cases; in some of these, tests of subsequent serum samples using individually specific antisera were unable to detect the monoclonal immunoglobulins, the monoclonal immunoglobulin spike (IgG, IgA, or IgM) disappearing within one month to two years. The monoclonal immunoglobulin level was less than 1 g/100 ml in all cases but one. Five of these nine patients were infants and only two were over 60 years. Three patients had primary immunodeficiency diseases. In a 20-year-old woman an IgG monoclonal immunoglobulin (2.5 g/100 ml) appeared three months after the onset of acute viral hepatitis and disappeared completely one month later. No antibody activity against Australia antigen was detected in this monoclonal immunoglobulin. We believe that these transient spikes of immunoglobulin probably reflect the production of a monoclonal antibody.

In some of our patients who were thoroughly studied the classical features of multiple myeloma developed progressively a few months or years after a monoclonal immunoglobulin had been detected. In these patients the level of immunoglobulin gradually increases, and even in slowly progressive cases myeloma could usually be suspected at the initial examination after careful studies of the bone marrow and immunoglobulins. In the vast majority of persons with a monoclonal immunoglobulin detected in the absence of overt myeloma the monoclonal immunoglobulin level of this remains stable over the years. This is true for most cases of monoclonal immunoglobulin associated with malignant lymphoma or chronic lymphocytic leukaemia (where double spikes are not unfrequent). In these latter conditions the monoclonal immunoglobulin may be more often the consequence of the associated immunodeficiency rather than directly related to the lymphoid proliferation.

Patients without Myeloma

We have studied 58 patients with an IgG or IgA spike and without evidence of myeloma after thorough clinical, haematological, and x-ray examination at the time of detection and after a 3 to 8 years' follow-up (or complete postmortem study). In only two cases did the level of the monoclonal immunoglobulin rise significantly after it had been stable for some time; in them the level reached a new plateau and the patients did not develop myeloma subsequently. The levels of monoclonal immunoglobulin and of the normal serum immunoglobulins as well as the presence of Bence-Jones proteinuria are useful criteria at the first examination for distinguishing myeloma from benign monoclonal gammopathy. Nevertheless, among our 19 patients who did not develop myeloma after five years' follow-up, the initial level of monoclonal immunoglobulin was between 1.5 and 2.5 g/100 ml in three instances; normal immunoglobulin levels were decreased in four instances but remained stable throughout; and Bence-Jones proteinuria was present in five patients (always less than 0.2 g/24 hours). This series excludes patients with primary immunodeficiencies and malignant lymphomas. None of our patients in whom a monoclonal IgG or IgA was associated with polyclonal hyperimmunoglobulinaemia proved to have myeloma. On the other hand, this is not true for patients with IgM spikes, since high levels of IgG and IgA are not uncommon in malignant macroglobulinaemia.

In a few well-documented cases (especially in Waldenström's series) patients whose monoclonal immunoglobulin levels have been perfectly stable over many years may suddenly develop myeloma with a rapid increase of the monoclonal immunoglobulin level. We suggest that these cases constitute a separate entity from slowly progressive myeloma and that the presum-

ably benign proliferation expressed by the stable monoclonal immunoglobulin may suddenly get out of control and become malignant. Whether this sequence has occurred in many patients seen with myeloma is at present a matter for speculation.

IgG Subclasses in Relation to Viscosity and Cryoglobulin Syndromes

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Serum hyperviscosity is a relatively common complication of macroglobulinaemia. It often coexists with cryoglobulinaemia and results from high levels of circulating IgM. Comparing viscosities and concentrations of IgG, IgA, and IgM monoclonal proteins, probably lower concentrations of IgM are required to raise the viscosity to higher levels. There are four subclasses of IgG occurring with frequencies of IgG₁ 72%, IgG₃ 10%, and IgG₄ 4%. Comparing IgG₃ and IgG₁ proteins it was found that IgG₃ raises viscosity at lower levels than IgG₁. It has been postulated that IgG₃ tends to form concentration-dependent aggregates. This tendency towards interaction between similar molecules agrees with the prevalence of IgG₃ proteins among IgG cryoglobulins. The basis for this interaction may be some configurational peculiarity, an assumption supported by indirect evidence. Less is known about IgG₂ proteins, the other important subclass among IgG cryoglobulins.

One therapeutic aim in hyperviscosity and cryoglobulinaemia is to reduce the circulating level of the abnormal protein. As cytotoxic drugs usually take some weeks to produce this effect, palliative measures become necessary. Plasmapheresis is the classical approach, but the administration of thiols deserves some consideration. The main effect of thiols in macroglobulinaemia appears to be to decrease IgM levels, by suppressing its synthesis and perhaps by increasing its catabolism. These effects might also reduce IgG protein levels, but possibly also thiols may prevent aggregation, particularly of IgG₃, and thus render a given concentration of paraprotein less likely to precipitate on cooling. Hence this therapy should be re-evaluated in hyperviscosity and cryoglobulinaemia associated with IgG monoclonal proteins.

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Urinary Low Molecular Weight Products in Neoplasia

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Some low molecular weight products in urine (molecular weight under 500) can be separated by simple low-voltage paper electrophoresis and easily detected (without any staining) by their fluorescence on the dried paper strip viewed under ultraviolet light. A wide range of substances can be detected if different wavelengths of ultraviolet light are used for fluorescence stimulation.

The zones can be measured by the fluorescence intensity emitted at an angle of 45°. The height and area of the peaks over the different zones corresponding to the fluorescence emission of that zone may be measured as relative percentages of the total fluorescence. The method uses unconcentrated early morning urine: 20 µl are applied to paper and electrophoresed for four hours at 200 volts in Michaelis buffer (barbital/acetate), pH = 8.6, μ = 0.075. Measurements were made on a Zeiss spectrophotometer PQ2 with the Sterzl additions of fluorescence equipment, scanner, and recorder. The irradiating light is passed through filter M 365, fluorescence being measured at 460 nm (maximum of fluorescence emission after excitation at 365 nm).

With this method the urine of healthy persons usually shows a characteristic pattern, with a maximum of 5 zones. Another finding is the occasional presence of an additional band. Whereas only 12% of normal people were found to have these, among a group of patients later proved to have carcinoma of the body of the uterus some 70% showed extra bands. Furthermore, extra bands are a common finding in many patients with other proved carcinomata.

Of 58 patients with proved myelomatosis with paraproteins, 47% showed extra bands. Of 14 patients with proved soft-tissue plasmacytoma, 42% of the preoperative urines showed extra bands. In addition, in cases of paraproteinaemia the ratio of fluorescence intensity from the slowest migrating zone (zone A) to the middle zone (zone B) is obviously altered compared with normal cases; indeed, a reversed ratio was seen in 96% of the patients. In five patients with proved myelomatosis, without paraprotein, the reversed ratio was found in all five, though no extra bands were seen.

The compounds detected by fluorescence emission at 365 nm remain as yet uncharacterized. They are unrelated to any chemotherapy used, and also are distinct from the urinary excretion products of pain-relieving drugs such as aspirin, etc. Possibly they are related to indoles. It is too early to be sure but we believe that this simple test of urine may prove of value for detecting the presence of occult cancers.

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Treatment of Myelomatosis— M.R.C. Trial

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Until the mid-1950s myelomatosis was treated with little success. Pain could be relieved by local x-irradiation and a minority of patients were improved by treatment with steroids or urethane. In the late 1950s Russian workers reported some success with sarcolysin, the unresolved DL form of phenylalanine nitrogen mustard. Earlier, Bergel and Stock had purified the D and the L isomers, and Haddow and others had shown that the L isomer melphalan was usually much more active than the D isomer. It was therefore decided to start therapeutic trials in myelomatosis with the L-form. The good results reported by the Russians for sarcolysin were amply confirmed for melphalan, and it seemed probable that the intermittent method of administration was less damaging to the bone marrow, and was more often accompanied by sustained increase in the haemoglobin

concentration. Meanwhile, apparently equally good results were reported for cyclophosphamide, but no direct comparison had been made. In September 1964 the M.R.C.'s working party on therapeutic trials in leukaemia started a comparative trial of melphalan; patients were entered until 31 July 1968 and surviving patients were followed up to 31 May 1970 for the present analysis.

In the first comparative trial both drugs were administered continuously at low daily dosage. All new patients with the prospect of continuous follow-up were eligible, provided they had received no previous chemotherapy, other than prednisone for the treatment of hypercalcaemia. Radiotherapy for the relief of local pain did not preclude entry. The minimum diagnostic criteria for eligibility were two of the following: firstly, abnormal plasma cells in the bone marrow; secondly, a monoclonal M-component in the serum, urine, or both; and, lastly, radiological findings compatible with myelomatosis.

There were 276 cases for analysis—142 men and 134 women; only 7% of the patients were below 50, but compared with the national distribution patients over 70 were somewhat under represented. In respect of all the main clinical features the two treatment groups were similar, while equal proportions had received local radiotherapy before they started chemotherapy, and during the course of the disease, as well as being treated with prednisone for hypercalcaemia.

Though the main purpose of the trial was the comparison of the effects of melphalan and cyclophosphamide, no significant difference emerged in their therapeutic efficacy, or in their effect on survival, so the following account is based on the total series of patients. Many of the clinical features at presentation were correlated with survival when considered separately, but two features—namely, the blood urea and the serum albumin concentrations—were strongly and independently correlated with survival. When the correlations with survival of all the other factors were adjusted for the effect of the blood urea and the serum albumin concentrations, their effects largely or entirely disappeared. The explanation of renal damage is that the tubules are damaged by long-continued passage of Bence Jones protein and by its precipitation within the tubules. In our series the prognostic influence of Bence Jones proteinuria was strongly correlated with the presence of uraemia, and disappeared when adjusted for it. This again correlates with the clinical impression that if Bence Jones proteinuria can be reduced by treatment before renal function has become irreversibly impaired the process can be arrested and the patient may survive. It is interesting that none of the radiological findings had any prognostic significance. Indeed, 24% of all the patients had no radiologically detectable lesions.

Type of Protein Abnormality

The possible effect of the type of M-component has been of interest since Bergsagel's original observation of a difference in therapeutic response to melphalan of patients with kappa (K) or lambda (L) type light chains. In our series the survival was rather worse in L-type cases, but these included a higher proportion of patients with a high blood urea level, and when this was allowed for the adverse influence disappeared. The relationship perhaps depends on the duration of exposure of the renal epithelium to the light chains, and our data provide some evidence of this: twice as many of our IgGL patients as IgGK patients had more than 100 mg/100 ml of Bence Jones protein in their urine, the mean concentration being 291 mg compared with 64 mg/100 ml for the IgGK cases.

In our series the initial level of the serum albumin was strongly correlated with survival, and the influence was independent of the blood urea concentration. We do not know whether the fall in serum albumin level was a result of a reduced rate of synthesis or of an increase in the catabolic rate, but it was not a result of loss in the urine. The survival curve of the 276 patients shows an