Kwantitatieve bestudering der rouleauxvorming van erythrocyten door reflectiemeting (syllectometrie)
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SUMMARY

In chapter I a description is given of the rouleaux formation of erythrocytes in normal human blood and its increase in disease (viz. fig. 1 and 2). This is followed by an exposition of the principles of the method for quantitative studies on rouleaux formation as it has been developed in the Physiological Department of the University of Groningen. This method has been denominated "syllectometry" (from συλλέγων = to gather). In syllectometry the decrease in light reflection of blood, caused by rouleaux formation, is recorded with the aid of a reflection oximeter. The method has been developed from a reflection technique for instantaneous determination of the oxygen saturation of blood during cardiac catheterization. Rouleaux formation of erythrocytes was found to cause a decrease of the reflection of the blood in the oximeter cuvette. To eliminate this effect of rouleaux formation a small iron mixing rod, driven by a magnetic stirrer has been introduced in the cuvette. Immediately after the stopping of the mixing rod, rouleaux formation starts, causing a steep reflection decrease.

In chapter II a survey of the literature on rouleaux formation is presented. This includes
a. the discovery of the phenomenon, vivaciously described by Fähraeus 9, 7, 8
b. a description of several factors that have an influence on the rouleaux formation 5, 6, 7, 9, 10, 14, 21, 27, 33, 34, 39, 42
c. numerous theories to explain the mechanism of the rouleaux formation 2, 8, 11, 27, 39, 42
d. the importance of rouleaux formation as a factor in intravascular sludging 6, 7, 14, 37, 38, 39, 40, 41

In chapter III the apparatus and the operation procedure are described. For routine syllectometry a "cyclops" reflection oximeter * or a CC-oximeter * may be used. The light spot galvanometer used in clinical oximetry has to be substituted by a recording mi-

* Kipp - Delft - Holland

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crovoltmeter („Micrograph“) *. The blood sample is pipetted in a small cuvette provided with a small mixing rod (fig. 5). This magnetically driven rod sets the blood in rapid circular motion and breaks down the rouleaux formed before the experiment. Fully oxygenated blood is used to eliminate differences in reflection due to variations in oxygen saturation. For the study of the influence of differences in temperature another type of cuvette assembly has been designed, in which the blood cuvette is surrounded by a space for circulating water of a certain temperature (fig. 8). A third cuvette, the „spinning-bottom-cuvette“ (fig. 9 and 10) has been devised for imposing a calculable force upon the erythrocytes of existing rouleaux. This force causes a partial disintegration of the existing rouleaux. The full oxygenation of the blood is necessary for differences in reflection due to temperature change, which is obvious from the experiment. Full oxygenation of blood is obtained by recording oxygen formation in normal human blood (fig. 11) and determining the rate of formation of the moment when the first half of the decrease in reflection takes place. This was proved to be a suitable standard for characterizing the graph. A second standard, expressing another feature of the syllectogram,

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is the percentage of decrease in reflection (1R). This standard has shown to be of minor value; it offers however some indication for the final length of the rouleaux. The chapter ends with the reproduction of some experiments that are proof of the good reproducability of the method.

In chapter V some factors acting on the velocity of rouleaux formation are discussed:
1. the suspension medium: the presence of at least one macromolecular colloid proved to be essential for rouleaux formation. By lowering the concentration of this colloid too much, rouleaux formation could be suppressed (as was shown by Thorsen and Hine [39]). No specific function of haptoglobin was shown to be present.
2. the erythrocyte concentration: the concentration of the erythrocytes was found to be of great importance. Lowering of the erythrocyte concentration results into a decrease of the speed of rouleaux formation. If the HWT was determined in a series of dilutions of the same blood, a linear relation was observed between the log. of the Hb-concentration and the log. of the HWT (fig. 23 and 24). This linear relationship enabled to make a correction to a standard haemoglobin concentration for accurate comparative studies. As standard 15 gr % Hb was chosen.
3. the viscosity: only considerable variations in viscosity of the medium exert a significant influence on the velocity of rouleaux formation; the higher the viscosity, the longer the HWT gets (fig. 25). The relatively small differences in plasma viscosity values occurring in human blood may be disregarded in comparative studies.
4. pH: variations in the hydrogen ion concentration of the plasma were shown to have little or no influence on the velocity or the extent of rouleaux formation.
5. the temperature: a rise of temperature slightly increases the velocity of rouleaux formation. It is most probable that this is caused by the decrease in plasma viscosity. The usual, small variations in laboratory room temperature are of no influence.

In chapter VI the relation between rouleaux formation and erythrocyte sedimentation rate (ESR) is discussed. Both phenomena are influenced by the erythrocyte concentration, however in opposite directions. A decrease in erythrocyte concentration diminishes the velocity of rouleaux formation but causes higher ESR values. The ESR has proved to be unsuitable for accurate studies on rouleaux formation. By means of syllectrometry, on the other
hand, a reliable expression of the velocity and the extent of rouleaux formation may be obtained. It may be that for several applications the ESR will be replaced by the syllectogram.

In chapter VII some theoretical problems are discussed. In the first section some considerations are presented on the relationship between the decrease in reflection and the number of cells in the rouleaux. We did not succeed in formulating an exact quantitative expression for this relationship, but a general insight has been obtained.

In the second section of the chapter a calculation is given of the force which keeps the erythrocytes together in the rouleaux. In normal human blood this force is about 200 x 10^{-10} dyne. Further calculations have shown that the energy needed to separate two erythrocytes is about 1600 x 10^{-11} erg. This is about 400 times the thermal energy. So it seems highly improbable, that heat motion can break down rouleaux. If on the other hand, two erythrocytes are in touch only over a small surface area, thermal energy can easily shift them from each other.

In the third section an outline of the mechanism of rouleaux formation is presented. Brownian movement is necessary to bring about the first contact between the erythrocytes. The surface tension is the main cohesive force, i.e., the surface tension between the medium and a jelly-like colloid layer that is formed at the surface of the erythrocytes, where the colloids in the medium tend to concentrate. The formation of this colloid layer may be influenced by the properties of the erythrocytes surface. This may explain why some erythrocytes (ox, sheep, goat) form no rouleaux.

In the last chapter a few applications of syllectometry are described. Syllectometry is useful for research on the relation between rouleaux formation and intravascular sludging, especially in testing the usefulness of solutions of macromolecular colloids (dextran for instance) as blood substitutes. In a (as yet small) series of patients we found a significant increase in the velocity of rouleaux formation lasting several days after a single infusion of dextran solution.

A second application of the syllectometry lies in the field of radiobiological studies since X-ray radiation was found to be a sufficient stimulus to evoke a moderate rouleaux formation in rabbits. Increased formation of fibrinogen seems to be the cause of this reaction in the rabbit.