Electrical Resistance of Whole Blood

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The circumstances accompanying blood coagulation are not yet clearly understood. It is probable that several components and one or more reactive processes are involved prior to the ultimate conversion of soluble fibrinogen to insoluble fibrin. The exact points of attack by the anticoagulants, heparin and dicumarol, are also not clearly defined. That the therapeutic use of these agents is not unattended with risk is well known. Clinical administration of the anticoagulants is commonly directed according to the observed clotting time, but this property appears not to be an infallible indicator. It is uncertain whether or not the too-frequently-unpredictable dosage responses arise from errors in the measurement of the clotting time or whether the extravascular clotting time is a relevant guide to therapy. Perhaps when the whole phenomenon of blood coagulation and the action of the anticoagulant drugs are better understood, some more pertinent index for clinical evaluation and drug application will be set up.

Further, the methods employed for the measurement of clotting time are highly subjective; the Lee-White method, which enjoys the widest use, yields reproducible data in skilled hands, but these data are not strictly referable to the data of other laboratories or technicians. It appeared, therefore, that it might be profitable to investigate other properties of the blood which might bear some relation to coagulation or which might change in a manner indicative of the clotting time. These properties must be susceptible to rapid measurement without introduction of extraneous mechanical or chemical factors such as agitation or dilution.

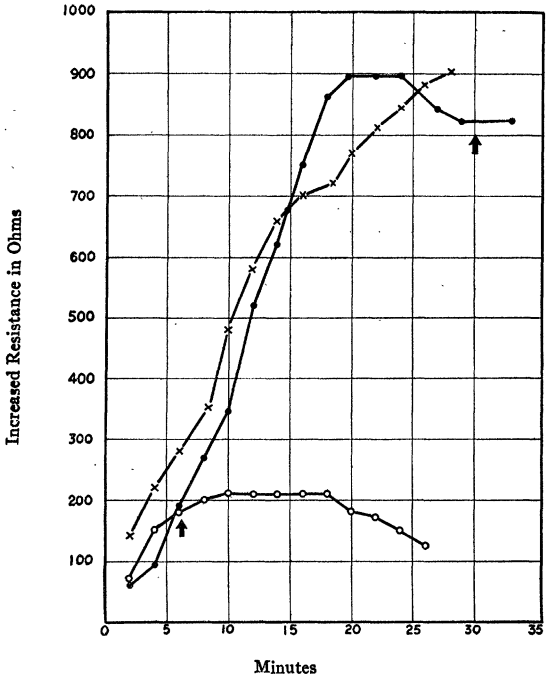

FIG. 1. Representative resistance-time curves: O——O Typical normal blood; ●——● Blood from patient receiving heparin over 48-hour period; ×——× Normal blood with excess heparin *in vitro*; ↑ Clot by Lee-White.

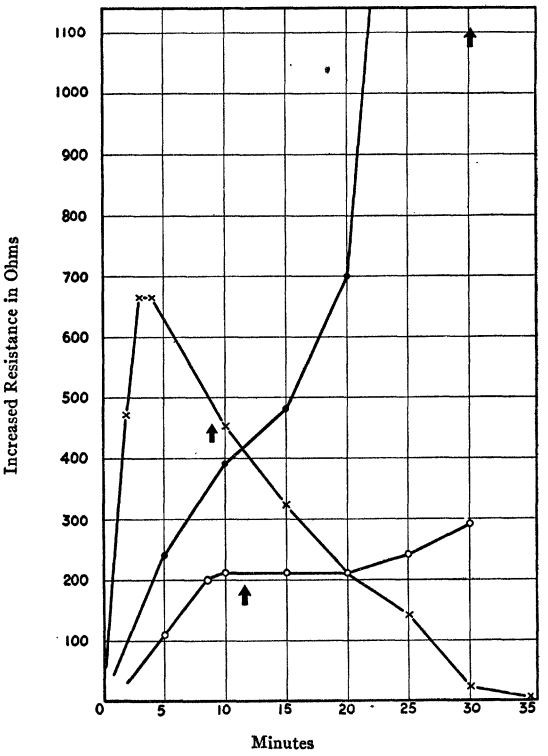

FIG. 2. Alteration in resistance-time pattern by administration of heparin: ×——× Initial blood before heparin; O——O Bood from same patient after heparin treatment for 18 hours; ●——● Blood from same patient after heparin treatment for 24 hours, last 8 hours under increased dose; ↑ Clot by Lee-White.

It was anticipated that electrical conductivity might be such a property and, even though it might reveal nothing further, it was expected that the resistance of the freshly drawn blood would increase until coagulation supervened, at which time an inflection in the resistance-time curve would occur. Figs. 1 and 2 demonstrate how well this prediction was realized, but—and this is perhaps of greater significance—these data

also reveal certain wholly unexpected phenomena. In those instances where the coagulation time has been delayed by drugs *in vivo* or *in vitro*, there is an inordinate increase in resistance preceding clot formation when the latter is measured by the Lee-White method. Fig. 2 depicts one example where some intravascular defects were anticipated but wherein the extravascular clotting time was not greatly delayed. The blood specimen taken before medication exhibited a very high initial resistance with an accelerated change in resistance before coagulation. The accompanying curves show the alterations in the blood of this patient after administration of heparin.

These data appear to warrant further intensive investigation of the electrical resistance shifts in freshly drawn blood; such an investigation is under way in our laboratories. For the present we offer the speculation that this increased and increasing resistance is a consequence of the orientation or unfolding of certain plasma proteins in such manner as to form electrically neutral and unionized dipoles. The conductance of the proteins themselves might be thus inhibited, or

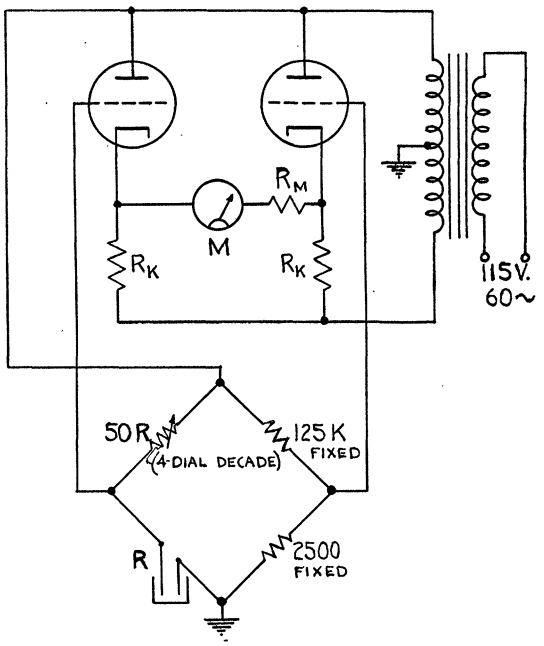

FIG. 3. Alternating-current electrolytic resistance bridge.

the plasma electrolytes might be bound in the hypothetical double layer. The physiological significance of this phenomenon remains to be seen, but it is probable that the latter is affected significantly by the charge of the container—in this instance, pyrex glass. The hypothesis appears to be susceptible to experimental exploration.

The measurements of electrolytic resistance were made with an alternating-current bridge[1] especially designed for this purpose (see Fig. 3). The use of 60-cycle alternating current eliminates polarization in the cell. The voltage across the cell is constant at balance and is equal to about 5 volts r.m.s.; this corresponds to a maximum power dissipation of $\frac{1}{8}$ watt in the cell. In order to minimize the possibility of modification of the reactions in the cell arising from the passage of the measuring current, a switch is provided for closing the bridge energizing circuit only when a reading is taken.

A vacuum tube phase-detector and amplifier is used to amplify the bridge output voltage. A zero-center microammeter connected to the amplifier output is calibrated directly in the percentage by which the cell resistance deviates from the value indicated by the four decade dials of the variable arm of the bridge. The scale of the meter is graduated linearly from −15 to +15 per cent deviation. Cell resistances within the range of 200–10,000 ohms may be measured. The instrument is compact and portable and may be plugged into the house current supply at the bedside.

The conductivity cell constant was approximately 12 reciprocal cm.; this brought the measured resistance into the most accurate range of the bridge. Since the frequency is low and the electrodes small, it is obvious that the inductance and capacitance factors are minimal; certainly, the change with time of these parameters must be negligible except in so far as they might be affected by the speculative double layer.

[1] Manufactured by Matthew Conrad, Rahm Instruments, Inc., 12 West Broadway, New York City.

Tracer Micrography[1]

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In the well-known method of radio autography a radioactive isotope is introduced in a biological or other system, and the distribution of that particular element within the system is determined by bringing the sample in close contact with a photographic emulsion. This method lacks resolving power because, even in the case of perfect contact of the sample with the photographic emulsion, the circle of confusion produced from every point of emission is so great that details less than .1 mm. are very hard or impossible to distinguish.

In order to improve the resolution of this tracer method, electron optical image formation was used for the determination of distribution of a radioactive element within a given sample. This is based on the emission of high-speed electrons by many tracer elements and the use of electron optical lens elements for forming an image on a photographic plate or other suitable recording surfaces. In the absence of any method for correction of the chromatic aberration of electron optical lenses, the first attempts were limited to elements which are emitters of monokinetic β-rays (internal conversion electrons). After some attempts with Cb^{93}, Y^{87}, $Sr^{85,87}$, and Pa^{233}, Ga^{67} was selected for the tests. Gallium chloride was prepared by chemical separation from zinc, bombarded by deuterons in the Department of Terrestrial Magnetism cyclotron, and the solution evaporated drop after drop on a $\frac{1}{4}$-inch tantalum

[1] The early phase of this work was carried out while one of the authors was attached to Stanford University. During that time work was carried out under a Rockefeller grant and with a considerable amount of collaboration on the part of J. Hamilton and E. Segrè. Their cooperation and the help of the Rockefeller Foundation is gratefully acknowledged.