carcinoma of the breast, prostate, and stomach (Table II).

In the future, to the breakdown shown in Table III will be added patients in whom the monoclonal disturbance is confined to IgD, to IgE, and to other identified immunoglobulins of specific character. IgD and IgE are present in normal serum in such small quantities that gross disturbances in their

TABLE II

PERCENTAGE DISTRIBUTION OF MONOCLONAL PROTEINS FROM THREE SOURCES TOTALLING OVER 1,000 PATIENTS

	No. of Cases		
	400 ¹	456 ²	225 ³
Multiple myeloma	65.5	67	65
Macroglobulinaemia	10.25	12	15
Heavy chain disease	0.75	—	—
Lymphoma and lymphatic leukaemia	5.75	6	8
Unrelated neoplasia	7.75	4	7
Idiopathic	10.0	6	4

¹Osserman and Takatsuki (1964)

²Hobbs, J. R. (1967). *Brit. med. J.*, 2, 699.

³Martin (unpublished series)

Hobbs also refers to 'other diseases, liver gut etc.' 4% and 'transient'. We have 10 cases unplaced, including four 'transient' cases

TABLE III

BREAKDOWN ACCORDING TO SPECIFIC IMMUNOGLOBULIN ANALYSIS OF 500 CASES

	Principal Deviation in Serum (%)	Proportion of Column ¹ Bence Jones Protein in Urine (%)	κ (%) ²	λ (%) ²
IgG	68 (47)	45 (15)	61	39
IgA	23 (20)	50 (6)	61	39
IgM	4 (14)	10 (1)	60	40
No gross change in serum	5 (20)	100 (20)	57	43

¹Data from series of Osserman and Takatsuki (1964).

²Data on κ and λ chains from series of Imhof, Ballieux, Mul, and Poen (1966).

level may occur without disturbing the total serum protein electrophoretic pattern. Such cases undoubtedly account for some of the patients described in whom Bence Jones protein was demonstrable in the urine without gross evidence of disturbance of the serum protein distribution. This is exemplified in three out of the six patients with IgD myeloma described by Hobbs *et al* (1966).

THE COMMON CLINICAL STIGMATA ASSOCIATED WITH MONOCLONAL PROLIFERATION

These are Bence Jones proteinuria; recurrent infection; renal damage associated with proteinuria; anaemia, (a) normocytic normochromic with a raised ESR, and (b) leucoerythroblastic anaemia, usually a terminal event resulting from extensive marrow invasion; space-occupying lesions, which may be skeletal localized vertebral collapse, spontaneous fractures, diffuse generalized osteoporosis, with serum alkaline phosphatase levels normal in 90% of patients, or visceral with enlarged lymph glands or spleen; cryoglobulinaemia, Raynaud's phenomena; hypercalcaemia; amyloidosis; and serum hyperviscosity.

BENCE JONES PROTEINURIA The increasingly common practice of concentrating fresh urine specimens by pressure dialysis and other means before subjecting them to electrophoresis and immunological inspection has given a fresh view on the incidence of free light chains passed in the urine.

Patients with Bence Jones proteinuria—if by that we imply those in whom the peculiar thermolability of the protein first described by Bence Jones is demonstrable in the fresh, unconcentrated specimen of urine—number between 40 and 60% of a total series (Kubota, Schwartz, and Putman, 1956; Martin, 1961) when four consecutive specimens are examined following the initial diagnosis. Surprisingly it is only demonstrable in 10% of patients suffering from primary Waldenström macroglobulinaemia.

Berggard and Edelman (1963), examining concentrates of pooled normal human serum, demonstrated the presence of proteins having thermolabile properties similar to Bence Jones protein. Physicochemical investigation suggested that these were in fact light chains either the result of immunoglobulin degradation, or, as in myeloma, the result of overproduction and extracellular release of uncoupled light chains. Martin (1961) emphasized that repeated examinations of urine were required before the absence of Bence Jones protein might be assured even by old-fashioned techniques. Using modern methods of concentration, dialysis, and immuno-

chemical techniques of identification, it is probable that light chains will be found in every urine and that the differentiation between normal and abnormal persons depends on the amount passed and the characteristics of the electrophoretic analysis of the urinary proteins (Dominico and Waldenström, 1968). The light chains excreted from normal urine or from polyclonal hypergammaglobulinaemias will present as a relatively diffuse band or as a series of bands, those from the monoclonal conditions as a discrete tightly packed band.

Hobbs (1967b), using a relatively simple technique for the concentration of urine, found light chain concentrations above 1 mg/100 ml in 172 out of 223 patients examined. He emphasizes that had the urines not been concentrated, Bence Jones protein would have been missed in 90 patients. His results for the group of patients with excess of IgM in the serum show that by refined techniques 32 out of 34 patients were excreting light chains, though in 26 of these the urinary concentration rate was less than 20 mg for 100 ml urine.

Six patients with IgD myeloma (Hobbs *et al*, 1966) are interesting because in three the gross serum concentration of IgD and IgG immunoglobulins totalled 920, 660, and 920 mg/100 ml, that is, well within normal limits of immunoglobulin concentration. Yet IgD levels were six times higher than normal, and, since IgD has a much shorter half life than IgG, it implies a considerable increase in the specific plasma cell population. Two of the patients in the series were producing profuse amounts of Bence Jones protein. It may well be that some of the cases reported in the earlier literature as having a normal serum protein pattern with gross Bence Jones proteinuria were, in fact, cases of IgD myeloma. If they were, the striking 'flaming appearance' in the cytoplasm of the plasma cells seen on marrow sampling may give a hint of the true diagnosis.

RECURRENT INFECTION Bøe (1945) described two patients having classical myelomatosis who had multiple pneumonic episodes. Marks (1953) made a detailed study of antibody formation in 17 patients suffering from myelomatosis when challenged with staphylococcal antitoxin and streptolysin O (Fig. 2). These were compared with the response of 112 normal persons and show a clear-cut diminution in capacity to produce antibody. Other patients with hypergammaglobulinaemia, the consequence of hepatitis and rheumatoid arthritis, showed no such diminution in their response. Lawson, Stuart, Paull, Phillips, and Phillips (1955) reported on nine cases, stressed their liability to pyogenic infections, and showed that all had a constant and characteristic

FIG. 2. Plot of antistreptolysin titre of myeloma patients compared with normal controls showing the defective reaction of the patients with myelomatosis. Data from Marks (1953).

deficiency in circulating antibody. One of their patients had had three attacks of lobar pneumonia in the four months before admission to hospital and another had seven attacks between 1950 and 1954. These patients in their clinical history were somewhat reminiscent of Bruton's boy (1952) who had a primary globulin deficiency, and it is evident that myeloma must be regarded as a form of immunological paralysis.

Porges (1956) reiterated the liability of these patients to pyogenic infection, but stressed that the deformities of the chest wall associated with bony lesions and the anaemia might be significant contributory factors in the recurrence of pulmonary complications. This was clearly not the situation in the patient reported by Baker and Martin in 1959, who had had a pleural effusion in 1951 and was under surveillance at a chest hospital in 1952, for it was not until 1957 that she developed bone lesions.

The proliferation of a single or very limited number of clones of cells (Ballieux, Imhof, Mul, Zegers, and Stoop, 1968) is always associated with some degree of immunoparesis though the cell-mediated immune response may remain undamaged. Indeed, in 10% of patients with malignant immunoproliferative diseases recurrent infection is the primary manifestation. In all these conditions there is some demonstrable reduction in normal levels of immunoglobulin whether the technique employed be electrophoretic (Laurell, 1961) or specifically immunological (Fahey, Scoggins, Utz, and Szwed, 1963; Cwynarski, 1968). Patients with myelomatosis show a diminished response to pneumococcal polysaccharide and to typhoid and to influenza vaccines. Fahey *et al* (1963) stressed the difference in primary and secondary response in three patients, while Cone

and Uhr (1964) showed that only 50% of their patients could be sensitized by dinitrofluorobenzene.

In their detailed study of the pattern of recurrence of infection in 46 patients with myelomatosis or macroglobulinaemia, Fahey *et al* (1963) indicated that pneumonia and pyelonephritis were by far the commonest areas of infection noted and that the incidence of infection per patient per month was significantly higher in the patients with myelomatosis than in those with macroglobulinaemia. Six of the patients suffering from macroglobulinaemia were in relatively good health despite impaired antibody response.

Miller (1962) has studied the pattern of immunological deficiency in the lymphomas and leukaemias. Of 61 patients suffering from chronic lymphatic leukaemia, 21 had associated hypogammaglobulinaemia. It is not surprising, therefore, that there should be a high incidence of infection in these patients. Patients with 'Hodgkin's disease', taking that group to embrace the granulomata, the paraneoplasms, and the sarcomata, were not so prone to bacterial infection, 12.5% against 37.0% of the cases with chronic lymphatic leukaemia. Delayed hypersensitivity as indicated by skin tests showed a marked difference between the two groups: 80.6% of patients with chronic lymphatic leukaemia responded as compared with 25% of the patients with Hodgkin's disease. Cone and Uhr (1964) have compared the immunological response of small groups of patients suffering from chronic lymphatic leukaemia and myeloma in some detail. Both showed delayed type sensitivity to at least one of a range of commonly encountered antigens. But while five out of 11 patients with myeloma gave a positive response to sensitization with 2,4-dinitrofluorobenzene only one out of nine of the patients suffering from chronic lymphatic leukaemia did likewise.

RENAL DAMAGE More than 50% of patients have impaired renal function; 5% present with acute renal failure and uraemia is second only to pneumonia as the ultimate cause of death in this group of diseases.

Compared with other causes of chronic renal damage, oedema, haematuria, and hypertension are not common.

The primary renal lesions as observed at necropsy or by renal biopsy lie in the distal segments of the nephron: the tubular epithelium in the area is swollen and degenerate and the lumen is blocked by obstructing casts of protein which extend upward to involve the entire length of the tubule (Oliver, 1944-45).

Renal biopsy studies indicate that initially the glomeruli are not involved and function adequately,

Bence Jones protein being filtered through them effectively (Greenwald, Bronfin, and Auerbach, 1953).

Batts (1939), from a review of 40 cases, indicates that the severity of renal damage cannot be correlated directly with the amount of Bence Jones protein passed at any time in the urine.

The functional capacity of the kidney must be affected by a variety of other factors, such as dehydration, hypercalcaemia, anaemia, and increased blood viscosity in individual cases.

Occasionally the renal damage may be the consequence of paraamyloid infiltration or diffuse infiltration with plasma cells.

Figure 3 shows the levels of blood urea in 100 consecutive patients on their admission to hospital.

FIG. 3. Levels of blood urea in 100 consecutive patients admitted to hospital.

Of the four with blood urea levels higher than 100 mg/100 ml, three were admitted in advanced renal failure, the diagnosis of myelomatosis not having been suspected, and in two of these the monoclonal activity was producing IgA.

ANAEMIA Some degree of anaemia is present in nearly all cases during the course of the disease. Figure 4 shows the Hb levels on admission of 140 consecutive patients suffering from IgG and IgA myelomatosis compared with 45 consecutive patients suffering from macroglobulinaemia (IgM). Specimens of blood taken from the latter patients frequently show clumping and rouleaux formation. The anaemia is usually normocytic and normochromic and frequently refractory to haematinics. The origins of the anaemia are complex, being a combination of the invasion of normal marrow, the direct interference in the development and survival of the erythron, and, particularly in the macroglobulinaemias, persistent intermittent haemorrhage, with interference in the blood clotting mechanism arising

from interaction of the immunoglobulin with the platelets and the coagulation factors VI and VII and fibrinogen (Niléhn, 1962; Frick, 1955).

Glueck and Hong (1965) have described the interference with the action of the antihæmophilic globulin by an IgA globulin from a patient with myelomatosis.

FIG. 4. The haemoglobin levels of patients suffering from macroglobulinaemia at first examination compared with those suffering from myelomatosis at first examination.

SPACE-OCCUPYING LESIONS These are as a rule osteolytic but in a few cases may be visceral.

Skeletal The characteristic lesions in myelomatosis are osteolytic and in 90% of patients are associated with normal serum alkaline phosphatase levels (Fig. 5). The first indication of the lesion may be vertebral collapse or a spontaneous fracture. Five to 10% of patients have a diffuse osteoporosis without the characteristic localized osteolytic lesions. Discrete skeletal lesions are rare in the primary macroglobulinaemias.

Visceral lesions In 20% of patients the deposits are primarily visceral in the spleen or a lymph node, though in these marrow puncture almost invariably shows an excess of plasma cells. The plasma cell leukaemias merge imperceptibly with this group. Many of these patients develop demonstrable skeletal lesions as the disease progresses, though the primary macroglobulinaemias are an obstinate exception.

FIG. 5. The serum alkaline phosphatase levels in a series of patients suffering from myelomatosis at first examination.

FIG. 6. Calcium levels in a series of patients suffering from myelomatosis on first admission.

CRYOGLOBULINAEMIA AND RAYNAUD'S PHENOMENA Cryoglobulinaemia is not pathogenomic of the monoclonal proliferations, for it may be observed in any condition in which there is gross overproduction of immunoglobulins, particularly where there is an associated marked disturbance of the albumin/globulin ratio.

Because of the physicochemical properties of IgM and the relatively low temperatures at which they may precipitate, peripheral circulatory disturbances, such as Raynaud's phenomena, accompanied by superficial skin ulceration, may be the presenting symptom in patients with macroglobulinaemia. Of five patients we have seen in whom this was the situation, one had a markedly positive Wassermann reaction, and had been receiving treatment for syphilis (Martin, 1960).

HYPERCALCAEMIA Figure 6 shows the calcium levels in 80 consecutive patients at first examination.

A patient admitted after the collection of this series deserves mention. Admitted from the Out-patient Department complaining of polyuria, he rapidly became disorientated and lapsed into coma. He had marked nitrogen retention (blood urea 110 mg/100 ml) and a serum calcium level of 17.6 mg/100 ml. Under vigorous treatment with prednisone and disodium phosphate his serum calcium level dropped to 9.0 mg/100 ml over the next 20 days and his blood urea to 37 mg/100 ml. There was no history or evidence of any discrete skeletal lesions on radiographs. The diagnosis of myelomatosis of the IgG group was established from the findings in the serum, the urine, and on examination of the bone marrow. He made a

good immediate clinical recovery on immunosuppressive drugs, but died the following year when the diagnosis was confirmed.

Lyall Watson (1964), in a study of the effects of hydrocortisone levels on hypercalcaemia in neoplastic disease, showed that of 12 patients eight showed a well marked drop in plasma calcium. In one the osteolytic lesions appeared to diminish in extent.

AMYLOIDOSIS Amyloidosis is not a common complication of the monoclonal diseases. Five to 10% show paraamyloid deposits. Contrariwise, any patient with so-called primary amyloid lesions in the skin or tongue should be examined to exclude the presence of myelomatosis.

VISCIOUS SERUM AND THE HYPERVISCOSITY SYNDROME Steel (1959) and Fahey, Barth, and Solomon (1965) have pointed out the striking difference in viscosity between IgG and IgM, when their relative viscosity is plotted against protein concentration. Franglen (1968) has pointed out an equally striking difference in the temperature/viscosity ratio. Fahey, Barth, and Solomon (1965) have outlined a clinical picture of recurrent spontaneous haemorrhage associated with symptoms of impaired circulation, together with ocular and neurological manifestations which occur when the relative serum viscosity exceeds six. These features are most common in essential macroglobulinaemia with excess of circulating IgM, but they are observed in patients with myelomatosis associated with excess of IgA and occasionally with IgG.

MACROGLOBULINAEMIAS The advances in our knowledge of the distribution and detailed structure of the macroglobulins necessitates a recasting of the classification of diseases associated with overproduction of these molecules.

The classical Waldenström macroglobulinaemia is associated with massive amounts of an immunoglobulin having a sedimentation coefficient of about 19 Svedberg units, which, on immunochemical analysis, can be differentiated from IgG and IgA, the antigenic behaviour of the μ chain being specific. Cwynarski (1968), examining six cases of macroglobulinaemia, demonstrated that in them the levels of IgG were diminished or at best normal. This is an important criterion in establishing 'primary' macroglobulinaemia of the IgM type.

Though there is considerable overlap in the clinical picture, this form of clonal proliferation is usually distinguishable from myelomatosis in that males predominate, that the incidence is at a somewhat older age, that osteolytic lesions are uncommon, while striking haemorrhagic episodes are frequently the presenting symptom. On examination the patient often has some degree of lymphadenopathy and a palpable spleen. The bone marrow is infiltrated with cells of the lymphocyte series. As mentioned earlier, Bence Jones proteinuria occurs in no more than 15% of patients. The sera display an exotic array of agglutinating phenomena, the consequence of the excess of IgM.

Of 70 patients in whose sera we have been able to demonstrate excess of macroglobulins, 45 might reasonably be regarded as cases of primary Waldenström type macroglobulinaemia. Almost without exception these patients showed some degree of anaemia when first examined. In 17, severe local haemorrhage or the dramatic consequence of local haemorrhage was the presenting symptom. In 10 of these there were visual disturbances ranging from unexplained diminution of vision to a quite sudden blurring of vision. Fortunately, these alarming visual disturbances usually subside.

The typical retinal picture with the peripheral microaneurysms has been well described by Ashton, Kok, and Foulds (1963). The picture is not strictly pathogenomic, occurring occasionally in patients suffering from myelomatosis and polycythaemia.

Microdissection and histochemical investigation show the aneurysmal walls to be degenerate and to contain PAS-positive material. This material is also seen in the lumen surrounding clumps of red cells. These degenerative changes in the small vessels are seen in other parts of the body and contribute to the violent nasopharyngeal and gingival haemorrhage experienced by some patients. The interference with the blood-clotting mechanism already referred to

make these haemorrhages unusually difficult to control.

Unexplained cyanosis, bruising, and Raynaud's phenomena were the presenting symptoms in five patients and two presented with flat serpiginous ulcers on the legs and back. In these the exotic serology had led to an unwarranted tentative diagnosis. In six patients there was an antecedent history of respiratory infection.

Serial studies of the cause of infection in the newborn show that the initial response is accompanied by an outpouring of the IgM immunoglobulin followed by a rising outflow of IgG. Serial studies of the serological changes in infective hepatitis and infective mononucleosis show a marked initial rise in IgM which may persist in some patients, while a significant number of patients suffering from viral pneumonia with haemolytic complications show extremely high cold agglutinin titres and demonstrable increases in IgM. Though Gordon (1953) has shown that cold agglutinins are macroglobulins, it cannot be assumed that all macroglobulins are cold agglutinins. Ritzmann, Thurm, Truax, and Levin (1960) report a patient in whose sera a gross excess of macroglobulin could be demonstrated but there was no evidence of the presence of cold agglutinins. Finally, there are a number of protozoal infestations, such as those with *Trypanosoma leishmanii* and malaria, which produce a marked IgM response. All these situations must be regarded as examples of 'secondary' macroglobulinaemia, and, although in the majority the diagnosis will be evident, the occasional atypical patient may present a problem.

It is vital, therefore, that any diagnosis should be backed by serial differential analysis to demonstrate that the IgM titre is high and remains high and that IgG and IgA titres are not markedly increased. Thus, there is the well documented and puzzling case of the patient first seen in 1954 (reported by Ferriman and Anderson in 1956) who four years later (Anderson and Ferriman, 1960) was perfectly well and whose sera at that time showed no excess of macroglobulins.

In the vast majority of these secondary cases, as with those in which an excess of IgM is associated with a pleomorphic tumour, the high level of IgM will be associated with an increased level of IgG.

THE IgM MONOMERS The pentameric structure of the IgM molecule put forward by Miller and Metzger (1965, 1966) suggests immediately the possibility of IgM monomers circulating either in conditions associated with excess production of the pentamer, Waldenström's macroglobulinaemia, or independently. When the serum globulins from such patients are analysed on a Sephadex 200 column, small peaks or irregularities on the forward edge of

the 7S peak are sometimes seen (Fig. 7). Moreover, when the final effluent is concentrated and inspected using antisera specific for the μ chain, in addition to positive reactions in the forward peak associated with the 19S globulin, reactions are noted with material obtained from the leading edge of the area associated with the 7S globulin. This suggests, though it does not prove, that in certain patients the heavy chain monomer or a fragment of that chain is manufactured in excess and released into the serum alongside the pentamer in a manner analogous to the liberation of the Bence Jones protein in IgG and IgA myelomata. Though our present methods of identification may be crude and insensitive this does not appear to occur in more than 20% of patients with macroglobulinaemia.

Solomon and Kunkel (1967) published a detailed clinical picture of a woman of 67 who appears to have been suffering from IgM monomer disease. The general course of her disease was not unlike that of patients suffering from heavy chain disease (Fc fragment). The total protein level, 6.3 g/100 ml, was not raised, but an anomalous peak was noted between the β and γ globulins. It seems clear from the careful physicochemical and immunochemical analysis that this aberrant protein contained heavy chains with immunological properties resembling the μ chain and light chains of the λ type. Ultracentrifugal analysis of the serum indicated that there was no demonstrable excess of 19S component. Ultracentrifugal analysis of the isolated anomalous protein indicated that its sedimentation velocity was 6.5S. It could thus be regarded as the IgM monomer or molecule akin to the monomer. We have seen two other patients in whose sera μ G monomer appeared to be the predominant atypical protein.

Rothfield, Frangione, and Franklin (1965) had noted an antinuclear antibody in the sera of patients suffering from systemic lupus erythematosus in the active phase which has antigenic behaviour similar to IgM but migrates both in the ultracentrifuge and in the Sephadex column with the fractions rich in IgG and not with 19S IgM. Stobo and Tomasi (1967) confirmed this finding in 52 cases examined suffering from disseminated lupus erythematosus, the sera from 17% of these containing demonstrable amounts of low molecular weight IgM. These were predominantly males and particularly males with low or absent serum IgA. It appeared that the presence of IgM was inversely proportional to that of IgA. These observations suggest that the comparative anatomy of the heavy chains of IgA and IgM requires investigation.

Though IgM monomer is present in the serum of 20% of patients suffering from Waldenström's macroglobulinaemia, there is as yet insufficient

FIG. 7. Serial separation on a Sephadex column of the serum proteins from a patient suffering from macroglobulinaemia. The black blocks represent the immunological response of successive samples coming off a fractionation column to specific antisera, to μ chain, α chain, and γ chain.

evidence to decide whether the presence of the monomer is indicative of the primary or the secondary condition (Martin, 1968).

'HEAVY CHAIN' DISEASE Franklin *et al* (1964) described a syndrome associated with the circulation and excretion of a peculiar protein with a sedimentation value of 3.6 to 3.8. This they called 'heavy chain' disease. Detailed studies of the protein indicate that it is, or is closely related to, the Fc fragment of IgG. Seven cases have been described in satisfactory detail, others have been observed but not established beyond doubt.

The clinical picture is of a male over 40 with a generalized lymphadenopathy and splenomegaly, often of rapid onset, and painful. This is accompanied by fever and in three cases notable uvula and palatal oedema. After the initial onset a proportion of cases regress, but all suffered from recurrent infection, two dying of pneumonia and one of generalized sepsis.

The patients are anaemic and generally lymphopenic. There is gross proteinuria, but no demonstrable Bence Jones protein. Though the ESR is raised the levels do not approach those commonly seen in patients suffering from myelomatosis. Serum electrophoretic analysis displays a tightly packed band running ahead of the normal position of the IgG band. The protein isolated from both the urine and the serum does not react with either κ or λ antiserum. It does react with antisera to the γ heavy chain and to antisera specifically prepared against

the Fc fragment. Physicochemical measurements of the protein suggest a molecular weight of between 52,000 and 58,000 and that the individual molecules are symmetrical dimers stabilized by an S:S bond and show Gm specificity. Prahl (1967), examining the N and C terminal sequences of the protein chain, noted the persistence of the 'initiator' of the N area, but apparent deletion of the cistron corresponding to the main Fd area, biosynthesis recommencing in the Fc area.

Alternatively, Askonas and Williamson (1966) have interpreted the quantitative data as suggesting a transposition of the initiating site so that an internal codon is 'read' as initiator. These speculations about a rare disease suggest interesting ways in which 'freak' proteins may be produced.

LYMPHOMA, LYMPHATIC LEUKAEMIA, AND NEOPLASIAS UNRELATED TO THE LYMPHORETICULAR SYSTEM In an analysis of 110 patients suffering from chronic lymphatic leukaemia, Fairley and Scott (1961) described one patient in whose serum there was unequivocal evidence of an excess of IgM. Hällén (1966), in a series of 59 patients with chronic lymphatic leukaemia, identified four in whom there was an increase in IgM. Lymphatic leukaemia might be considered as a manifestation of a monoclonal disease. However, in the patient described by Fairley and Bodley Scott there were demonstrable excesses of 7S globulin (IgG). Excess of IgM has also been observed on occasion in such pleiomorphic conditions as Hodgkin's disease (Martin, 1968).

Finally, in any large series of cases there are a residuum, 2 to 5% of patients, usually in the older age group, with primary neoplasia unrelated to the lymphoreticular system, such as the epidermis, breast, stomach, and prostate, whose sera on electrophoretic analysis show a compact band in the region of immunoglobulins. These globulins may have immunological relationships to IgG, IgA, or IgM (Waldenström, 1961).

'IDIOPATHIC' MONOCLONAL PROLIFERATION The occurrence of monoclonal proliferation producing an electrophoretic pattern in all ways similar to that seen in myelomatosis in persons devoid of any symptoms that could reasonably be associated with the biochemical findings has remained something of a puzzle ever since Waldenström (1944, 1965) described 'essential hypergammaglobulinaemia'.

Norgaard (1964) describes five patients in whom there was a lapse of six, 10, 13, 13, and 17 years between the first identification of a serum protein pattern suggesting monoclonal proliferation and recognition of overt myelomatosis. Wallerstein

(1951) described one patient in whom the time lapse was 17 years. Well documented cases with three to four years' history before overt symptoms are not uncommon (Baker and Martin, 1959; Hobbs, 1966). In the light of this experience it is difficult to regard any monoclonal proliferation as 'benign' and it is prudent to regard each case as potentially malignant. This does not imply that with our present knowledge these patients should be treated with our present array of cytotoxic drugs but they should be followed with scrupulous care.

CONCLUSION

The myelomatoses, the macroglobulinaemias, and associated diseases characterized by the release of excessive amounts of specific immunoglobulins or their component chains into the vascular space, must be regarded as a group within the framework of the lymphoreticular dysplasias. Any neoplasia of the lymphoreticular system may on occasion be accompanied by an outpouring of excessive amounts of immunoglobulins, a partial expression of the dislocation of the immunological machinery with which the tissues are normally associated.

The peculiarity of myelomatosis, primary macroglobulinaemia, and of the directly related diseases, such as the μ G monomer disease, is that they are regularly associated with a gross overproduction of a single immunoglobulin and/or its constituent parts. Rarely two immunoglobulins may be secreted, suggesting that two clones of cells are developing independently. In these cases the analyses of the constituent molecules of the isolated immunoglobulins never give the complex pattern displayed by their normal counterpart. In considering the machinery of recognition and defence, it is customary to consider individually the cellular and humoral component. This is an arbitrary division dictated by the interests of the investigator. The majority of lymphomata are associated with no gross disturbance of the circulatory levels of immunoglobulins except under challenge. When there is a disturbance it is usually a deficiency. Nevertheless, a small number of lymphomata and lymphatic leukaemias are accompanied by an excessive release of immunoglobulins into the vascular space. The same is true of the multicellular processes grouped under the heading 'Hodgkin's disease'.

A detailed analysis of the globulins produced in myelomatosis suggests a relatively simple situation in which there is a rapid multiplication of one plasma cell series devoted to the production of a single immunoglobulin. In so far as the matter has been taken there seems to be a concomitant reduction in the production of other immunoglobulins, and

devices normally calculated to stimulate humoral antibody produce only a poor response. Plasma cells are constantly being developed as a part of the normal response to antigenic stimuli. The multiplication of the 'rogue clone' inhibits either the multiplication of the normal plasma cells or suppresses their capacity to produce the normal range of immunoglobulins.

In the expanding field of tissue recognition and transplantation, it is recognized that the small lymphocyte is a critical mediator in homograft rejection. In this field, in recent years, attention has been focused on antilymphocytic globulins produced by the collection of peripheral lymphocytes or lymphocytes formed from the thoracic duct of one species and their injection into another. Such globulins have been prepared in horses from humans and used as an immuno suppressive adjuvant. The action appears to be restricted and primarily effective on the thymic-dependant lymphocytes. At the present time the preparation is crude and of variable potency, but there is little doubt that with modern techniques an effective element or elements will be isolated and identified. This will open the way to the production of synthetic homologues. Such a development might prove valuable to surgeons interested in transplantation.

Equally interesting, if the clonal concept of myelomatosis is correct, would be the production of antiplasmodic globulin against a specific plasma cell clone, presumably in the first instance γ A or γ G. The evidence seems to suggest that the 'rogue plasma cell' in myelomatosis is a pure bred line and should be the ideal area in which to attempt the production of such serum. In spite of relative success with synthetic totipotent immunosuppressives, myeloma stills remains a lethal disease.

The production and purification of 'naturally' occurring antiplasmodic substances could prove a real therapeutic advance in the treatment of this group of lymphoreticular dysplasias.

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