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A. L. COPLEY, THE MEDICAL SCIENTIST AND BIORHEOLOGIST

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As Al Copley liked to explain, he decided to become a student of medicine when he discovered that he wanted to go into psychiatric counseling. In the Germany of his days you could not become a practicing psychiatrist without a medical degree.

During the course of his medical studies he developed, quite unexpectedly to him, an extra-curricular taste for scientific research into basic medical questions. What interested him in particular was the blood system, blood flow and the field of blood clotting and hemostasis. He became fascinated by the problem of the arrest of bleeding and how to manage and measure it. He was, for example, not satisfied with existing measurements of bleeding time and so Lalich and he, in 1942, developed a most ingenious test, which unfortunately has not come into general use. After the infliction of a small wound in a finger, the finger is suspended at the base of the heart level in a temperature controlled bath containing physiological saline. Bleeding is allowed to proceed and the time when it stops spontaneously is recorded. Much more accurate results can be obtained by this carefully controlled way of measurement.

Copley noted that blood clots formed in a wound seldom became dislodged by blood pressure manipulation in normal individuals. Renewal of bleeding in normals is thus extremely rare. The so-called "wound thrombus" resistance is high. Not so, however, in the case of hemophiliacs. Even though bleeding times for the hemophiliac might be in the normal range, the clot formed is easily dislodged and bleeding is resumed. Copley, in pondering this phenomenon, concluded that wound thrombus is a function not only of the mechanical strength of the clot but also of its ability to adhere. Wound thrombus resistance is thus a measure of something quite other than bleeding time, which is a measure of the rate of onset of hemostasis. So what causes and controls the adherence of the clot?

Copley thus became interested in the structure of the vascular wall and the phenomena of capillary fragility and permeability. Capillary fragility, he concluded, depended upon the integrity of the basement membrane and thus resided in its composition and structure. It depended on the tendency, or otherwise, of the basement membrane to fracture under certain mechanical circumstances. Capillary permeability, on the other hand, he attributed to a layer of biopolymers over the endothelium which he assumed extended also to the gaps between the endothelial cells. A removal or weakening of the structure of this layer, which he saw as a form of gel, would increase capillary permeability and could possibly lead to bleeding. An increase in strength and thickness, on the other hand, could lead to thrombus formation and to occlusion of the vessel!

Copley's thinking was influenced and stimulated by the eminent position, in those days of the field of Colloid Chemistry, a field which is today no less important but has, for obscure reasons, been renamed Complex Fluids. As in Colloid Chemistry generally, Copley's ideas were rheological in nature (even though Rheology was then only an emerging discipline). How then was it that Copley should have come to such ideas, when after all he was a student of medicine?

Copley completed his medical degree in Heidelberg in 1935. The repressive measures imposed by the then German government under Hitler did not make this at all easy and he left Nazi Germany at the very first opportunity thereafter. He went to Basel, Switzerland, and began his practice of medicine there. In addition, however, he used his stay in Basel in a very interesting fashion. As a side-line, he began to study physical chemistry and the insights so gained not only roused and satisfied his scientific curiosity, but also began to guide his thinking and his imagination on the nature of the physiological phenomena, thrombus formation and blood clotting, with which he was most concerned medically and physiologically. Thus, it was natural for him to see blood clot formation as an example of a complex process of gelation, to which he began to apply his physico-chemical insights. He had great success with his model building and with his thinking in general. It is not surprising, therefore, to find him attending the First Congress of Rheology in 1948 and to announce the concept of biorheology as a scientific discipline to the world on that occasion.

Everyone who has ever observed blood flow in microvessels is aware of the so-called plasmatic zone, a layer region near the vessel wall essentially free of red cells, but not, strangely, of platelets and granulocytes. Poiseuille already had speculated on this zone and had proposed that it consisted of a no-flow and a more luminal regime. Hence, Copley in his first modeling of the endothelial layer and the plasmatic zone, accepted that there are two such regions. Very ingeniously, however, Copley proposed that it is gel formation that produced the immobile layer and that on its surface, competing reactions—one that tends to extend the gel layer and one that tends to dissolve it away—stabilize the thickness and structure of the layer over the endothelium. A physiological steady state arises which is normally well controlled. For the gel network-forming substance, he had fibrin in mind, which is formed from fibrinogen under the action of thrombin. For the dissolution process, he postulated enzyme-directed fibrinolysis. Model experiments in glass tubes coated with fibrinogen and fibrin seemed to lend support to his idea that special surface properties are conveyed by fibrinogen. Even though the physico-chemical results were very hard to interpret, Copley was encouraged by these data to coin the term "endo-endothelial fibrin lining" for the layer. Throughout almost all his remaining years, he spent much time and effort trying to elaborate the concept, initiate or instigate experiments that would underscore it and, in particular, to scan the literature for support of his ideas.

As it happens, such support does exist. Very early on, Danielli, and later Chambers and Zweifach, using light microscopy showed the existence of a layer of unknown composition over the luminal aspect of the endothelium. Later, more detailed investigations by Luft, and separately by Palade, using electron microscopy led to the same conclusion. Luft in fact showed, very elegantly, that the layer was rich in carbohydrates. It was thus most probably composed of glycoproteins. This conclusion also satisfied Copley, since fibrinogen, like most proteins, contains some carbohydrate side chains. Luft's results, however, indicated that a much richer carbohydrate source was most likely involved. To Copley's great satisfaction, more direct confirmation for the presence of fibrinogen in the plasmatic zone was brought by Witte who found, using fluorescent labelled fibrinogen injected into the microcirculation, that it had made its way into that layer. Antibody work by Palade also showed the presence of fibrinogen and fibrin. With this much support, Copley's ideas should have been taken up very seriously.

What spoiled matters was his insistence that thrombi formation in blood vessels is the result predominantly, if not solely, of the growth of the immobile layer. He claimed that there was no need for platelet participation. Many found this view difficult to accept or even consider and produced many skeptics, who in doubting this tended to reject the whole idea. Though the layer almost certainly exists, there is still today almost no direct information about its structure and composition. We don't know its thickness and what controls it, what function it fulfills and how this is related to its chemistry and structure. What else in addition to fibrinogen and possibly fibrin does it contain?

In defense of Copley's skeptics, it should be stressed that most scientists today think of platelet function in terms of platelet activation by some stimulus, followed by the release of platelet constituents from storage granules and a major shape change and, in the presence of calcium, by platelet aggregation and platelet thrombus formation. Platelets upon activation release additional fibrinogen and thrombin so that fibrin network formation to consolidate the plug should occur. A well-known list of other proteins and factors make the emerging thrombus adhere to the endothelium at its damaged site. Platelet thrombus formation is generally seen as the first line of defense before blood clotting *per se* follows.

Copley tended to minimize the importance of this mechanism. The platelet role that he emphasized is one that others generally tend to neglect. This is the protection of the organism against intruding microorganisms. Platelets have the ability, as he demonstrated, to envelop bacteria and viruses in a clump that contains the offending organism at its center. Phagocytosis of these clumps then eliminates the invader.

To Copley, the flow of a dense suspension of flexible red cells through vessels with elastic walls coated with his endo-endothelial layer clearly had a host of rheological implications. To mark their special character, he called studies in this area Hemorheology, but soon came to realize that not only the rheological properties of blood, but also the rheological character of other body fluids and the deformation characteristics of body tissue in general have to be studied at the same time and with the same physico-chemical approach. All these data interdigitate and the field should thus be termed Biorheology, as he had proposed in 1948. We can look upon Copley, in every way, as the founder and propagator of biorheology. his ideas, indeed, were almost always far ahead of their time. It is for this reason that they were so often ignored and the importance of their message not recognized. I feel convinced that the endo-endothelial layer, under whatever name it will eventually become popularly known, is a vascular feature for which Copley will one day be given outstanding credit. His emphasis, in particular, of its gel structure, its role on vessel wall permeability and the idea that its thickness is subject to competing processes that set up a steady state, constitute the elements of a model that we cannot idly dismiss.

In all he did, Copley always thought along unconventional lines. He enriched our world with ideas that should have been accepted with much more alacrity and much more enthusiasm. He will I am sure eventually come to be widely recognized as the prophet and genius that he was—one who was appreciated, but not nearly adequately, by far too many of his contemporaries.