



Pergamon

Clinical Hemorheology, Vol. 16, No. 1, pp. 3-9, 1996  
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0271-5198/96 \$15.00 + .00

PII S0271-5198(96)00002-X

9TH EUROPEAN CONFERENCE ON  
CLINICAL HAEMORHEOLOGY  
Siena, Italy 28 June - 1 July, 1995

## Fåhræus Lecture

### Quo vadis Clinical Haemorheology?

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(Accepted by Editor-in-Chief)

Ladies and gentlemen, dear colleagues and friends,

To be awarded scientific honours is an exceptional event by itself - moreover to be awarded the Fahræus medal is a great honour.

For me, the name Robin Fahræus is not only associated with my research on erythrocyte aggregation and erythrocyte sedimentation, but also with very personal memories. On the occasion of the First International Congress on Haemorheology in Reykjavik/Iceland in 1966, I had the pleasure to sit next to Robin Fahræus during a bus tour through the island's hinterland. He spoke German very well and I was fascinated by his wide knowledge as well as his courteous and restrained, distinguished nature.

Ladies and Gentlemen!

At the end of a Fahræus Lecture, it is customary to express one's thanks to all bearing a share of the responsibility for this award. Contrary to this tradition, I would like to do this right away and only after that deal with my actual subject: "Quo vadis Clinical Haemorheology". Moreover, I shall not refer to my past or present merits, but leave the tradition also in this respect.

First of all, I would like to express my thanks to all members of the jury, who judged my scientific work worthy to give me their votes. The clear result allows me to presume that my consequent engagement as Secretary General of the ESCH may also have been appreciated in spite of the recent disagreements.

Secondly, I would like to thank Hoechst France for having sponsored this award again and for putting it at the disposal of the European Society for Clinical Haemorheology.

Furthermore, I would like to thank in particular my friend, the president of the ESCH, Prof. J.-F. Stoltz, who gave the laudatio, having done this excellently. I have never before had the opportunity to hear my curriculum vitae in such a condensed description, and I am surprised myself at how much has accumulated. A German writer and humorist once said: *One must only persevere a matter long enough, then honours come by themselves.*

Though a scientific award is given to only one person, those who stimulated, initially supported initially and backed my work should be mentioned here too. In the prologue of my book "Therapeutic Hemorheology", I have listed many of these names; as an example, let me mention just one - my friend, the late A.L. Copley.

Many of my publications arose in collaboration with scientific co-workers of the past 30 years, who are too numerous to name. Without their help and loyalty, my team at the University Clinic in Frankfurt would not be what it is today and our extensive research would not have been possible. Here representing all involved, I would like to name my companion of many years, Prof. Landgraf now from Berlin, as well as my senior physician, Dr. Bauersachs, from Frankfurt. Finally, I would like to thank my family, my wife Gabi and my sons Michael and Karsten. Without their understanding and patience my scientific career would not have been possible.

I would now like to address the actual topic: Quo vadis Clinical Haemorheology.

I have chosen this topic quite consciously, as there are trends and campaigns in our field, which are questionable, and which in my opinion should be discussed to enable us to take countermeasures. I have not changed this topic, although I knew that J.-F. Stoltz would give an opening speech entitled "Past, present, and future of Haemorheology". John Stuart's Fahræus Lecture in 1991 already bore the title "Blood Rheology 1991 - 2001". Thus, there is obviously an existing demand for discussion. To say it beforehand: my analyses will be much more critical compared to those of Stuart, as 4 years have gone by in the meantime and new perspectives are to be considered, and also since I cannot agree with some of his statements.

While 30 years ago only very few clinicians understood the word 'rheology', today terms such as flow properties of blood, viscosity, and microcirculation disturbances have become common. Therapy principles like haemodilution, fibrinolysis, and others are acknowledged.

The Hyperviscosity syndrome, inaugurated by Dintenfass - even though semantically doubtful - has become a regular term. In many countries research teams have formed, which, I am pleased to say, continue to search for ways in which haemorheological findings can be transposed into clinical practice. Does this mean that everything is fine? I think that at least some scepticism is advisable. In my opinion, Clinical Haemorheology is entering a state of crisis, reasons which ought to be evaluated and eliminated and for which proposals should be made. Just as any doctor I would, therefore, like to try to ascertain a case history, show findings, and make a diagnosis in order to be able to give therapeutic recommendations.

#### **Scientific aspects:**

First of all, we must realize that in our discipline on the part of academic research, the input - in particular from pre-clinical research - has decreased considerably compared to twenty years ago. Looking at the publications of the past years in '*Biorheology*' and '*Clinical Hemorheology*' it appears that there are only few fundamentally new findings in classical haemorheology which were taken up and found application by clinicians. Essential factors of the flow properties of blood are already determined and well known, and partly also transposed into clinical practice. It seems to be difficult to find new fundamental factors. Evidently, the number of corpuscular components in blood, which also have an influence on the flow properties of blood, are numerically limited. After a

phase of dominance of erythrocytes for many years, research today is concerned with white blood cells as well. It seems to confirm, however, as Holger Schmidt-Schönbein once formulated, that the significance of the white blood cells in microcirculation is to be evaluated not so much mechanically, but rather biochemically. The next group to come would be the platelets, indeed eager research has already been undertaken by both haematologists and haemostasiologists.

This aspect leads to a second point that is worth the reflection on the future of Clinical Haemorheology. We must accept that entirely new trends have arisen in the field of microcirculation during the past two decades. Here, I would only like to mention the most interesting field of vessel hormones such as endothelin and NO, kinines, and other substances, to be found in the living microcirculation, but of course not in the in-vitro instruments of the classical haemorheologist.

It appears that A.L. Copley's endothelial fibrinogen lining, by many previously not understood or taken seriously, has gained an entirely new importance. We must realize that classical conventional Clinical Haemorheology, which orientated itself in the concepts of the eighties and nineties, suddenly is in competition with the new field of endothel research. This not only takes away a lot of research activity, but also a great deal of financial support. I shall deal with the impact on economical consequence later on.

Let me discuss two further points (you might call them "symptoms"), which in my opinion have led to a certain stagnation in haemorheological research. At the beginning, I already mentioned the lacking input on part of theoretical medicine. Also in clinical medicine some groups put main emphases on research, but their topics already revealed that neither visions nor new aspects can be expected. Some groups have tried extensively to accelerate the standardisation of haemorheological investigation methods. Of course, it is important to do so and, as is the case with all laboratory methods, to introduce quality control. However, can this really be the main objective of Clinical Haemorheology? I have my doubts about that, since we all know to which extent in-vitro results of haemorheological parameters have to be put in relative terms in the in-vivo situation. What is the use of an improvement on the precision of a rheological measuring result in-vitro, if the situation on the physiological part already shows large deviations in-vivo. In contrast to the seventies and eighties, when innovations in the field of haemorheology could be reported, currently in our field something is up more likely consolidating, which easily could - with some nastiness - be called "school-teacher-like".

Similarly, the increasing number of publications dealing with the assumed significance of rheological risk factors are to be regarded critically from my point of view, especially if seen from the view of the treating doctor. There is no doubt that one can well take therapeutical measures against increased results of fibrinogen (as one of the currently often mentioned risk factors). In this connection, I refer to our early investigations on fibrinolysis with Streptokinase and Urkinase as well as to the defibrinageneration with snake venom Ancrod).

Even though it is indisputable that in certain syndromes such intravascular coagulation, acute myocardial infarction, or angina pectoris such treatment is indicated due to rheological abnormalities, one has to ask oneself, which consequences result from a statistical-epidemiological study, in which a collective of patients for a particular disease, particular parameters and as a rule, even a great number of those, are being found abnormal. It is worrying that in some of these publications on risk factors reference is in

general not only made to the statistical significance, but at the same time a causal relevance is being suggested. Considering the low acceptance and large criticism regarding the question of the increased cholesterol level in connection with cardiovascular diseases, one has indeed to be very careful with the interpretation of such epidemiological studies in view of the acceptance by our practising colleagues. Should we give a fibrinogen decreasing therapy to every cardiovascular patient with increased fibrinogen concentration, even though none of these therapy methods are free of side effects? In context with the question relating to the scientific aspect, it is interesting that statistical correlations between diseases and laboratory parameters can be found. The application of such findings in practice, however, turns out to be extremely difficult.

#### **Economical aspects:**

When I spoke of a crisis in Clinical Haemorheology, it is also because of economical reasons. For didactic reasons, let me follow again the scheme: case history, symptoms, results, diagnosis, and therapy to make my thoughts clear. From the historical point of view, Clinical Haemorheology (even if not called that way in those days) has always been supported by the pharmaceutical industry; I am thinking here of *Pharmacia* with its product *Rheomacrodex* and of the *Hoechst* company with its product *Pentoxifyllin / Trental*. We all have seen nothing bad in this, but appreciated this support without which haemorheological research, in particular Clinical Haemorheology, would not be what it is today. Yet, when I am looking back on the initial push of Tony Marcel's idea, which actually helped a great number of interested French clinicians and scientists to get their first rheological instruments, one can understand what I mean.

Today, however, we are facing a different situation. We have experienced a world wide recession, within the frame of which also the economic resources of the research active pharmaceutical companies have been diminished significantly. In particular, the sponsoring of academic research by industry was decreased, whereas for clinical studies and marketing, these bottlenecks did not show that clearly i.e. for projects directly affecting the credit side of the company. Within the frame of the above mentioned public budget cut, of course the health insurance companies have not failed to reduce the income of the pharmaceutical companies drastically (Foremost, I am thinking here of the cheap generic products). However, we must not close our eyes to the fact that our patients will become more and more independent in the future, and that they generally behave more reserved towards a critical application of therapeutic measures and especially towards chemical products. All these factors unfortunately lead to the fact that the pharmaceutical industry can no longer largely support scientific work and clinical scientific work, and this of course is also reflected in the output of scientific publications.

On the other hand, this process, as unfortunate as it is, must not only be regarded as negative. Although it will lead to a reduced participation of our colleagues at scientific congresses, it will also lead to a concentration in the sense of streamlining with a - let me put it scientifically - higher specific-scientific activity.

In times of crisis, the distinct influence of the industry on free funded research certainly is a further problem which not only concerns Clinical Haemorheology - definitely hard to influence. It is known that interesting issues are more likely to be supported than problems of pure research. The investigator's risk of financial dependence on the sponsor thus does not get smaller.

**Organisational aspects:**

It is only characteristic that in times of crisis organisational, administrative and last but not least personal disagreements also become visible - disagreements which are in fact causing harm to Clinical Haemorheology in a scientifically and economically difficult time. Many of you may have noticed the power struggles of the past two years, others may have not, and I do not want to ignore this point even during this ceremonial hour. Here, there is also a case history, we have symptoms and a diagnosis and here one can also make proposals for a therapy.

Already in 1991, Stuart criticized the absence of any formal administrative structures and suggested an international society for blood rheology (ISPH), whose major task should be the standardization, instrumentation, safety, quality control, statistics, clinical trial design, and scientific links - those days still under the imagination of a task force. The ECCCH rejected these proposals at that time, since de facto a well operating structure existed, however, not in form of a de jure society.

Then, in Vienna 1993, surprising to most of us, there was the foundation of an international society on the basis of individual membership. Even friends of the initiators of that time called this foundation and the particular circumstances that led to it, incorrect. Apart from American physiologist, Mr. Meiselman, the executive committee consisted of Europeans only and was thus not internationally representative at all. As a result of these activities, the official foundation of the federate *European Society for Clinical Haemorheology* formed soon after. Two years of dissent and mental commitment but also time engagement in this controversy followed, which indeed was unfavourable for our joint concern. Today, almost all European countries, in which Clinical Haemorheology is being practised, are federatively integrated in the European society. I think that now a good proposal is on the table, that is to say: Let us get over the present disagreements and establish a democratic, federate international society on the basis of chapter solutions of each individual continent, as the society for microcirculation has shown us already. This would bring an end to the dispute and normalize scientific life.

With respect to the above, I would also like to make a personal comment. In the occasionally vehement discussion regarding the true way, and also unfortunately in connection with the Fåhræus Award, a few colleagues approached me with the criticism that I did not consider the friendship between the members of the respective boards, which, in their opinion I should have. Let me put it this way: To me, friendship in fact is very important, but naturally also a very subjective matter. In controversies about competence, at the search for superior solutions and the drafting of constitutions, however, one must not be guided by subjective considerations, but must take up positions as neutral as possible. It goes without saying that overlaps with subjective feelings might occur, but here it is again necessary that the superior aim has priority. A Secretary General of a society who would not consider this, would be out of place. Egotistical particular interests of individual persons have to take second place in view of the present scientific and economical problems.

**Consequences:**

In the past twenty minutes, I have tried to demonstrate at least some reasons for the current crisis in Clinical Haemorheology. We spoke about case history, symptoms, and findings and have come to the diagnosis: Clinical Haemorheology in crisis. It would be wrong to gather from it that the patient is now seriously ill and a soon end is in sight. However, as we know from clinical medicine, the symptoms must be taken seriously and countermeasures have to be initiated. Therefore, I would be a bad doctor, if my critical comments would not be followed by therapy proposals.

Again: Quo vadis Clinical Haemorheology means: where and in which direction is Clinical Haemorheology going. As I have been involved in Clinical Haemorheology from the very beginning I think I am qualified to make suitable proposals for therapy, and at the same time permit myself to criticise those therapy proposals of others which I believe are inappropriate or inadequate. John Stuart for example spoke of an interactive network of scientists of other disciplines. This is basically correct, however, the closest discipline, that is to say microcirculation, was not even mentioned.

The clinical trials which he complained about at that time were already state of the art in those days, and the question for design of such clinical trials has developed relatively independent of rheological questions. The steps Stuart has been asking for like standardization, instrumentation, safety, quality control, statistics are general requests which fail if the relevance of such in-vitro tests is slipping more and more away from clinical reality. - I shall return to this point in a moment. - Remaining of his proposals are scientific links, rheological journals, and sponsorship for the training of young scientists. From my point of view, these are all general requests, not specifically limited to our field. A patient having a crisis wants to have a vision of recovery and does not want to know a catalogue of technical details. I think in the first phase of the treatment the patient has to realize that he is in need of treatment, i.e. that a crisis does exist. Without this understanding, no countermeasures will be taken. Without this sense, the patient is getting worse and worse. One of the most essential insights that we as Clinical Haemorheologists should have, in my opinion is the fact that we are thematically, professionally, and instrumentally all in the same boat with Clinical Microcirculation. Already our forefathers, like Ottfried Müller in Germany or Robin Fahræus in Sweden, never regarded these two subjects as two separate ones and even the mentor of our special field, Alfred Copley, also considered haemorheology and biorheology always as an inter-disciplinary scientific branch, just as microcirculation should also be seen. As sad as this may be for some of us, the isolated contemplation of haemorheological parameters is obsolete from my point of view. For good reason, here the words "in-vivo veritas"; are not unfounded, as a great number of working teams have introduced microcirculatory methods in addition to haemorheological methods and put them in parenthesis to clinical methods. This was also the reason for the renaming of the '*Deutsche Gesellschaft für Klinische Hämorheologie*' (German society for clinical haemorheology) into '*Deutsche Gesellschaft für Klinische Mikrozirkulation und Hämorheologie*' (German Society for Clinical Microcirculation and Haemorheology). I am not that much concerned about the naming; what matters to me is the integration of two so closely related fields. Rheological effects simply cannot just be demonstrated or refuted in-vivo ("in-vivo veritas"). Since the in-vivo studies in laboratory animals or healthy volunteers could possibly only be meant, I want to make a further step and attribute scientific investigations on patients, including rheological, microcirculatory, macrocirculatory, and other components introducing the slogan "in aegroti realitas", as after all, we physicians are being appraised on clinical success.

In addition to these general comments on "therapy", I would like to let myself be carried away and make two concrete proposals which I think may stimulate Clinical Haemorheology beyond the year 2000. I think that we as clinical haemorheologists should be dealing to an increasing degree with the interactions between haemorheology and haemostasiology. From my point of view, there is still much research potential existing - only think of the relations of the coagulation factor plasmin with endothelial factors. The second point is: We should integrate the interesting field of research on the endothelia, its hormones and kinines into our scientific considerations and not leave the field solely to others. In shortened form, my strategy is: Clinical-experimental ideas and innovations are more important than pseudo precision of isolated in-vitro tests.

We must, of course, continue our efforts of passing on our scientific findings and transposing them into daily practice. That is also, where I see a true, realistic possibility to help the young societies beyond the former iron curtain and to accelerate and promote their integration into the international scientific community. In the end, as already mentioned above, administrative homogeneity and transparency are - in view of haemorheological societies - substantial factors not to impede the development of Clinical Haemorheology, but affect it positively.

In conclusion, I would like to state that crises are there to be overcome. This does not happen by proclamations only, also not by well-meant declarations of intent, but only by new ideas and consequent actions. There is certainly no one having expressed this better than Johann Wolfgang von Goethe in "*Faust*", part 2: "*Wer immer strebend sich bemüht, den können wir erlösen*". ("He who strives on and lives to strive can earn redemption still").