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

G. VIRELLA

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.