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HIGHLIGHTS OF THE IIIrd YAROSLAVL INTERNATIONAL CONGRESS ON HEMORHEOLOGY, July 29-31, Yaroslavl, Russia.

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This congress, which is the third of this series, was organized by our Russian colleague Alexei Muravyov and his coworkers under the auspices of the International Society of Clinical Hemorheology and the European Society of Clinical Hemorheology. It included 95 papers from 289 authors, most of them from the Community of Independent States (Russia, Ukraine, Belarus), but also from Austria, Bulgaria, France, Germany, Greece, Hungary, Italy, Turkey, United Kingdom and United States of America. On the whole, these two days of lectures, oral presentations and posters provided a synthesis of the modern concepts in hemorheology and demonstrated the wide interest for clinical hemorheology in the countries of the former Soviet Union, with a constant attention to the complementarity between in vitro rheological measurements and in vivo hemodynamic studies.

Vitality of hemorheology in Russia is further demonstrated by the appearance of a new international journal called "Thrombosis, Hemostasis & Rheology" **.** Founded by Eugene V. Roitman and NA Kalinin, this journal (texts mostly in Russian and abstracts in English) includes a lot of papers related to hemorheology. Informations can be found on the website at www.aha.ru/~hemostas. Contact address: Eugene V. Roitman at hemostas@aha.ru.

The congress started with a plenary lecture on the modern aspects of disseminated intravascular coagulation (DIC) by prof I. Bokarev (Moscow). Prof Bokarev pointed out that physicians are not always aware that there is a constant presence of markers of intravascular coagulation in plasma even in healthy individuals. Some physiological situations such as exercise may exacerbate this process. One could thus define physiological boundaries for "normal" DIC. Beyond these

boundaries, excess DIC will induce bleeding, multiple organ damage, and become an extremely severe disease.

BASIC CONCEPTS

A plenary lecture by H. Schmid-Schönbein (Aachen, Germany) reviewed the rheological factors that determine both intravascular flow and transcapillary exchange, under the light of a new heuristic mathematic backgound: the percolation theory [1]. This theory belongs to the field of non-linear rheological physics, and is employed to describe the universal traits of evolutions converting oceans with discrete islands into continents with discrete lakes. This theory can be applied to describe the phase transition from the fluidal to the aggregated state of individual erythrocytes. Blood can be actually described as a multiphase suspension with transition from the behavior of a highly fluid (and self-fluidizing) emulsion-like material to that of self-viscidizing compacted suspension. Transition between these two states can be extremely rapid due to the self-amplification that characterizes both situations. This approach provides a clear theoretical background of several complex hemorheological phenomena such as the axial drift of red cells with formation of the free-plasma layer, the Fahreus and Fahreus-Lindquist effects, the network Fahreus effect and the reversal of the Fahreus-Lindquist effect in venules due to hypokinetic flow conditions. On the whole, professor Schmid-Schönbein insisted on two simple messages for hemorheologists. First, whole blood viscosity is a totally irrelevant measurement for the physiologist, and should be replaced by measurements of hematocrit, plasma viscosity, red cell deformability and aggregability, each of them indicating actually a "potential risk of heterophase transition" from a fluid to a near-solid state. On the other hand, beside hemodynamic consequences of these heterophase effects, hemorheologists should give more attention to two important phenomena related to these effects: hidden acidosis in perfused tissues, and white cell margination due to red cell aggregation (Fahreus-Vejlens effect), which is probably important in white cell physiology and even more in pathophysiology.

Hematocrit

H. Schmid-Schönbein [2] reminded us the importance of this simple factor, which was in fact already demonstrated many years ago by epidemiologists when pernicious anemia was not treated: anemia, in that case, appeared the only epidemiological factor associated with a reduced incidence of atherosclerosis in western countries. Hematocrit is one of the factors that can locally induce the process of reversible solidification of blood in some territories. Therefore, reducing it has large beneficial consequences. L. Bogar (Pecs, Hungary) reviewed the large body of evidence supporting the validity of normovolemic hemodilution in vascular diseases and proposed a large multicentric trial on this procedure [3].

Red cell aggregability

Why do red cell aggregate? In early studies in the seventies, Shu Chien gave some evidence for the theory of bridging: macromolecules would induce bridges among erythrocytes, leading them to aggregate. However, the two complementary lectures given by HJ Meiselman (Los Angeles, USA) and O Baskurt (Antalya, Turkey) seriously challenged these classical statements [4-5]. First, red cell shape and surface properties modify red cell aggregability (for example less deformable red cells are

generally also less aggregable). In addition, the elegant model of PEG-coated red cells developped currently by HJ Meiselman's team in Los Angeles gives some evidence that cell surface depletion is likely to be the major explanation for aggregation. However, this model is still under development.

Little by little, HJ Meiselman's statement that one should always study separately red cell and plasma factors in situations where RBC aggregation is increased are more widely followed by all clinical hemorheologists. In animals, M. Rampling (London, UK) reminded us the strange, albeit classical observation that red cell aggregation is higher in "athletic" species, ie sheeps aggregate very little compared to lions or horses. It can be demonstrated by suspension experiments on various dextrans (compared to plasma) that this difference is due to red cell properties, regardless hematocrit and plasma. Athletic animals have, for some until now unknown physiological reason, more "sticky" red cells [6]. A pathologic condition where RBC aggregation is also frequently found to be increased is diabetes. Very interestingly, M. Rampling (London, UK), when studying separately red cell factors and plasma factors, demonstrated that the diabetic red cell is inherently less aggregable although its surrounding medium is frequently rich in pro-aggregating proteins that result into higher aggregability in native plasma. This finding is also reported by TA Blokhina (Ivanovo, Russia) who observes that diabetic red cells are actually less aggregable when resuspended in a standardized medium rather than native plasma [7].

Some red cell factors of erythrocyte aggregability have been investigated by the team of Alexei Muravyov in Yaroslavl. Consistent with some previous studies of HJ Meiselman's group, A Muravyov demonstrates the importance of red cell calcium in this process. He observes that the calcium blocker Verapamil decreases red cell aggregability, regardless the age of red cells, without any effect on deformability [8]. I A Tikhomirova (Yaroslavl, Russia) studied red cell aggregation after incubation of cells in presence of chlorpromazine (a calmodulin inhibitor) and provided some evidence of a role for calmodulin in calcium-related pathways involved in the regulation of aggregability [9].

A lot of information concerning plasma factors involved in red cell aggregation was also presented. In his lecture, H. Schmid-Schönbein (Aachen, Germany) showed that experimentally rising fibrinogen levels always resulted in a decreased microcirculatory perfusion with 30-40% veinules excluded from perfusion. On the whole, plasma levels of fibrinogen in all of us seem to be far above what is needed for normal clotting. They might reflect some degree of chronic inflammatory status which is deleterious for microcirculation. Experimentaly, reducing fibrinogen below this level improves microcirculatory perfusion. [1]. TA Blokhina (Ivanovo, Russia) also observes that red cell deformability and aggregability are dependent upon composition and physico-chemical properties of the plasma [7].

Another important and until now poorly known factor might be acid-base status, as shown by I A Tikhomirova (Yaroslavl, Russia) who studied red cell aggregation after incubation at various pH levels from 7.2 to 7.8, and showed that alcalosis increases aggregability [10]. Hormonal status also markedly modifies red cell aggregation. Two posters by the team of Prof. U Windberger from Vienna (Austria) gave a description of the hemorheological tableau of two spontaneous endocrine diseases in dogs. Diabetes mellitus results in a hyperviscosity syndrome due to increased aggregability and increased pro-aggregant plasma proteins, as previously observed in humans. This hyperviscosity does not appear to be related to prognosis [11]. The Cushing syndrome is also

associated with increased viscosity, apparently explained by high plasma fibrinogen, high plasma viscosity and high red cell aggregation [12]. Sex hormone status in females was investigated in rats by Yerer (Kaysery, Turkey) who showed that ovariectomy did not modify red cell rheological properties, while very high dose estrogens (20 µg/d, ie the estrogen content of a human contraceptive pill designed for the size of a human body) decreased red cell deformability [13].

Finally, the old question: does red cell aggregation improve or impair microcirculation? It is known that in physiology aggregation is a major mechanism of the Fahraeus-Lindqvist effect and thus to improve microcirculatory hemodynamics. In pathology, on the other way about, it is associated to impaired oxygen distribution and increased peripheral resistance. Clearly, the two mechanisms can be induced in the same animal, as shown by H Belabbas (Montpellier, France). This investigator reported in rats from the same breds that increased red cell aggregation in the case of a physiological improvement by training is associated with a decrease in peripheral resistance while in the case of experimental angiotensin II-induced hypertension it is associated with an increase in peripheral resistance. [14]

Red cell deformability

Red cell deformability remains an important factor to study in physiological and pathological conditions, as was reminded in H. Schmid Schönbein's lecture [1]. Its fundamental mechanism, the "tank treading" motion has now been extensively investigated and it has become clear that it is not a simple in vitro observation but that it occurs in the whole circulation. A special problem related to tank treading is that the surrounding environment (plasma, vessel wall) influences this process and thus deformability itself, which is not in fact a property of the RBC "alone" but a property of the RBC in interaction with its environment. This has direct consequences on in vitro assessment of deformability. For instance calculation of RBC deformability indices from viscometry (such as the Ditenfass's "Tk") is also influenced by hematocrit and plasma viscosity.

Some technical works on new methodological approaches of this measurement by rigidometry associated to morphologic analysis were presented. They appear to be sensitive enough to detect very early disturbances [15].

Experimental stress rigidifies the RBC. Experimental oxidant stress thus reduces the ability to transfer O2 to tissues, a pathologic disturbance which does not appear to have any adaptative role in physiology, according to Dr Zinchuk (Grodno, Belarus) [16]. Some new drugs developped from ecdysteroids found in plants in the team of MB Plotnikov (Tomsk, Russia), such as Ascovertin, improve red cell deformability, while they decrease hyperaggregability and fibrinogen [17]. More classically vitamin C has also an almost complete protective effect on RBC rigidification induced by experimental oxidant stress [18].

Ageing is a situation which rigidifies the red cells and makes them more aggregable: these two phenomena are to some extent dissociated since the calcium blocker verapamil reverses hyperaggregability but not stiffening [19]. In addition, the older is the blood donor, the faster his red cells become hyperaggregable and less deformable when stored in vitro: this suggests that red cells from old people are prone to accelerated ageing, at least from an hemorheologist's viewpoint [20].

Relationships between aggregability and deformability of red cells were also studied by J Rozenberg (Moscow, Russia) with red cells resuspended on dextrans. On the whole the more pro-aggregant is the medium (plasma>dextran 70>dextran 40), the longer will be the RBC transit through 3 µm pores, as previously shown with 5 µM pores [21].

EXERCISE AND OTHER STRESSES

Hemorheologic fitness: four steps?

Exercise has several hemorheological effects that have been previously proposed to be classified as a triphasic phenomenon: acute effects (hyperviscosity mostly due to hemoconcentration but also to some erythrocyte alterations) ; delayed effects (hyperhydration resulting in hemodilution and hypoviscosity) , and a chronic situation which can be termed hemorheologic fitness. Dr Brun (Montpellier, France) focused in his presentation on this last stage of hemorheologic effects of exercise, pointing out that, according to training intensity, it may result in different aspects. In endurance athletes (eg, cyclists), there is mostly a chronic "hyperhydration-dilution status", but some intriguing modifications of red cell properties can also be found, in connection with metabolic and hormonal changes (insulin sensitivity, growth hormone and IGF-I status...). In sports where strength is improved rather than endurance red cell aggregation and deformability are improved without marked changes in body fluid status, and are correlated to body composition (percentage of fat) and the balance of substrate oxidation at exercise. In markedly sedentary obese, insulin resistant patients submitted to a therapeutic protocol of training, the parameter which is mostly improved is plasma viscosity, which appears to reflect in this case the plasma protein pattern related to the metabolic disorders (fibrinogen, lipoproteins...). Finally, overtraining reverses this picture of "hemorheologic fitness", mostly by inducing a reversal of the "hyperhydration-hypoviscosity" pattern [22]. Consistently, a study by Dr Konstantinova (Minsk, Belarus) shows a negative correlation between cortisol (a hormone depressed by training and activated by overtraining) and blood fluidity in athletes [23]. On the whole, according to the training volume, there are at least four different aspects of this chronic hemorheologic effect of regular exercise [22].

H. Schmid Schönbein mentioned recent experiments in his laboratory that lead to the conclusion that hemodynamic conditions in muscular microvasculature result in a very special rheological behavior of blood components. Hematocrit in exercising muscle has no influence on muscle perfusion, while it is of course, at rest, when shear stress decreases, a factor favorizing hydrodynamic viscidation and even in some situations stop flow (as observed in EPO- doped athletes). Actually during exercise the intramuscular viscosity of blood becomes that of plasma alone, allowing red cells to circulate very easily regardless their individual rheological properties [1]. Accordingly, plasma viscosity is likely to be the most relevant hemorheologic determinant of microvascular circulation in the exercising muscle.

Acute effects of exercise have been investigated in several papers. A Muravyov [8] compared the hemorheological response to exercise of "young" and "old" red blood cell and observed that postexercise red cell stiffening mostly affects young erythrocytes, ie those which migrate at the top of the RBC suspension after centrifugation. O Yalcin (Antalya, Turkey) investigated carefully the time-course of selected parameters during and for 24 hr after "aerobic" and "anaerobic" exercise bouts in

sedentary men. This study evidenced strong hemorheologic alterations during the anaerobic exercise (Wingate test) and even more interestingly after 45 min a delayed peak of leukocytosis which was followed by a further rigidification of red cells [24]. This kind of ultra-short "all of out" exercise induces thus acute and delayed metabolic and hemorheologic disturbances which result in a transient hypeviscosity which was not observed after aerobc exercise. Actually, the term "anaerobic", albeit classical, is not physiologically accurate for such exercise bouts where there is apparently no lack of O2 in tissues. Nonetheless, the massive processing of carbohydrates through the initial steps of the glycolytic pathways results in a huge production of blood lactate (above 10 mmol/l) which may explain a part of the observed phenomenon.

True anaerobiosis may be found at exercise in the case of peripheral vascular patients, as investigated since more than 15 yr by the team of S. Forconi (Siena, Italy). This team presented an analysis of the consequences of exercise in normal and vasculopathic patients during and after exercise stress testing [25]. The postexercise transient hyperviscosity has a longer duration in arteriopathic patients. For the authors, this is due to the endothelial dysfunction which blunts an homeostatic mechanism involving NO in response to the increased shear stress resulting from hyperviscosity. In addition, there is an increase in red cell intracellular calcium as a consequence of exercise.

Another intriguing example of differences in hemorheological response to exercise among papulations was reported by Ph Connes (montpellier, France), who described higher hematocrit and hematocrit response to exercise in elite underwater fishermen compared to endurance athletes, the latter exhibiting by contrast a paradoxical decrease in red cell rigidity at exercise. The authors hypothesize that both particularities could have a physiological significance related to the kind of exercise these athletes regularly perform [26]. One of the major factors of hemorheologic fitness was well analyzed by A.A. Melnikov (Yaroslavl, Russia) who shows that blood rheology is highly correlated to the lipid profile even in a physiological range, so that in physiological conditions, far from the situations of lipids disorders that have focused all the attention until now, triglycerides and cholesterol are important determinants of red cell deformability and aggregability in athletes [27].

The effect of nutrition on hemorheology in athletes was investigated by several authors. O. Kuru (Antalya, Turkey) reported that vitamins C and E prevented RBC stiffening induced by exhaustive exercise in rats, probably via an anti-oxidant effect as suggested by TBAR measurements [28]. Zaitsev (Yaroslavl, Russia) studied the effects of 3 weeks vitamin and micronutrient supplementation in students involved in leisure sports. This treatment improved iron status and immunity [29].

Smirnov (Kostroma, Russia) aimed at comparing two examples of circulatory hypoxia: one induced by acute hemorrage and characterized by an hypoviscosity syndrome (low hematocrit beside 30 % , plasma viscosity lowered by 14%) with decrease in TcPO2 by 80-95%, and on the other way about exhaustive physical overload, which results in hyperviscosity (raised hematocrit and plasma viscosity by respectively 5% and +12%) with an increased TcPO2 (+24%). This comparison between two extreme examples of hemorheologic changes associated with major alterations in O2 transfer to tissues needs to be more extensively developped. [30].

CLINICAL SITUATIONS

Prof. S. Forconi (Siena, Italy) analyzed from the clinician's point of view the relationships between flow and pressure properties of blood in both arterial and venous circulation [31]. In ischemizing vascular diseases there is a “Blood Hyperviscosity Syndrome” which has been referred as “Secondary” because blood rheological variations are due to flow and pressure variations occurring in the arterial tree, while in the case of “Primary Blood Hyperviscosity Syndrome” there is a primitive blood hyperviscosity which determines a reduction of the blood perfusion in the tissues. In veins, during artificially provoked stasis there are drammatic changes in the flow properties of blood and simultaneously a release of substances coming not only from circulating cells but also fom the endothelium. Actually, current physiology challenges the concept of "blood viscosity" and clinicians should be aware that viscosity values *in vivo* are not the same in all the different sections of circulation, since they change according to the modifications of the flow, volume, velocity and pressure of the blood, both in normal and pathological conditions. In addition, measurements of rheological parameters *ex vivo* give different values depending on the site of withdrawal, so that rheological properties of blood are different in the arterial tree and in the venous tree. Thus, measuring "viscosity" is surely irrelevant, and we should rather try to select parameters indicating a "risk of heterophase transition" in given territories and situations. According to this concept, AG Gushchin (Yaroslavl, Russia) proposed a classification in three degrees of hyperviscosity syndromes analyzed by the viscosity parameters and not by viscosity alone [32].

On the other hand, these considerations imply that it is interesting to always try to analyze hemorheological data in association with hemodynamic measurements. For instance the microcirculatory impairment found in acute respiratory infections and influenza has been studied by Devyatckin (Moscow, Russia) and appears to be related to red cell hyperaggregability, so that, interestingly, its severity is greater in diabetes [33]. Another example of clinical study combining microcirculation and hemorheology is the preliminary report by E. Konstantinova (Minsk, Belarus) of a relationship between red cell rheological properties and TcPO2 in patients suffering from coronary heart disease [34].

A large interest for the hemorheologic consequences of acute phase reaction can be seen when looking at the list of papers presented. For instance, Utkina (Yaroslavl. Russia) observed in systemic lupus erythromatosus the classical pattern of free-radical related hemorheologic syndrome with an increase in both red cel rigidity and red cell aggregation [35], as did also Korotaeva (Moscow) in osteolytic psoriasic arthritis. Lebedeva (Ivanovo, Russia). described in patients with acute rheumatic fever and rheumatic heart disease an increase in both stiffness and aggregability of erythrocytes and hypothesized that this pattern may affect circulation in these patients [36]. Vilanskaya (Minsk, Belarus) reported a hyperviscosity syndrome in rheumatoid arthritis, and described its modifications during drug therapy [37]. A.P.Malkova (Yaroslavl, Russia) observed in rheumatoid arthritis more rigid red cells, which became more deformable after interval hypoxical training [38]. Baev (Perm, Russia) also described a hyperviscosity syndrome in young men suffering from herpes infection [39].

The first description of the hemorheologic characteristics of Gaucher's disease was given in a poster by Bax (London, UK) who compared 11 splenectomized patients suffering from Gaucher's disease, 16 non-spelenectomized patients, and 12 controls. Actually the picture is not very clear since a higher red cell aggregability and rigidity (associated with a higher MCV) was observed only in the

group who had undergone splenectomy. Thus, whether the disease itself when it becomes severe and requires splenectomy, or splenectomy alone, are the explanation of this picture is not clear [40].

Pulmonary edema, another mysterious pathologic process involving microcirculation, was studied by V.P.Mikhailov (Yaroslavl, Russia) who evidenced a pivotal role for endothelial cells in lung capillaries, as can be also reflected by circulating endothelial cells in rats plasma, which could have some diagnostic value at least in the case of experimental pulmonary edema [41].

Sirotin (Khabarovsk, Russia) investigated microcirculation in hemorragic fever with renal syndrome (HFRS) and observed a microvascular dysfunction associated with a red cell hyperaggregability [42]

Diabetes is traditionally one of the most widely investigated diseases in clinical hemorheology. However, the team of HJ Meiselman (Los Angeles, USA) presented a new study on erythrocyte aggragability during improvement of glycemic equilibrium by treatment. In type 2 (non-insulin-dependent diabetes) they were able to demontrate that improvement of the metabolic equilibrium was associated with an improvement of blood rheology, and that actually, beside the well known changes in plasma factors, there was also an already unknown improvement of corpuscular factors of red cell aggregation, which remains to be studied more extensively [43]. On the whole, the hemorheologic alterations observed in diabetes are an example of the relationships between metabolic disturbances and hemorheology. More generally, all states of low insulin sensitivity are associated with hemorheologic alterations, the most specific, albeit poorly sensitive, being high plasma viscosity which is in turn easily improved by treatments aiming at correcting the metabolic defect. In addition, another hormonal axis that has surprisingly received until now little attention from hemoheologists seems to be the growth hormone - IGF-I axis which is a major regulator of body composition (fluid volumes, fat mass) and plasma protein composition. Growth hormone itself seems to be a regulator of sweating capacity which may influence plasma viscosity, IGF-I seems to have direct effects on red cells (decrease in deformability?) and the binding protein IGFBP-1 seems to modify body fluids in some situations while it exerts direct effects on bone marrow erythropoietic stem cells [44].

The evolution of blood rheology and microcirculation during the course of chronic renal failure was investigated by TM Nenasheva who found a decrease in microvascular blood flow with a parallel increase in red cell aggregation, associated with the development of more arterio-venous shunts and rised plasma levels of fibrinogen B [45].

A poorly investigated field in hemorheology is that of congenital heart disease which was studied by E Roitman, (Moscow, Russia). Investigating by sophisticated viscometry the suspension stability of blood, this author evidenced several degrees of compensation of the hemorheologic disturbances. In the case of low stability of blood, there was a higher hematocrit associated with microcirculatory disturbances [46].

Ischemic heart disease has been studied by Konstantinova (Minsk, Belarus) who found high blood viscosity correlated to the importance of lipid abnormalities. High cholesterol was correlated with low red cell deformability and high triglycerides were correlated with high red cell aggregation [35]. Accordingly, in 25 elderly patients aged 60-74 yr, Lishnevskaya (Kiev, Ukraine) evidenced

correlations between serum triglyceride and cholesterol levels and the extent of both RBC stiffness and aggregation. Interestingly, membrane lipids were also assayed and appeared to explain this relationship [47].

The hemorheologic aspect of neurotic disorders was studied by Ryantsieva (Tomsk, Russia) who showed elevated values of both rigidity and aggregability of red cells in the initial period. The authors proposed that these alterations were related to stress.

Pudova (Moscow) compared the hemorheologic aspects of several types of hemolytic anemia. The most marked alterations were found in hereditary spherocytosis where red cell deformability was markedly decreased, while red cell aggregation strength was unaffected.

Several interesting studies were devoted to stroke. AP Skorokhodov (Voronezh, Russia) presented a large study on 425 patients with stroke, always confirmed by tomodensitometry and nuclear magnetic resonance imaging, and showed their biologic profile which includes high hematocrit, high fibrinogen, and an hypercoagulability state [48]. A more precise analysis of this picture was given by Prof Ionova (Moscow) who presented a study on hemorheology, hemostasis, and fibrinolysis in the acute phase of cerebrovascular diseases in 146 patients with atherosclerosis. The study included 33 reversible cerebrovascular events. It appeared that hyperviscosity was a common feature of all cerebrovascular events, but irreversible ones were also characterized by an hypercoagulable state which was not seen in reversible events. This suggests that during reversible events the vessel wall has conserved its fibrinolytic potential which may thus prevent the hypercoagulability state [49]. An interesting approach to the pathogenesis of these hemorheologic and hemocoagulatory disturbances observed during stroke was shown by Petrischev (St-Petersburg, Russia) who investigated experimental stroke induced by clamping of the two carotid arteries in rats. Interestingly, this experiment induced in mesenteric vessels alterations of thromboresistance which were preventable by the NO-antagonist L-NNA. Thus, postischemic reperfusion of the ischemic brain has resulted in an inadequate release of NO which has induced systemic disturbances measurable in mesenteric microcirculation [50]. IE Savelyeva (Ivanovo, Russia) presented an interesting relationship between the size of cerebral infarction as measured by tomodensitometry and nuclear magnetic resonance imaging and blood rheology. She observes that red cell rheologic abnormalities (mostly deformability measured by the initial flow rate of filtration, but also aggregation) reflect the size of the ischemic lesion [51]. On the whole this series of russian papers presented at this congress appear to give a new interest to the quite classic question of hemorheology and stroke.

LEUKOCYTE STUDIES

The leukocyte, the most mysterious frontier of current hemorheology, was far to be absent from this congress. Fyodorova (Yaroslavl, Russia) described changes in adhesive properties of white blood cells in response to overheating and experimental inflammation, while water deprivation alone did not affect these properties. [52]. S.V. Mainugin (Yaroslavl) observed that the treatment of leg ulcers by discrete plasmapheresis reduced blood viscosity, red cell aggregability, fibrinogen and red cell adhesiveness [53].

THERAPEUTIC APPROACHES

The most efficient hemorheologic treatments, hemodilution and plasmapheresis, were presented. Hemodilution was reviewed by Prof L. Bogar (Pécs, Hungary), who stressed that, despite its great efficiency which is now well established, it needs now multicentric high standard trials [3]. Discrete plasmapheresis was studied by SV Mainugin (Yaroslavl, Russia) who showed a reduction of blood viscosity, red cell aggregability, fibrinogen and red cell adhesiveness under this treatment in 23 patients suffering from venous leg ulcers and exhibiting markedly disturbed hemorheologic parameters [53].

The treatment of hypertension by angiotensin converting enzyme inhibitors (ACEI) was extensively studied by V.V. Yakusevitch (Yaroslavl, Russia) who demonstrated a decrease of red cell aggregability under five ACEIs, the strongest being spirapril (10 mg/d) (-36%) followed by fosinopril. These drugs also decrease fibrinogen. A moderate but significant improvement of blood rheology was also found with the diuretic indapamide (1.5 mg/d) which decreases both hematocrit and plasma viscosity [54]. Pliachiechnikov (Barnaul, Russia) reported also an improvement of blood rheology in patients treated with ACEI (enalapril and fosinopril compared to controls) 24-72 hr after acute myocardium infarction. This treatment reduced red cell aggregation as soon as the 1st week, and more later, at the 3rd wk, red cell rigidity. Plasma viscosity did not differ with the control group [55].

Beneficial effects of new rheo-active drugs developped in Russia were also described. Aliev (Tomsk, Russia) described the properties of plant extracts containing ecdysteroids [56] such as ascovertin which improves red cell deformability and decreases both red cell aggregability and fibrinogen [17]. TM Plotnikova also described a reduction of red cell aggregation with a parallel improvement of blood flow with cerebrocrast (derived from 1-4 dihydropyridine) and nooglutil (derived from 3-oxypyridine) in the initial stages of experimental cerebral ischemia [57].

Sirotin (Khabarovsk, Russia) investigated the effects of a new drug developped in Russia, dalargin, which is an analogue of the neuropeptide leu-enkephalin, on blood rheology and microcirculation in 115 diabetics. There was an improvement of red cell deformability and a decrease in hyperaggregability, associated with measurable microcirculatory improvements. Given intravenously, this peptide seems to be beneficial for wound healing in diabetic feet [58].

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