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Hyperviscosity Syndrome in Plasma Cell Dyscrasias[1]

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Introduction

Vascular symptoms arising from the abnormal rheological behavior and cryosensitivity of the blood are sometimes encountered in certain forms of plasma cell dyscrasias. The idea that alterations in the plasma proteins may more or less directly cause significant clinical consequences is comparatively new but is rapidly gaining ground. To some extent, this may be an expression of the more general recent interest in the hyperviscosity phenomena of the blood and its components. This is reflected in, for example, editorials and short reviews which have appeared in various reputable journals [5, 30, 56, 57, 126, 149, 210, 213, 220, 222, 227, 228]. Partly, however, this interest has a purely practical basis, since the manifestations of organ dysfunctions and disturbed homeostasis are often dramatic.

On the other hand, certain new methods of treatment which have been developed, especially plasmapheresis, have proved very effective in alleviating of the symptoms. In addition, they have definitely helped us to understand the pathogenetic mechanisms of the serum hyperviscosity syndrome. The determinants of this syndrome have recently been much clarified, partly by remarkable findings made by means of advanced immuno- and physicochemical methods developed for protein and rheological studies, and partly by planned observations both in man and in animal models.

With these significant but very scattered new achievements in mind it was felt that it might be useful to try to review the main facts that are now known about the serum hyperviscosity syndrome (HVS). This paper will also include, in a short discussion, the author's personal views on the suggested pathogenetic mechanisms and the development of the HVS together with some practical suggestions on the study of hyperviscosity cases.

Classification and Some Basic Features of Plasma Cell Dyscrasias

The designation *plasma cell dyscrasia* has been suggested by OSSERMAN as a substitute for the synonyms *paraproteinemia, monoclonal gammopathy, dysgammaglobulinemia,* etc. [152, 235]. It is intended to refer to a clinically relatively infrequent group of pathologic conditions, the basic feature of which is the uncontrolled and usually excessive proliferation of a single clone of immunoglobulin (Ig) producing cells [133]. This unbalanced, malignant proliferation of plasma cells may express itself in a variety of clinical syndromes, of which the serum hyperviscosity syndrome is one example. Structurally and electrophoretically homogenous monoclonal (M-type) protein(s) usually appear in abundance in the blood, where they can commonly be demonstrated as a narrow based prominent spike on electrophoresis (fig. 1). By physicochemical and immunological methods these M proteins

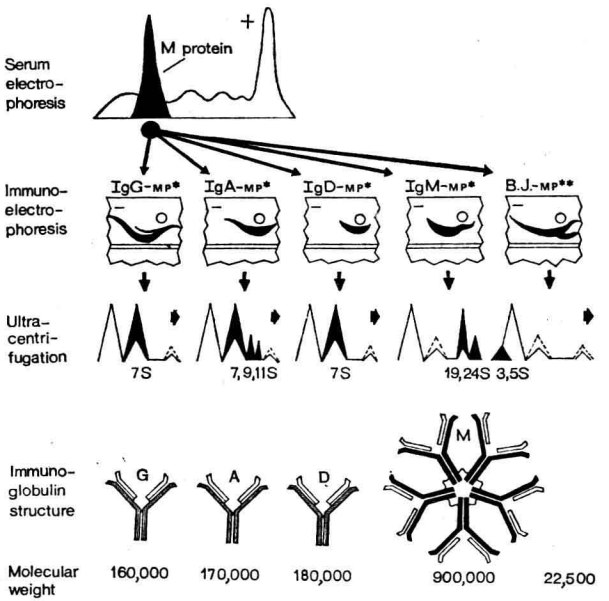

Fig. 1. Diagram showing the electrophorectic, immunoelectrophoretic and ultracentrifugal characteristics as well as the schematic immunoglobulin structures and approximate molecular weights of the principal M proteins. Redrawn in a slightly modified form from figure 3 in RITZMANN *et al.* [153] with the kind permission of the authors and publisher.

can be identified as belonging to one of the currently known categories of immunoglobulins or to heavy or light polypeptide chains of one of these classes (fig. 1).

Multiple myeloma (MM), plasma cell myeloma, is the most common form of plasma cell dyscrasia. It may present itself in a wide variety of clinical expressions [180]. Some of them are fairly generally thought to be caused by the increased quantities and by the specific physicochemical properties of the M proteins (paraproteins) demonstrable in the blood of a great majority of cases [132]. In high concentrations, and possessing some unusual properties, such myeloma proteins may, indeed, give rise to dangerous clinical situations, but fortunately this is a rather rare occurrence. Of the presently known varieties of myeloma, the two most common ones, IgG and IgA, have been found to have clinically important rheological consequences [182].

Waldenström's primary macroglobulinemia (MW) is a relatively infrequent neoplastic disorder of the lymphoreticular system characterized by an increase, usually marked, in the serum IgM (macroglobulin) concentration. Its clinical manifestations may display a

wide spectrum [113, 134, 154, 200, 203], and are dependent on the stage of the disease and on the special properties of the circulating IgM. Many of the expressions of the classic disease have been attributed to the increased serum viscosity levels caused by an excess of macroglobulins and by their physicochemical characteristics [58, 134, 154, 200, 203, 235]. Of these special features, the cryosensitivity which is found in up to one third of the macroglobulins is especially noteworthy [141, 150].

Cryoglobulinemia is a term coined by LERNER and WATSON [104] in 1947 to describe serum proteins which have in common the unique feature of reversibly precipitating, gelling or crystallizing in the cold [8, 150, 223]. They have now been found to consist most frequently of mixtures of immunoglobulins and components of the complement, but quite often they are also observed in sera from MM and MW patients, and have been usually identified as IgG or IgM M proteins [8, 61, 125, 153, 223]. Owing to differences in the clinical pictures of the basic diseases [8], to the variable physicochemical properties of cryoproteins, and to the fact that the amount of cryoglobulinemia in a given patient does not necessarily show a good correlation with the severity of his clinical symptoms [141], the clinical expressions of cryopathies may be very heterogenous [117, 150]. However, HVS has been sometimes reported as occurring in connection with cryopathies [8, 141, 144, 150, 194].

On the other hand, to the best of the author's knowledge, no HVS in its strict sense has yet been reported in association with the *chronic cold agglutinin syndrome or disease* [151, 153, 173], although some investigators [151, 173] consider its idiopathic form as a variant of MW, which thus implies the presence of large amounts of circulating IgM proteins.

Concept and Evolution of the HVS

The HVS consists of a variable complex of clinical symptoms and signs [58, 59, 220], which in the presence of raised serum viscosity quite frequently complicate primary MW, but which seem to be uncommon in MM. Its occurrence and pathogenesis have been ascribed mainly to increased amounts of the monoclonal proteins occurring in these diseases and especially to their specific molecular characteristics and interactions. Despite its relative rarity in clinical experience this situation is potentially lethal and needs promt recognition and therapy. These must be based on an understanding of its nature and special features.

The first observations on elevated serum or plasma viscosity and descriptions of HVS seem to be found in the papers of REIMANN [148], MAGNUS-LEVY [116], WINTROBE and BUELL [214], ALBERS [3] and VON BONSDORFF *et al.* [24] in connection with MM [182]. These isolated and, at that time, puzzling findings were obviously given no great attention until the early 1940s. In 1944 WALDENSTRÖM described three patients in whom he had observed manifes-

tations deviating from those of classic MM and had found elevated serum viscosity values due to globulins of abnormally high molecular weight, later designated 'macroglobulins'. Since WALDENSTRÖM's inspiring pioneer reports on macroglobulinemia [200–202], more widespread studies on the usefulness of serum (plasma) viscosity as a parameter in the clinical evaluation of various immunoglobulin abnormalities have been published in the 1950s and early 1960s [7, 74, 86, 90, 120, 147, 154, 155, 166, 182, 186, 203].

The concept of HVS was, however, defined and made generally known by the excellent papers of FAHEY and co-workers [11, 58, 59, 175, 176, 181]. In these reports it was convincingly shown that a great majority of patients with MW had clinical symptoms and signs directly attributable to increased serum viscosity with attendant changes in the microcirculation. These studies also demonstrated the effectiveness of plasmapheresis in reducing the serum hyperviscosity with a concomitant alleviation of the clinical symptomatology. The observations of FAHEY and his associates were soon followed by reports on similar hyperviscosity states in cases of MM, too [19, 21, 93, 95, 179, 182, 190]. In many of them vigorous plasmapheresis regimens were used to control the potentially fatal symptoms.

The author's studies on serum hyperviscosity [182] were mainly aimed at a comparison of viscosity data with plasma protein changes and molecular properties as they are made manifest by clinically used methods, and thus at assessing the applicability of viscometry as a laboratory tool in the evaluation of the various plasma cell dyscrasias. Similar correlative protein-viscosity studies in various diseases have been conducted by several authors [12, 53, 55, 74–76, 84, 97, 101, 102, 124, 139, 147, 155, 185, 186, 201–203, 207].

Recently, the pathogenesis of serum HVS has been greatly clarified by the discovery of increased plasma volume (hypervolemia), another hemodynamically important factor in addition to hyperviscosity [20–22, 77, 95, 110, 114, 131, 231]. Consequently, in recent years the basic mechanisms of serum hyperviscosity and the concomitant clinical syndrome in MW and MM have been the object of more extensive study by immunologists, hematologists and rheologists [31, 79, 98, 109, 114, 119, 187, 193, 196–198, 215].

The ingenious use by ROSENBLUM of an animal model for macroglobulinemia has greatly added to our knowledge concerning the pathogenesis of increased blood viscosity and its associated microcirculatory events [157–164].

The intention in the following chapters is to review the current knowledge of serum hyperviscosity and HVS in the light of the recent achievements mentioned above.

Determinants of Serum and Plasma Viscosity

The viscosity of a protein solution is determined by several factors, of which only those most relevant to the scope of this paper are presented here. For more detailed discussion of these matters, the reader is referred to papers and monographs by HESS and COBURE [78], JIRGENSONS [88], SOMER [182] and HARKNESS [74].

Viscosity is usually defined as the property of a rheological material (fluid) to resist flow. Viscosity is one of the fundamental characteristics of colloidal solutions like human serum and plasma. In addition to experimental conditions it is mainly determined by the concentrations and molecular characteristics of the proteins in solution [10, 74, 182].

In this context, it is unnecessary to describe the viscometers used for the determination of serum and plasma viscosity or symbols and terms for the viscosity, since they have recently been discussed by several authors [10, 50, 73, 74, 99, 100, 182, 208]. In HVS cases due to plasma cell dyscrasias, the viscosities of serum and plasma have most frequently been measured using the Ostwald viscometer or its modifications. With these, the normal values of relative serum viscosity range from 1.4 to 1.8 [58, 59]. In recent years, the use of a convenient semiautomatic capillary viscometer, designed by HARKNESS [73], has become more general, since its accuracy and rapidity makes it highly recommendable for large-scale screening studies.

The Effect of Protein Concentration

The viscosity of any colloidal solution increases with an increasing concentration of the solute. Several investigators, reviewed by the author [182] and by HARKNESS [74], have confirmed this relationship between the plasma proteins and the viscosity. Thus, the more the plasma contains proteins, the greater will be its viscosity. In principle, this increment is nonlinear provided that sufficiently concentrated solutions are studied. The shape of the concentration-viscosity curve, however, is determined mainly by the properties of the proteins concerned.

The Effect of Intrinsic Viscosity

The rheological effects of various proteins are best characterized by their intrinsic viscosity, which is mainly a function of the size and shape of the protein studied. From the classic works of COHN *et al.* [42], ONCLEY *et al.* [130], HESS and COBURE [78], STEEL [185], and EASTHAM and MORGAN [55], we know that the smaller serum proteins have lower intrinsic viscosities than the larger ones. Accordingly, the viscosity of a spheroprotein is practically independent of the particle size, whereas with linear proteins (like fibrinogen) the viscosity is correlated to their size (molec. wt) and especially to their shape, which seems to be the most decisive of the factors which determine the viscosity of a protein solution [74, 182]. This is best illustrated when we recall the major molecular characteristics of the principal plasma proteins. Fibrinogen has been found to have the highest intrinsic viscosity among the plasma proteins [130]. Consequently, its intrinsic viscosity number exceeds that of IgM, despite the fact that the latter has almost three times the molecular

weight of fibrinogen. On the other hand, fibrinogen is known to be a long, nodular rod-like protein, with axial length-width ratio of 15:1 [127, 208], whereas single IgM molecules, according to recent electron microscopic studies [37], appear to be 'spherical', five-legged spider-like particles (fig. 1), which, however, easily may aggregate and thus form hyperviscous 'macromolecules'.

When the effect of the protein concentration on the viscosity of a solution is now considered in the light of the above molecular characteristics, it can be better understood why an increase in the concentration of a protein with a higher intrinsic viscosity augments the viscosity of the solution more than a similar increase in the concentration of a protein with a lower intrinsic viscosity. These facts explain many of the rheological and concomitant clinical effects of various hyperproteinemic states, as will be discussed in subsequent chapters.

Several investigators (10, 31, 86, 88, 115, 154, 182, 185] have, however, observed considerable individual differences in the concentration-viscosity behavior and/or in the intrinsic viscosity of 'similar' proteins. These different rheological properties may be partly explained by variable experimental conditions, but presumably they also reflect the fact that factors other than concentrations and molecular characteristics influence the viscosity of isolated protein solutions. Such additional variables may be differences in hydration (solvation), flexibility, pH, ionic and temperature sensitivity and protein interaction (aggregation tendency) due to variable intrinsic molecular properties and to variations in lipid and carbohydrate contents [78]. So far, the influence of these determinants of viscosity has been documented only in a few studies [31, 88, 182, 185], presumably because of their minor effects and more especially because of difficulties in methodology.

The Effects of Protein Interaction (Aggregation)

In view of the ensuing discussion of the pathogenesis of HVS, the influence of physical protein-protein interaction (aggregation) on the viscosity will be briefly reviewed here on a physicochemical basis.

The preceding presentation has shown that the more asymmetrical a protein molecule is, the higher its viscosity will be. It is known from the colloid and polymer sciences that macromolecules like proteins may have two types of molecular interaction, namely, purely physical ones and 'chemical' ones. The physical effect is enhanced in more concentrated solutions, where it is more likely that molecules, and especially asymmetrical ones, will come in contact and eventually become linked by weak bonds. The conditions most favorable for such associations and formations of new structures (aggregates) are these: If the temperature is sufficiently low; if the basic molecules have favorable intrinsic properties which enable new linkings (like Y- or 'spider'- shaped polypeptide chains of immunoglobulins, molecules with different electric charges, etc.); and if the molecules can bond water because of their high carbohydrate content (like IgM and IgA) and thus become more swollen and more viscous [78, 88]. If the solution, moreover, is minimally disturbed mechanically, it may change from a sol to a gel. Such reversible sol-gel transformations have been called thixotropic and the phenomenon itself thixotropy [50, 208]. As a consequence such a 'solution' begins to conform to non-Newtonian rheological behavior and its 'viscosity' is no longer constant but usually decreases with increasing shear stress and shear time [50, 170, 208].

Considering the above remarks on the physical basis of molecular interaction, it is not surprising that in some pathological cases of plasma cell dyscrasias, hyperviscosity of the plasma and the whole blood have been shown to occur as a combined result of protein-protein and red cell-protein aggregation [179, 182, 208].

With regard to human blood plasma and serum, we can summarize it thus: the more they contain proteins of large molecular size and anisometric shape which are also sensitive to changes in the surrounding temperature, pH and hydration, the higher will be their viscosity [74, 182].

The Clinical HVS

Prevalence

Information about the prevalence of HVS in plasma cell dyscrasias is very sparse, primarily because of the relative rarity of the basic diseases. Moreover, until quite recently the concept of the syndrome and its importance have been appreciated by only a few investigators and clinicians interested in rheological phenomena connected with immunohematological disorders. Even among them, the concept of HVS is so new that it has not been possible so far to delineate it thoroughly by means of a symposium, or in some similar way. It is shortly dealt with in recent editions of textbooks, monographs and articles on internal medicine, hematology and related subjects [36, 50, 61, 99, 100, 132, 134, 170, 180, 224]. It is hoped that these will broaden the interest in phenomena related to blood and plasma hyperviscosity and thus, presumbly, we shall be better informed about their pertinent features in the near future.

For the reasons discussed in previous chapters, a clinical hyperviscosity syndrome quite frequently complicates primary MW. In their concluding paper, FAHEY *et al.* [59] report that 18 of their 25 (72%) MW cases had symptoms and signs attributable to hyperviscosity. MACKENZIE *et al.* [114] first reported clinical manifestations of the HVS in 10 out of 15 MW patients (66%) at some time during follow-up, but more recently in a larger material they found them to exist in only 33% [113]. That serum hyperviscosity produces clinical symptoms and signs in more than half the MW cases has been also reported by others [147]. On the other hand, further authors have observed them more infrequently (90, 108, 153, 217]. The present author's experience with 24 cases of macroglobulinemia showed that hyperviscous sera

caused clinically detectable symptomatology in about a third of the cases, but a considerable number of them had rather low macroglobulin levels [182]. When the possible incidence of HVS is calculated according to the criterion of a relative serum viscosity of 5 or more, about 55% of the cases in reported series seem to exceed this limit and may thus be potential candidates for hyperviscosity manifestations. As a matter of interest, it may be mentioned in this connection that a fatal hyperviscosity syndrome due to macroglobulinemia has been recently described in a dog [85].

From the above observations it can be concluded that on an average a clinical HVS occurs in about half of the classic cases of MW.

In contrast, the prevalence of HVS in MM seems to be considerably lower [31, 56, 57, 82, 95, 115, 144, 179, 182, 194, 215, 220, 235]. Among the 39 MM cases of AZZENA *et al.* [5], hyperviscosity was present in four (2 IgG, 2 IgA) cases, i.e. 10%. In a smaller series with MM, clinical evidence for HVS was reported in 2/16 of those with IgG myelomata (12.5%) and 2/5 of those with IgA myelomata (40%) [216]. The author has found three cases out of 30 IgG MMs (10%), and two clinically evident HVS cases in a total of 12 patients with IgA MM (16.6%) during the course of ten years. In two recent series of IgG myeloma [144, 230] the frequency of the HVS was 4 and 8%, respectively. Thus, the average prevalence of clinical HVS in MM seems to be about 8% when all forms of MM are considered, including the not-so-infrequent Bence Jones (light chain) myelomatosis, where clinical hyperviscosity manifestations have not been observed [182].

Clinical Manifestations

Owing to the scope of this review, only those clinical symptoms and signs of MM and MW that are pertinent to the rheological abnormalities in these diseases will be considered in what follows. Also, treatment and pathogenesis will be dealt with from the rheological point of view after the clinical symptomatology and laboratory findings of HVS have been discussed.

General symptoms. Plasma cell dyscrasias commonly display some symptoms that are also encountered in other malignancies. Although such general symptoms as weakness, excessive fatigue, dyspnea, anorexia and weight loss are usually regarded as products of anemia, toxemia, hypermetabolism, impaired renal and neurological function, etc., it seems, however, that abnormal blood rheology may also be partly responsible for them. A significant

reduction of serum hyperviscosity by plasmapheresis has been reported to give both subjective and objective improvement in these general expressions of the diseases [6, 58, 77, 144, 175, 179, 181, 215].

Bleeding. Apart from the above general symptoms, a diffuse hemorrhagic diathesis constitutes the most common presentation of HVS both in MW [32, 59, 77, 90, 103, 105, 113, 121, 135, 138, 147, 153, 154, 175, 200, 203] and in MM [3, 4, 6, 14, 25, 44, 47, 62, 93, 95, 138, 144, 179, 187, 191, 215, 232]. It frequently occurs as a spontaneous epistaxis or oozing from the gingivas, and undoubtedly forms the most upsetting manifestation for the patient and the medical personnel. Sometimes purpura, ecchymoses, rectal or vaginal hemorrhages or persistent bleeding after tooth extraction or after similar minor procedures cause admission to hospital. Infrequently, even melena or hematuria can be prominent symptoms [6, 19, 44, 103, 113, 135, 144, 172, 179, 191, 232]. Especially, however, nasal bleeding has been reported as severe, recurrent and difficult to control [59, 95, 131, 144, 179, 215]. Patients have often woken up with their mouth full of blood [203]. In some cases indeed, bleeding, has been so profuse that it has prompted repeated transfusions and iron therapy because of the progressive anemia. There is, however, sufficient positive evidence in favor of plasmapheresis as the first choice of means of controlling the bleeding in HVS of plasma cell disorders [6, 67, 77, 95, 103, 131, 153, 175, 179, 181, 232]. In certain cases a dramatic stopping of the bleeding, with simultaneous other beneficial effects, has been noted after the removal of as little as 500–1,000 ml of plasma [67, 134].

Ocular manifestations have been observed in cases of HVS ever since this abnormality was first described by WINTROBE and BUELL [214] and by WALDENSTRÖM [200]. These occur in MM and especially in MW, and have been reviewed by several authors [16, 32, 45, 107, 176]. The early reports on ocular findings are quite comprehensible, because visual symptoms are common and can easily be confirmed by an almost pathognomonic ophthalmoscopic picture which has been called 'fundus paraproteinemicus' by BERNEAUD-KÖTZ and JAHNKE [16] and 'fundus viscoproteinemicus' by WALDENSTRÖM [203].

Ocular symptoms and signs are, indeed, the next most frequent abnormality of HVS after the bleeding tendency [6, 59, 105, 113, 123, 142, 144, 179, 220, 232]. The patients usually complain of a gradual, or more rarely of a sudden visual impairment, diplopia, haziness, loss of near vision, and even total blindness [6, 179, 181].

Serial *funduscopic findings* by FAHEY *et al.* [59] have revealed first a

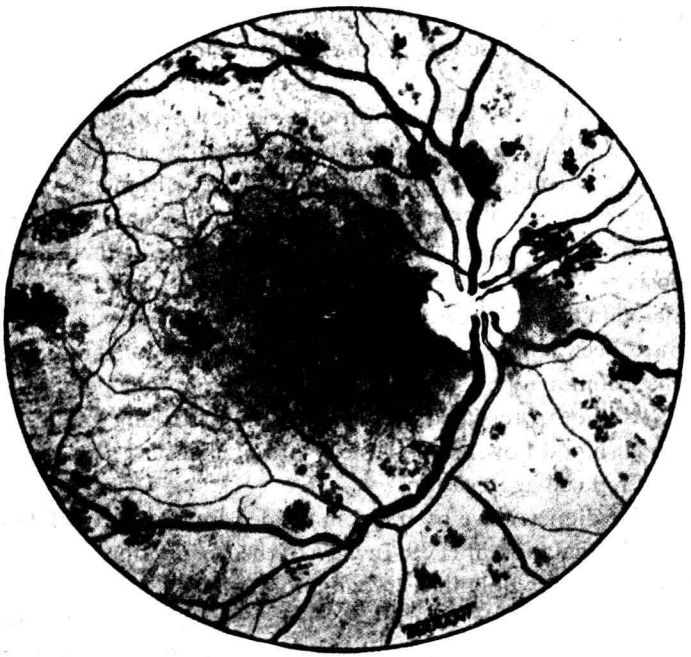

Fig. 2. Typical retinal picture in a case of macroglobulinemia with the HVS, showing dilated, tortuous, 'sausage-like' veins and scattered retinal hemorrhages. Reproduced from FERRIMAN and ANDERSON [60] with the kind permission of the authors and publisher.

progressive distention of retinal veins. This is followed by their increasing tortuosity, and 'sausage'-like appearence due to constrictions near a-v crossings and to beading and dilatation of small veins. At this stage (fig. 2), all types of retinal hemorrhages with subsequent exudates may appear between the vessels [16, 45, 59, 107, 142, 176]. Finally, the funduscopic picture may simulate true papilledema associated with retinal vein thrombosis. Therefore, it is not surprising that some reports mention suspicion of a brain tumor before the specific diagnosis of MM or MW was made [59, 191]. Most of the vascular changes thus occur in the venous side, but recently arteriolar-capillary microaneurysms have also been reported in some cases [59, 66, 107].

With possible exceptions of cases with cryoglobulinemia, this sometimes dramatic although individually variable retinopathy has shown a rather good correlation to serum viscosity values [6, 13, 59, 176, 179]. Moreover, in a surprisingly short time (one to two days) it can be almost normalized after specific therapy for hyperviscosity and hypervolemia by plasmapheresis [107].