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ESSAY

# HEMORHEOLOGY AND THE EXPERIMENTAL BASIS OF CLASSICAL HUMORAL PATHOLOGY

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## I. PATHOPHYSIOLOGY AND HEMORHEOLOGY

The foundation of the present new journal "CLINICAL HEMORHEOLOGY" best testifies the fact that rheological thinking is gaining ground in biology, medicine and surgery. The biomedical community, after having long neglected mechanical facts in general, and biorheological peculiarities in detail, is beginning to appreciate the theoretical and practical relevance of biorheology as a discipline devoted to the study of flow and deformation of complex materials. Nature, after all, has mixed "fluids" and "solids" in the tissues of plants and animals, and the classical physical laws established for elastic solids or pure liquids do not usually apply to the mechanics of biological materials. In the sense of classical mechanics, most biomaterials are "anomalous".In the laboratories of comparatively few centers, the causes of the often puzzling, or "paradox" mechanical abnormalities of cells, tissues, blood vessels and first of all of the flowing blood itself have been identified, sometimes even at the molecular level. At present, we witness the application of this knowledge to the understanding of the consequences of these "abnormalities" for the normal and the abnormal function of cells, of blood and of tissues.

Since so many important and medically unsolved circulatory problems in the vast field of degenerative and thromboembolic vascular diseases have a mechanical as well as a chemical basis, hemorheological concepts about causes and consequences of disordered blood flow are especially significant. Already now, hemorheological research has uncovered pivotal pathogenetic mechanisms in such fields as thrombosis and coagulation, degenerative vascular disorders, hemolytic diseases and inflammatory reactions.

KEY WORDS: Hemorheology, Humoral pathology.

At present, however, biorheology is far from an equality status with those established scientific concepts which medicine derives from biochemical, immunological, morphological, electrophysiological (or even sociopsychological) disciplines. In other words: While we are pleased about the friendly reception of diagnostic and therapeutic practices which we consider "hemorheological" in nature, we should attribute this trend to pragmatic successes rather than to the acceptance of hemorheological theories in medicine. Theoreticians in hemorheology are in the same position as theoreticians in other scientific fields: they have to explain in retrospect practical results found by practitioners. Furthermore, modern hemorheologists are in the fortunate position of being able to explain in retrospect the materialistic basis of the old doctrine of humoral pathology often misinterpreted as mythical.

## II. HUMORAL PATHOLOGY AND HEMORHEOLOGY

It is the merit of Robin FAHRAEUS to have uncovered the roots of humoral pathology at the very same time when he rediscovered the test of the sedimentation rate of blood (1). His lucid explanation of the theory of "dyscrasias" as the cause of diseases has not found the attention it deserves by the historians of medicine, presumably because they have the same "rheological scotoma" as the rest of the biomedical public. Even in recent texts about this history of hematology, the essence of FAHRAEUS' treatise were either neglected (2) or thoroughly misunderstood (3).

The doctrine of humoral pathology is generally considered as the first rational theory of medicine. It is attributed to Polybos, son-in-law of Hippocrates, who interpreted blood as one of the four "cardinal humours" (the other three being phlegma, bile and black bile). Most historians of medicine assume that Polybos deduced this theoretical concept from a more general cosmology of Empedocles,who regarded the universe as composed of four elements (fire, air, earth, water) with four cardinal qualities (hot,cold, dry and moist). The maintenance of health was held to depend on the normal blending of the humours ("eucrasia") and upon harmony of the four qualities (FIG. 1). Disease was explained by an abnormal mixture of the four humours ("dyscrasia").

Before citing FAHRAEUS, it is useful to remind the reader that from the times when man had reached the stage of reasoning, he must have realized as self-evident that the blood was essential for life. A primitive "physiology" of blood was derived from experiences such as: 1. in wild and domesticated animals as well as in man flourishing life expired quickly whenever large volumes of blood were voided, 2. it was common experience that blood was warm and liquid when it left the body, its cooling and clotting occurred simultaneously, 3. for reasons that are unclear, the practice of phlebotomy, i.e. the intentional removal of small volumes of blood from the veins was not only customary but also extremely popular.*

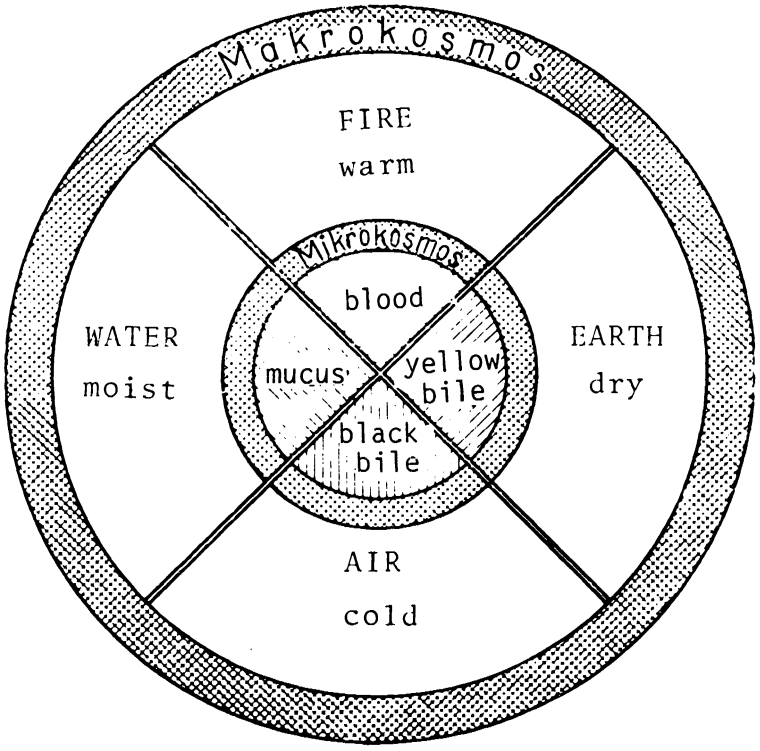


FIG. 1
Schematic representation of the integration of the humoral pathology into the natural philosophy of the Greeks: In the macrocosmos, four elements and qualities: fire (hot), earth (dry), air (cold) and water (moist) represent the composition of matter. In man, a microcosm reflecting the same basic scheme, the four elements are represented as four humours.

One is safe in assuming that the theory of the four humours when formulated by Greek physicians was amalgamated into a large body of prescientific knowledge about the pivotal role and behavior of blood. We shall recognize the attempt to formulate a theory from observations by inductive reasoning on a background of an aggregated mixture of mythical and pragmatic knowledge.

The observations that prompted the "humoral pathology" can best be represented in FAHRAEUS' own words:

*"At earlier periods of the development of medical sciences there were certainly lacking all the microscopical, physical, chemical, serological and*

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* Phlebotomy is not only described in numerous historical documents of most early human civilizations, but is also customary in contemporary primitive societies, for example in Papua tribes of New Guinea (4).

*bacteriological methods of research, of which the modern schools avail themselves; but, on the other hand, there was much richer material for observation of the macroscopical nature of the blood. And this, thanks to blood-letting, which from time immemorial up to the middle of the last century was without comparison that remedy most favoured by the medical profession and which was made use of in nearly all derangements in the state of health and also extensively by healthy people as a general preservative.*
*In most diseases the evacuated blood had quite a different appearance to that when in a state of health. When coming from a sick person it secreted a whitish substance of solid consistency which was absolutely lacking in the blood taken from a healthy person, but which in more severe cases of illness could perhaps take up more than half of the liquid volume evacuated.....*
*The most important cause of the origin of this phenomenon was this, that the subsiding speed of the blood corpuscles was increased. The appearance of the blood cake thus showed various degress of that property in the blood which I have called its suspension-stability. The buffy coat was a sign indicating that the suspension-stability of the blood was reduced.*
*There is probably no observation in the history of medicine which has played such a big part as has this phenomenon.....*
*The fundamental theory of the pathological philosophy of antiquity and the middle-ages and the greater part of more modern times was the humoral pathology, according to which all diseases were ascribed to alterations in the body fluids. This theory was not, as we generally imagine, a rootless abstraction, but was founded on the fact that the unhealthy blood, by reason of the presence of the white layer, differed so conspicuously from the healthy blood..."*

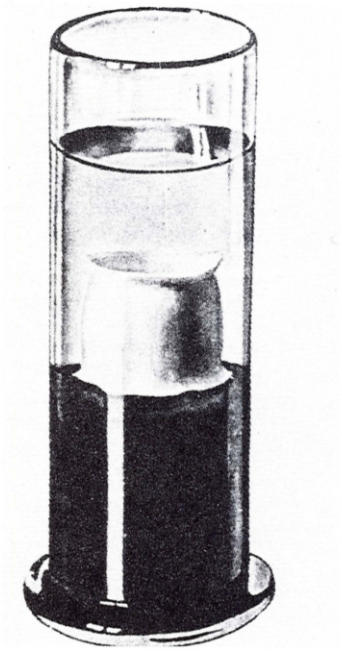

FIG. 2
Spontaneous coagulation of blood with high sedimentation rate: formation of the buffy coat or crusta inflammatoria (from FÅHRAEUS' original paper)

The progress since FÅHRAEUS allows us to identify in even more details the processes that lead to the formation of the "crusta inflammatoria" or "buffy coat". In the case of heavily aggregated red blood cells, their rapid sedimentation leaves as a supernatant not"plasma"but rather platelet rich plasma (PRP). In a fasting subject PRP is originally opaque, and after coagulation it spontaneously separates into a concentrically retracting disc of platelets, leucocytes and fibrin (the jelly-like crusta inflammatoria) and clear serum.

It is very easy to repeat the ancient procedure of inspecting the blood after coagulation ("hematoscopy") by pouring fresh blood into a flat glass vial (the experiment does not work in the long narrow test tubes used in modern hematology laboratories since the blood sedimentation is not fast enough to achieve separation before coagulation (FIG. 3)).

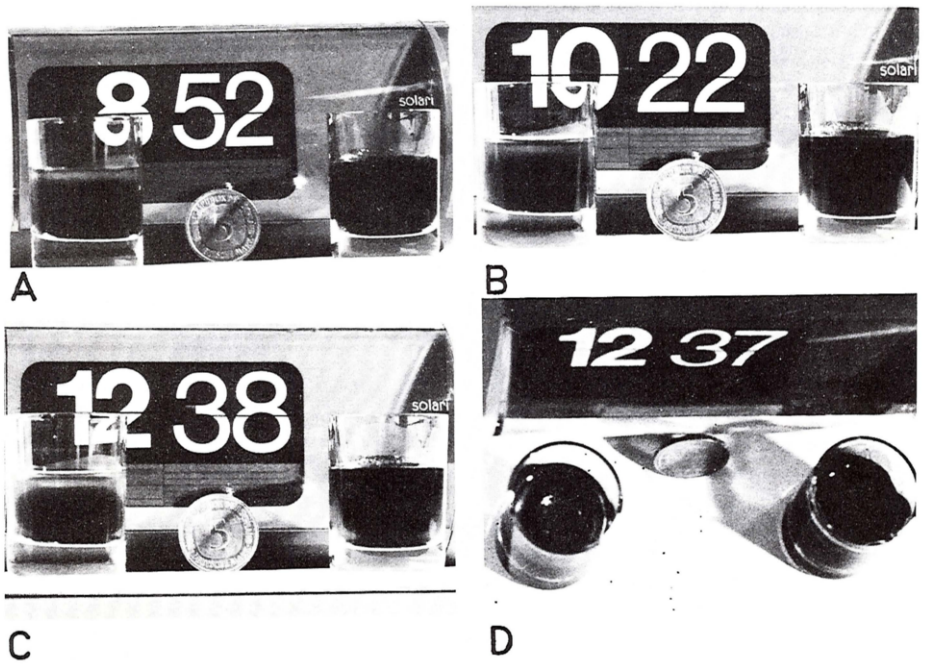


FIG. 3
Spontaneous coagulation of blood in a glass vial: comparison of normal blood and blood of a patient with high sedimentation rate. A: 3 min after the withdrawal of the blood, the sedimentation is clearly visible by the formation of a layer of platelet rich plasma. B: After 2 hours, both samples are clotted and the ring shaped contraction of the clotted platelet rich plasma begins. After 4 hours, the classical "buffy coat" is visible at the top of the clot from a diseased person, but not in that of a normal subject (C and D, view from above).

FIG. 3 shows the results of such an experiment. The venous blood of a normal subject and that of a pregnant young woman (with high sedimentation rate) was taken simultaneously without anticoagulant and was observed macroscopically (by time lapse motion picture). Already a few seconds after withdrawal of the blood (which had a distinctly different tint), the upper layer of the rapidly sedimenting blood became pale, and after 3 minutes the interface of red blood cells began to drop and left a layer of opaque platelet rich plasma which rapidly increased in height.

Without stirring or tilting the glass vial, we could not identify the actual moment of coagulation - but after about one and a half hours the retraction became visible. Here, again, a distinctly different pattern of retraction was seen. In the normal blood, in which no appreciable sedimentation had occurred before coagulation, the reddish coagulum was one solid mass which contained fibrin,platelets,white and red cells. - Later, as the clot retraction occurred, the light yellow serum began to appear. In the previously sedimented blood, a distinct layering was visible. On the bottom, a dark red (macroscopically almost black) layer of aggregated, deoxygenated red cells was seen, which gradually extended into a layer with lower hematocrit ( thence red colour), which no longer changed after clotting. The retraction of the fibrin-platelet-clot leads to the separation of the whitish buffy coat and the yellow serum. Even the black and white pictures in FIG. 3 reveal the separation of the pregnant woman's blood into four, of normal blood into two macroscopical distinct ingredients or constituents.

The molecular and rheological mechanisms which are responsible for the different spontaneous coagulation of normal and abnormal blood have been clarified beyond reasonable doubt: in almost all important diseases (inflammation, rheumatism, tumors, degenerative vascular and metabolic diseases) the plasma is characterized by an abnormally high concentration of macromolecules (e.g.fibrinogen, $\alpha_2$-macroglobulin, immune-globulin M and other "agglomerins") that lead to the formation of red cell aggregates or clumps. In addition, most diseases (especially in times where their prolonged course was not interrupted by specific therapies) were characterized by anemia, leucocytosis and bilirubinemia. It is well known that the anemia strongly favours the rapid sedimentation of aggregated red cells, the hyperfibrinogenemia and leucocytosis contribute to the mass of the buffy coat, the abundance of deeply yellow serum is a consequence of hemolytic anemia and bilirubinemia. Anyone seeing the experiment depicted in FIG. 3 would subscribe to the interpretation that the material obtained from the veins of patients is characterized by an abnormal mixture of fluids: the "dyscrasia" revealed itself clearly.

Our present knowledge of the chemical and cellular composition of the blood allows us to reduce these phenomena to a dysproteinemia of the plasma and a disturbance of the corpuscular composition of the blood. But it requires little phantasy to recapitulate the interpretation of observers that could only use their five senses. The notion that the yellow serum and the bile (content of gall bladder in all animals) were taken as one identical fluid, is

understandable, and so is the idea that the buffy coat or phlegma was identical with the sputum or the mucus excreted from lung and nose in inflammation. The black bile (melanchol) was considered to be a product of the spleen. Even this often misunderstood interpretation has a realistic foundation too: the spleen is the only organ which is normally almost black, simply because it contains very densely packed red cells (Hct > 80 %). Often, they are deoxygenated and thence much darker in appearance than any other organ. In animals dying in hemorrhagic shock (the usual fatality after stabbing), the preterminal splenic contraction leads to a tight stuffing of the vena lienalis with dark, highly concentrated blood. To a hunter eviscerating a dead animal, the dark splenic veins are much more readily visible than to the contemporary anatomist dissecting from the front. Since the splenic vessels communicate with the portal veins of the liver (where the production of blood was assumed) it is understandable that the spleen was taken as the source of "black bile". Thus, we understand why psychological disorders ("melancholy") have so long been associated with diseases of the spleen. To understand this, it must be stressed that not only Greek cosmology, physiology and pathology, but also psychology * drew upon the same scheme of four humours and qualities.

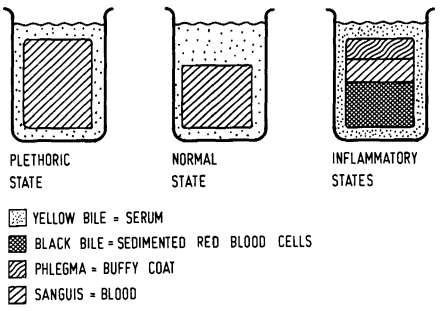


FIG. 4
Schematic representation of the macroscopic changes that can be seen in normal, plethoric and blood obtained from patients with inflammatory processes. For details see text.

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* This point cannot be pursued in the present context, any document of belletristic literature and fine arts will convince the reader that "prescientific" psychology was firmly based on a similar philosophy. The variant mixtures of the four humours in different men determined their "complexions" or "temperaments" (temperare = to mix). The ideal man was well "tempered", i.e. possessed a good blending of the four humours. Any predominance of one humour was made responsible for a "sanguinic", a "phlegmatic", a "choleric" or a "melancholic" disposition as well as for the physical and mental characteristics which the modern European languages still connect with these expressions.

## III. THE LOGIC OF PHLEBOTOMY: REMOVAL OF THE MATERIA PECCANS

Having familiarized ourselves with the macroscopic observations of the blood, it is now easy to understand a further logical step of the development of humoral pathology: the practice of phlebotomy. In various diseases mucus, bile, pus, bilious vomit, black bile (bloody stools and vomits) were "spontaneously" excreted. Furthermore, the actual discharge is well known to releave the suffering of the patient quite often. Thus, the intentional removal of noxious fluids ("materia peccans") by phlebotomy must have seemed a logical therapy, at any rate its integration in the theory of humoral pathology is utterly logical. Moreover, since phlebotomy can clearly releave symptoms (v.i.), the clinical success of this extremety popular procedure (well established at the time of Hippocrates ) must have been taken as a convincing corroboration of the entire concept of "dyscrasia" by physicians as well as the patients. In addition, the observation of the blood after phlebotomy brought to light the "truth" of the premisse since in patients (and not in healthy persons!!) it "revealed" conspicuously the abnormal mixture of humours. In retrospect, our present knowledge of the underlying abnormalities allows us to recapitulate the psychological motivation of the Greek founders and all their epigones to adhere to the teaching of humoral pathology: the theory possessed a powerful explanatory power, it predicted diagnostic observations that were regularly fulfilled, and it logically explained a therapeutic success.

Having verified the realistic basis of the theory and the diagnostic evidence, we can now turn to the "success" of the therapeutic phlebotomy: when done in small steps it must have led to an immediate, albeit symptomatic and palliative relief of symptoms. Before the advent of specific or at least more powerful palliative remedies, such a relief of symptoms must have been "sensational" and it would explain the popularity among physicians who were well aware of the dangers of excessive blood loss.

The symptomatic efficacy is best testified by the opinion of those physicians of the early 19th century (e.g. Magendie, Andral, Laennec in France, Bright, Addison, Hodgkin in England, Erb, Authenriet and Schönlein in Germany) all of whom ardently strove to overcome both the humoral pathology and the indiscriminate use of phlebotomy. In selected cases (e.g. rheumatism and severe inflammations, pneumonia, congestive heart failure, cerebral infarction and pulmonary edema) these authors admit the need for phlebotomy and praise the immediate relief of pain, of dyspnea, of angina or coma. Bauer (5), an uncompromising opponent of humoral pathology, resentfully cites positive opinion of the authorities listed above in his famous "Geschichte der Aderlässe" (1870). In pulmonary edema, phlebotomy is still used at present; in cerebral strokes it was widely used throughout the 20th century - and at present we witness the resumption of the idea to remove a "materia peccans". The success of plasmapheresis in severe cases of dysproteinemia and severe rheumatism, the success of plasma defibrinogenation in peripheral vascular diseases and

the successful practice of hemodilution (by infusion or exchange in ischemic diseases of the brain, the retina and peripheral limbs) can be explained by the removal of blood components,which, when present in excess, increase the viscosity of blood (6,7,8,9).

## IV. EARLY BIOFLUID-MECHANICS IN HUMORAL PATHOLOGY

The concept that dysproteinemia, polycythemia and coagulation disorders lead to diseases is probably one of the few ideas that have never disappeared from medical thinking since the times of Hippocrates. After the discovery of the circulation of blood by Harvey (10) this notion was supported by hydromechanical reasoning, which was introduced into clinical medicine by the famous Dutch physician Boerhave (11) at the turn of the 18th century. He studied the abnormal motion of blood in disease by intravital microscopy of the conjunctival blood vessels. His equally famous student von Haller (12) studied the reaction of the mesenteric blood vessels during phlebotomy of animals and reported an acceleration of blood flow by moderate hemorrhage, but a severe circulatory breakdown by massive bleeding.

The post-Harveyan extension of humoral pathology into hemodynamics is logically understandable and the compound of these two ideas must be regarded as the scientific root of our present concepts about the normal and abnormal flow properties of the blood. However, fluid-dynamic aspects of "dyscrasia" are much older than the discovery of the perpetual circulation of blood.

The writings of Aulus Cornelius Celsus (1st century A.D.), whose symptomatology of inflammation ("rubor", "calor", "dolor" and "tumor") has since been common knowledge of every medical student throughout the world, clearly reveal that the humoral pathology included theories about abnormal motion of blood in disease.Since the Alexandrian school of anatomy (Herophilus, c. 300 B.C.) it was assumed that the blood was in motion, normally flowing from the liver to the peripheral organs. Celsus teaches that the signs of inflammation, especially of traumatic inflammation, must be regarded as a local congestion as a consequence of blood stagnation or an inadequate discharge of blood immediately after the trauma (cited in Bauer, 1870).

This idea testifies that the doctrine of humoral pathology not only embraces qualitative, but significant quantitative considerations. The idea that disease is caused by too much blood in general ("phlethora") or by a local stuffing to an abundance of humors anticipates later concepts of hypervolemia, polycythemia and congestive heart diseases. In such patients, the abundance of blood was not only visible by the prominence of the cutaneous veins, by oedema and by cyanosis, but also by a distinctly different pattern of the blood when inspected after coagulation. Since the high hematocrit strongly retards red cell sedimentation, the red coagulum is enlarged more than proportionally. In addition, the clot retraction is very weak - and thence only small amounts of serum are found: macroscopically the diagnosis of a

phlethoric state must have been convincing. Thus, phlebotomy must have supported the assumption of a qualitative as well as quantitative disorder in "plethora" by subjective impromement as well as objective observations. For this reason, it is understandable that phlebotomy as a prophylactic measure in "plethora" was extremely popular throughout the ages (see FIG. 4 and citation Fahraeus).

As we see, the founders of humoral pathology even pursued "protohemodynamic" thoughts, which were obviously correct despite their ignorance about the blood circulation.

Celsus' symptomatology, as well as his pathogenetic theory has survived successfully and was later corroborated experimentally. Celsus' writings demonstrate an important additional rationale for phlebotomy: therapy of congestive states. Consequently, not only the amount of blood and the abnormal mixture of humours but the quality and filling of the veins was considered in the indication for phlebotomy. Again, we can clearly enter into the feelings of the ancient physicians and their patients: today as then, all symptoms of any trivial inflammation are clearly exaggerated by venous congestion, and immediately are relieved by decongestion (which is the most immediate consequence of a volume depletion of the circulatory system). Today we know that all inflammatory reactions are less severe in the presence of arteriolar constriction.

The practice of phlebotomy was extremely popular throughout the medieval centuries - the actual operation of a "venaé sectio" was performed by the barbers. The indication for the procedure as well as the site of the operation was prescribed by physicians.

Before the knowledge of the blood's circulation, veins close to the anatomical site where the disorder was seen (or suspected) were chosen by the physicians. In medieval illustrations depicting blood letting prescriptions we can identify every superficial cutaneous vein that can be filled by compression (FIG. 5). In addition, phlebotomy at a distance (the so-called "revulsive bleeding") was employed. "Revulsion" (from Latin "revellere", to draw back) by phlebotomy must have seemed logical to anyone believing that the blood flowed centrifugally from the liver to the veins. We can understand the basis of these interpretations, despite their totally erroneous assumptions. Immediately after Harvey(10), the essence of his idea of blood circulation was incorporated into the theory and practice of phlebotomy - and only those veins most prominent after ligature were used - although local blood withdrawal was not entirely abolished.

The influential Dutch physician Boerhave, one of the most prominent exponents of the so-called "iatrophysical school" incorporated the classical theory (to which he firmly adhered) into a pathogenetic theory which was rooted in the evolving laws of hydromechanics and he developed a hemodynamic pathophysiology on the basis of humoral pathology which has stood the test of time.

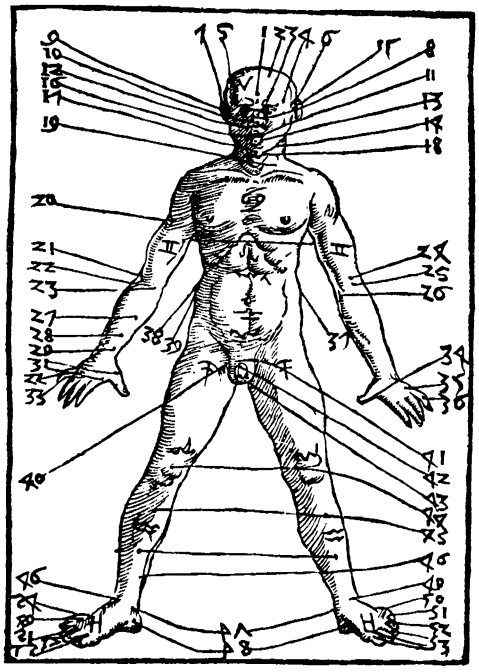

FIG. 5
"Blood letting man", illustration depicting the sites for phlebotomy for the relief of local or remote disorders ("revulsive phlebotomy"). Woodcarving from "Ein newe Badenfahrt", Strasbourg 1530

Boerhave was convinced that abnormal humours led to a clogging of the smallest blood vessels - and he studied the microcirculation in the conjunctiva of his patients with magnifying lenses. The Swiss physiologist Albrecht von Haller, one of Boerhave's many outstanding students, investigated the effects of phlebotomy on the mesenteric microcirculation of various experimental animals. Most textbooks of physiology cite him as a founder of modern neurophysiology, but he is also one of the early in vivo hemorheologists. In the attempt to understand the effect of phlebotomy, he studied the mesenteric microcirculation of cats and dogs extensively.

*"J'ai vû ensuite, que l'ouverture d'une veine occasionne un mouvement très rapide du sang veineux, même après qu'il a été long tems en répos, non seulement dans la veine ouverte & dans les rameaux qui s'y jettent, mais encore dans les troncs voisins, qui communiquent avec elle, & même dans les petites voisins, qui communiquent avec elle, & même dans les petites veines capillaires. Cette expérience ne manque jamais...."*

He continues later to discuss the clinical impact of these exper-


FIG. 6
Detailed prescription for phlebotomy at the junction of cephalic vein (G) and the basilic vain (F and C). The patient firmly holds and massages a stick in order to pump the blood. Copper engraving illustrating the "tractatus physico-medicus de homine" by Theodor Craanen, Leyden 1689.

imental observations:

*"Qu'enfin le grand Boerhave & avec lui presque tous les praticiens, espèrent qu'en faisant ouvrir une veine, ils y détermineront le cours du sang... & qu' ils rendront au sang sa fluidité...."*

We can clearly understand the impact of these often quoted observations onto the minds of any believer in humoral pathology. The development of intravital microscopy in the hands of pioneers of experimental pathology (e.g. Cohnheim 1882 (13)), clearly corroborated the pathogenetic hypothesis of Celsus. In all forms of acute injury (regardless of the cause) a typical sequence of microcirculatory changes accompanies the inflammatory reaction.The original description of Cohnheim has been copied almost verbatim in practically every textbook of pathology during the last century.

In his description of the microcirculation after injury we read:

*"Mit der Erweiterung, die allmählich sich entwickelt... beginnt dann im Mesen-*

*terium alsbald eine B e s c h l e u n i g u n g d e r B l u t b e w e - g u n g , am auffälligsten wieder in den Arterien, jedoch erheblich genug auch in den Venen und Capillaren. Doch hält die Beschleunigung des Blutstroms niemals lange an, sondern früher oder später... macht dieselbe ganz constant einer ausgesprochenen V e r l a n g s a m u n g der Stromgeschwindigkeit Platz, welche mehr oder weniger unter das normale Maass heruntergeht und fortan nicht mehr verschwindet...*
*... die Erweiterung der Gefässe ... nimmt ... sogar eine Weile lang noch zu und t r o t z d e m w i r d d i e B l u t s t r ö m u n g e r h e b - l i c h g e g e n d a s n o r m a l e M a a s s v e r l a n g s a m t ...*

To explain this he writes:

*"... da die Triebkräfte und das Blut selber keinerlei Änderung erfahren, so kann die lokale Verlangsamung der Blutbewegung nur von lokalen Widerständen herrühren... ist ... also in v e r ä n d e r t e n R e i b u n g s - und A d h ä s i o n s v e r h ä l t n i s s e n z w i s c h e n B l u t und G e f ä ß w a n d die Ursache gesteigerten Widerstandes zu suchen... Die Haarröhren sind dann ganz dicht mit Blutkörperchen vollgestopft, und zwar sehr überwiegend rothen,..."* (spacing in original)

This reaction in inflammation is common knowledge but it is often overlooked, however, that very similar intravascular changes are found in all forms of infarction. As a matter of fact, on the basis of these observations this type of tissue necrosis has been given its name (infarcire = to stuff). Here, again we best cite a contemporary textbook of general pathology (14).

The process of infarction is described as follows:

*"Infarction usually leads to a circumscribed area of coagulative necrosis... most infarcts contain a great deal of blood in the early stages, and are swollen and red in colour. The red cells entering the affected area escape through the damaged capillaries, and lie free in the dead tissue.There is also a great deal of fibrin derived from the blood (infarcire = to stuff). Infarcts have been classified according to their colour, but this is of limited value. It is apparent that most start by being red, and become white as blood is squeezed out and as the free haemoglobin is later removed."*

Space does not allow to penetrate deeper into the development of humoral pathology and of contemporary concepts of vascular pathology. The ecample cited, however, should be sufficient to convince the contemporary hemorheologist that - contrary to popular belief - the doctrine of humoral pathology is by no means only of "archeological" interest.

## V. CONTEMPORARY REPERCUSSIONS OF HUMORAL PATHOLOGY

Nobody will refute that modern pathological and pathophysiological concepts about inflammatory and circulatory diseases can be traced to their origins in the 18th and early 19th century. During this time, the "biochemical revolution" (Florkin, 15) and the discovery of cell biology led to the dominance of Virchow's

doctrine of cellular pathology. It is often overlooked, however, that Cohnheim's (13) description of the microcirculatory changes in inflammation and infarctions represent observations which are thoroughly "impregnated" (16) with theoretical concepts of humoral pathology. In other words, they reflect the adherence to the indisputable concept which attributed the observed flow retardation to compositional changes of the blood which interfere with its fluidity.

There is no doubt that this cardinal concept of contemporary hemorheology is basically correct. This idea continues to influence medical diagnosis, perhaps as unconsciously as "hematoscopy" influenced all physicians since the times of Hippocrates. Therapeutically, the fundamental motivation to remove noxious material ("material peccans") has led to such therapies as plasmapheresis and defibrinogenation. The indications for these remedies are exactly the ones laid down since Hippocrates for phlebotomy.

After the discovery of the essential role of the erythrocytes in oxygen transport, their intentional removal must have appeared as an absurd idea in the 19th century. After we have experienced the surprisingly good tolerance of the induced anemia in surgical patients (undergoing open-heart surgery) and more recently in patients with decompensated vascular disease, the simple notion that many red cells (high oxygen transport capacity) guarantee good tissue supply (high oxygen transport rate) deserves to be reconsidered. It looks at present, as if in severely diseased patients, who do not need to utilize the functional reserve of a high hemoglobin concentration, the benefits of a higher blood fluidity after isovolemic hemodilution might outweigh the drawbacks of anemia. Furthermore, it looks as if the evil symptoms of massive blood-letting might have been misinterpreted in the 19th century crusade against phlebotomy, since the consequences of hypovolemia (which are serious even at rest!) and those of anemia (which are serious only during exertion!) might have been confounded.

In the dawn of modern scientific medicine in the 19th century, humoral pathology was passionately condemned as the epitomy of irrational superstition. Despite Fåhraeus (1) this theory continues to be defamed. The following quotation from an important textbook of biochemistry by Florkin (15) may serve as an example.

*"This everlasting popularity evidently is the result of the antiscientific nature of the theory and of its direct appeal to realism and sensorial apprehension accessible to all individuals, even those incapable of abstract thinking ... In the medical development of the theory, the characteristics of the traditional approach of the clinicians are already recognizable. As based mainly on observation, medical science remains even today a retarded science... The retarded state of scientific pathology has long depended on the same obscurity as the pathological object remained occulted by the taste for the immediate sensible reality, common among the prescientific clinicians, prone to an overdetermined method of thought, was the mixing of the most heteroclitous observations, in which everything may be the cause of everything, and masking the real determination... In any case the handling of the diseases with observation, an aspect on which it is true that the Hippocratics devoted much atten-*

*tion, even if their medical theories have been, and still are, greatly overvalorized..."*

The best answer to this imputation is given by J.E. Thornton (cited as motto in (20)):

*"The more we treat the theory of our predecessors as myths, the more inclined we shall be to treat our own theories as dogmas".*

Nobody should misinterpret the present historical account as a"revival motion" for an outlined concept. Its aim is merely to remove the stains from a marvellously consistent medical theory 130 years after its sudden collapse. Virchow's criticism (17) of Rokitansky's attempt (18) to include the doctrines of humoral pathology into the evolving clinical and autopsy knowledge marked the sudden decline of this old philosophy and the victory of cellular pathology. One of the most impressing points of disagreement between these two giants of pathology and medicine concerned the physical and/or chemical nature of fibrin and/or fibrinogen. If one reads these arguments today, a large research programme of still unsettled problems comes to light, which remained unanswered simply because neither the morphological nor the chemical sciences employed extensively during the last 130 years offered any adequate "handle" to grasp these essentially hemorheological problems.

Thus, aside from solving these time honoured puzzles of great heuristical and practical importance, hemorheological research will continue to uncover the roots and ramifications of humoral pathology as it developed during the centuries. In the words of L. King (19) the lesson of history is best condensed as follows:

*"The doctrine of crases, like so much old medical theory, has been discredited. If we want to understand how it went astray, we should seek the implicit assumptions which had been accepted uncritically, and which distorted the measure of truth that may lurk even within error. The first assumption is a simple question of fact. When Rokitansky alleged a particular change in the blood, was that change "really" present? ... a second assumption, which complicates the question... may be called the assumption of homogeneity. That is to say, he was taking for granted that what he called fibrin in one case was the same as what he called fibrin in another case. ... The term "fibrin", as he used it, included a considerable number of factors which he could not discriminate.*

*... The third assumption concerns significance. Supposing that observations are factually correct... are they truly significant? Rokitansky believed that he observed certain changes in the blood in certain disease states. Assuming these to be facts, were they significantly related to the disease process?... A fourth assumption deals with unwarranted generalization. A formulation that might be plausible in one context should not be uncritically extended into other areas."*

Without referring to hemorheological research, King accounts for the conspicuous rise in "humoral" thinking as follows:

*"Rokitansky believed that humoral factors - blood proteins, for example - would explain disease processes. His insights,... have after a century and more received surprising support. ... Rokitansky has bet heavily on the blood as, somehow, the ultimate explanation in disease. Virchow, as we shall see, had bet on the cells, and superciliously dismissed the humoral factors. In the short run, knowledge of cells far outstripped chemical knowledge about the blood. Virchow seemed for a time to have backed the clear winner. But Rokitansky's horse, although a slow starter, had tremendous stamina, and after a hundred years began at last to reveal excellent form"* (spacing in original).

Risse (21) in a recent historical account of *"the renaissance of bloodletting"*, refers to *"withdrawal of blood"* as the *"rational therapy of plethora"* and quotes that *"all accounts"* testify to *"detectable objective changes"* and *"favourable objective manifestations in most patients, especially those affected by acute inflammations"*. This article scrutinously quotes the arguments of the last apostles of the old doctrine - and their refutation by the "new scientists" and their concepts derived from chemistry, morphology and conventional hemodynamics. Hemorheological pathophysiology - disease caused by abnormal blood flow behaviour - is accounted for in this article - but we look in vain for the explanation theories offered by Fahraeus. We are optimistic that King's predictions will come true - and we can hope that the present journal will have its shape in improving and shaping the form of a new "humoral pathology".

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