UNRAVELLING THE FUNCTIONS OF THE BLOOD

by

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In Northern Spain, not far from Altamira with its magnificent polychrome frescoes of stone age animals, is the cave of Pindal, and there it was, some twenty thousand years ago, that an Aurignacian man drew the outlines of a mammoth and then, in red ochre, marked in the heart and in creating the first anatomical picture, perhaps provided evidence of his understanding of the heart and the blood—its rhythmic beating continued as long as there was life; to strike the heart was a certain way to kill; as the blood ebbed from the wounds, so did the beast falter and die. On a winter's day the vapour from the blood would rise into the air and the stone age man might believe that with death, the vital spirit that endowed the animal with strength, escaped from the blood. We cannot say whether paleolithic man had these thoughts any more than we can be sure that the dark red mark on the shoulders of the Pindal mammoth does represent the heart, but certainly such beliefs are held by primitive races at the present day.

It is from Ancient Egypt that we can first trace an account of the blood, and even then the papyri are of the Pyramid period, when an organized way of life had been in existence in the Nile Basin for thousands of years. In the Papyrus Ebers we learn that food in the stomach was turned by the heart into blood; the heart was the central organ, the seat of nervous function and from it ran vessels to every part of the body, some of which contained blood but others were empty and contained air; these vessels also carried urine, tears, faeces, all of which came from the heart; the pulse was the heart speaking in the limbs. Disease was due to a disturbance of these vessels or their contents; if some of the vessels were filled with air, the heart would not speak and the pulse could not be felt; if the vessels of a limb were filled with faeces that part would die.

We see here a glimmering of the humoral hypothesis which was to reign supreme for 2,000 years and there is no doubt that Empedocles, who first put forward clearly the theory of matter based on the inter-relationship of the four elements—air, water, fire and earth—was influenced in his thinking by both Egyptian and Babylonian philosophies.

Empedocles also propounded the idea that the blood is the seat of the innate heat—'the blood is the life'—and that the heart was the chief organ of the pneuma, the vital spirit which was identified with both air and breath, and was distributed by the arteries, an idea gained from their emptiness in dead animals. It is uncertain when the doctrine of the four elements with their qualities of heat, cold, moisture and dryness was transferred to the four humours —blood, phlegm, black bile and yellow bile—which made up the body, but

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the humoral pathology is set out clearly in the treatise on the 'Nature of Man' of the Hippocratic code, which was written about 400 B.C. Historians have often regarded the Greek humoral pathology as a metaphysical concept, in which the humours had a dual meaning, in part the organic substances, blood, bile, phlegm, in part the metaphysical elements whose proper conjunction resulted in health and their disproportion disease. This dualistic view is an over-simplification for it is clear, as has been emphasized in recent years by Fahrëus, that though it is true that the humoral hypothesis was grounded in part on the philosophy of the four elements, stemming from the folk medicine of the early Egyptians, yet is was also based on clinical observations in blood letting, which as a form of diagnosis and therapy, can be traced back to the earliest forms of demoniac medicine.

The modern physician seldom has the opportunity to study the changes that occur when 100 ml or more of blood is allowed to flow rapidly into a tall container. At first it appears to be a uniform red fluid but then a change slowly takes place—the upper part clears and becomes a transparent yellow fluid, while at the bottom of the vessel accumulates a dark red, almost black jelly and at the surface there is a thin layer of bright red blood; in many diseases there will separate from the dark red jelly an upper layer which is pale greeny white. Here we have a demonstration of the dissociation of the humours from the blood, as it loses its innate heat and dies; the blood humour rises to the top, then comes the yellow bile and then the black bile from which the phlegm may separate. It was this separation of an apparent excess of phlegm in disease, which was to dominate pathology for over two thousand years and after a brief eclipse, when cellular pathology was in the ascendant, has returned to play a role in modern physiology and pathology. This was the layer known by innumerable names, the crusta phlogostica, the buffy coat, inflammatory pellicle or sizy blood, while nowadays we speak of a raised sedimentation rate and the interplay of fibrinogenesis and fibrinolysis in health and disease.

The Ancient Greeks held that the phlegm was formed in the brain and in health was blended with the other humours; indeed they were aware that it was mixed with the blood clot at the bottom of the bleeding bowl and that by shaking, it could be separated, so that the blood did not clot. In many diseases, caused by exposure, dietary indiscretions and so forth, there was an excess of phlegm, which could not be kept in subjugation or crasis but separated and congealed in the blood channels, impeding the spread of the pneuma. Disease was cured by a restoration of the balance of the cardinal fluids by a process of pepsis or coction, and the excess phlegm might be excreted from the body as vomit, sputum, pus, etc., at the turning point or crisis of the disease process; it was reasonable to assist nature by removing the disturbed humours by phlebotomy or purgation, and the necessity for this would be apparent by examining the blood and observing the presence of the crusta. Similarly a preponderance of any of the other humours might induce diseases which were sanguine, bilious or melancholic.

The other dogma—that of the innate heat—related to the humours, and yet distinct from them, was to survive until the seventeenth century and then to be transformed to the more restricted Hunterian view of vital spirits.

To the pre-Aristotelians, respiration was the chief path by which the vitalizing fiery spirit entered the body and the word inspiration recalls this ancient idea of the creation of life. To Aristotle, the innate heat, the implanted quality of life, was seated in the heart, but respiration, which drew the pneuma from the lungs through the body, had as its prime function the cooling of the animal heat, whether in the heart or in the blood, as Empedocles believed; the early observers had noted the differing colour of blood and attributed it to the presence of the vital spirits and it was this Aristotelian dogma, transmitted by Galen in a confused manner, which was to blind men's eyes to the call of the tissues for oxygen. Aristotle drew the analogy between the need of a candle and the innate heat, for air, but he believed that air was necessary to life and combustion, because it cools them and prevents them from burning out too rapidly, and that the warmer an animal is, the greater its needs for cooling. The heart was not only the source of animal heat, but it was also the source of sensation, the arteries conveyed messages to the limbs which provoked them to motion, this being achieved by drawing and slackening of the heart. The brain was mainly an organ which secreted certain cold humours that assisted the lungs in preventing overheating of the heart; the brain received the finer and purer blood from the heart, while the thicker and more turbid blood went to the lower limbs. Aristotle was pre-eminent as a natural historian because he was an observer and systematizer, whereas his physiology was a compound of philosophy and the views of others, as he had never dissected a human body.

The establishment of the Alexandrian Academy by Ptolemy I about 300 B.C. saw the rise of a school of experimental medicine whose importance it is hard to assess, for its literary achievements were totally destroyed and only survive in polemical fragments in Galen. Nevertheless it has been possible to determine something of the work of the early Alexandrian anatomists, Herophilus and Erasistratus; the latter came near to a discovery of the circulation.

Erasistratus, after an active life as a court physician at Antioch and elsewhere, devoted his later years to anatomical and physiological research. He considered that the body was compounded of atoms, vitalized by warmth derived from the outside. The foundation of energy was blood, which was propelled exclusively through the veins, and the pneuma, which was the energy carrier in the arteries. Renovation of the pneuma was achieved by respiration, by which air entered the left heart through the pulmonary veins and thence the vital pneuma passed into the arteries and regulated the bodily processes; the soul pneuma was carried to the brain and transmitted its effects through the nerves which were divided into those of movement and sensation. Blood was formed in the liver as a conversion product of ingested food and was carried by the vena cava throughout the venous system. Arteries and veins were related through ultimate venous ramifications—synanastomosis—which opened into the arterial terminations. Normally these communications remained closed, but in disease or injury they allowed blood to pass into the artery. If an artery was cut, the pneuma escaped and then, owing to the law of *horror vacui*, blood at once flowed through the synanastomosis and so venous blood escaped from the artery. The most frequent cause of disease was the overfilling of veins with alimentary matter—plethora, which interfered with the proper distribution of the blood in the veins and the movement of the pneuma in the arteries.

As can be seen, Erasistratus largely rejected the humoral hypothesis, replacing it by his theory of plethora, which was to persist until the eighteenth century and formed a justification for blood letting. Unfortunately Erasistratus maintained that scientific research, admirable for its own sake, was of little value in practical medicine and so his successors happily resorted to empiricism and no new concepts were to appear before the ponderous tomes of Galen fossilized biological thought for fifteen hundred years.

Broadly speaking the Galenical physiology corresponded to that of Erasistratus, but with several important differences, differences which impeded progressive thought until the sixteenth century. In the first instance, he rejected the idea of the facultative peripheral communications between arteries and veins and also rejected the idea that the arteries normally contained only pneuma; he showed by experiment that when an artery is opened no air rushes out and that it was possible to drain an animal of its blood by opening quite a small vein; indeed Galen held that the arteries contained blood of a special type which was thinner, purer and redder; blood was formed in the liver from the chyle and charged with natural spirits, carried nutriment and natural spirits through the veins to all parts of the body where it ebbed continuously to and fro; when the blood reached the heart it remained in the right ventricle for a while, parting with its impurities, which were carried off to the lungs by the pulmonary artery and exhaled to the outer air; hence the poisonous and suffocating character of the breath. But a small portion of the venous blood, still charged with natural spirits, passed through minute channels in the interventricular septum and so reached the left heart where it encountered the external pneuma and became converted into the vital spirits which were distributed with blood, to all parts of the body by the arteries, where it ebbed and flowed and could be felt to pulsate. The arteries to the brain, carrying blood charged with vital spirits, divided into minute channels, the rete mirabile, and there the blood was converted into animal spirits, an aethereal substance which was distributed by the nerves which were hollow structures. The structural basis for Galen's physiology is not man, but a complex of animals, and it only dawned on the Renaissance anatomists gradually that many of Galen's errors were due to his attributing to one animal the structure found in another.

As Galen rejected Erasistratus' synanastomoses, so he rejected his idea of plethora, supporting and elaborating the humoral pathology, so that it became a system of wonderful complexity. He was a great advocate of phlebotomy as a form of therapy—indeed it is in Galen's writing that the first account of the buffy coat is to be found—and furthered the idea that it mattered from which vein the blood should be taken and under which phases of the moon and stars; thus arose the science of judicial astrology, which so much occupied the minds of the medieval physicians; indeed the first medical texts to be printed were bleeding and purgation calendars.

The dead hand of Galen stifled biological thought for more than a thousand years and during this period all that we have is his ponderous works or commentaries upon them. It may be asked why did Galen have this great influence and the answer is twofold; he was an efficient, industrious man and his voluminous writings covered every branch of medicine; secondly and perhaps more important, he was a teleologist and of such a sort that his view conformed with medieval theology, whether Christian, Moslem or Jewish.

It is not necessary here to discuss why there was this aeon of darkness nor how it was that men began once more to question authority and look and think for themselves. The first overt break was on the question of blood lettings. It had been generally accepted, following the teaching of Avicenna, that blood should be taken as far from the lesion as possible or by revulsion as it was called. In 1514, Peter Brissot, a member of the Paris faculty, and a great admirer of the Greeks, concluded from his study of the original texts and his own observations, that the Arabic method was contrary to reason, experience, and the Hippocratic method, which advocated bleeding as near the lesion as possible, derivative or by diversion. This heresy engendered a furious controversy which ended in the defeat of the Arabists. These disputes on the site of venesection caused anatomists to pay more attention to the veins, and as a consequence their valves were recognized, the observation which chiefly directed Harvey towards the discovery of the circulation.

The strangling power of Galenical authority is well exemplified in Vesalius, the liberator of anatomy; as far as anatomical detail is concerned, he does not hesitate to question the Galenical canon, but when it comes to theory, he is more cautious and is unwilling, in the first edition of the *Fabrica*, to contest openly a doctrine accepted by both church and medicine. Twelve years later in the second edition he writes more freely:

Not long ago I would not have dared to turn aside even a nail's breadth from the opinion of Galen, the prince of physicians. . . . But the septum of the heart is as thick, dense and compact as the rest of the heart. I do not, therefore, know . . . in what way even the smallest particle can be transferred from the right to the left ventricle through the substance of that septum.

In 1553, for openly questioning the authority of the Church, Michael Servetus was burnt at the stake in Geneva; one of the arguments which he had used in his heretical views on the Trinity, was that the natural spirits of the blood did not pass through the inter-ventricular septum to form the vital spirit, but passed through the lungs.

There can be no question but that Servetus, in a theological disputation setting out the Unitarian viewpoint, displayed his recognition of the pulmonary circulation, gained perhaps as a student in Paris with Sylvius. It is equally clear that few, if any, of his medical contemporaries can have read his account, contained on two pages of a lengthy and involved theological treatise, of which the majority of copies were destroyed within six months of publication.

It is one of those insoluble priority wrangles, beloved of medical historians, as to whether Servetus' observation was known to his contemporaries or not, or who it was that first revealed to the scientific world this fundamental change in physiological outlook. Certain it is that it was the writings of Realdus Columbus that informed Harvey of the pulmonary circulation, however much it may be questioned as to whether the vain Cremonian really made the discovery himself.

There is no need to recall in all its details that memorable occasion on 17 April 1616, when William Harvey gave the first account of the circulation of the blood, but it will be necessary to consider a little the point which has puzzled so many historians, why it was that this momentous demonstration attracted so little attention, and for so long had so little influence on scientific thought. It is understandable that the small but select audience that listened to Harvey's second Lumleian lecture may not have grasped the significance of his conclusions 'whence it follows that the movement of blood is constantly in a circle and is brought about by the beat of the heart', but why, when his monograph on the *Motion of the Heart and Blood* was published in 1628, a treatise which has not its equal for conciseness and clarity of language, for logical sequence in which fact follows fact, argument on argument, proof on proof, did it cause such a slight stir in men's minds?

To the modern mind it changes everything, the spirits, the humours and the ebb and flow, these must all be cast away and in its place there is the transport of oxygen to the tissues and the removal of breakdown products, but this was not how it appeared to Harvey or his contemporaries, nor indeed to his successors.

In 1759, Richard Davies, a Cambridge scientist, wrote to Stephen Hale that:

> the discovery of the circulation has not been followed by so great advancement in the science of medicine as was naturally to be expected from it. The reason of which is, that our theory has not yet advanced much in the knowledge which is naturally founded upon this grand principle.

Davies has explained the paradox admirably; to his contemporaries Harvey had made some interesting anatomical observations, which might be open to dispute, and by mechanistic arguments, had propounded a remarkable philosophical theory, on Aristotelian principles, which differed from the Galenical system in vogue up till that time; but philosophical schools were always arising and disappearing, and if the blood did really move in a circle and moved so fast, what was the reason behind it all? Harvey was himself in some doubt; it was clear to him that the circulation of the blood was a microcosmic copy of the general cosmological concept and so conformed to the main Aristotelian tenets: the excellence of circular motion and the parallelism of the macrocosm and the microcosm, that is, the Universe and the living organism; but it was the purpose of respiration and the pulmonary circulation that was to remain unsolved, and until it was resolved, the disparity which Davies recognized was to persist.

At first Harvey accepted the view that the lungs were merely cooling fans which hindered the innate heat of the heart from causing its own destruction, and rejected the Galenic theory that, in addition to the cooling, some of the air inspired is retained in the blood and performs some useful function. In later years, he rejected the cooling theory as well and was frankly at a loss to explain the purpose of respiration; Curtis puts it:

Harvey's own clinching statement that the heart drives into the aorta at least one thousand drachms of blood in half an hour, this *reductio ad absurdum*, which cut the ground from under the feet of his opponents, left him helpless in his turn to account for the need of so huge a flooding of the arteries.

One of the immediate consequences of Harvey's demonstration were attempts at transfusion of blood. The earliest that we know of, was made in 1649 by Rev. Francis Potter, an ingenious and eccentric Fellow of Trinity College, Oxford, who may well have learned about the circulation from Harvey himself. The experiments failed on technical grounds, but there is a manuscript note on Potter's account 'Hanc Designationem Dr. Harvey frivolam et impossibelem omnino esse asseruit; sed tamen quaere'.

In 1656 Christopher Wren showed that a dog became exceedingly drunk when ale or wine was injected into the veins, which he felt 'to be of great concernement and which will give great light to the theory and practice of physic'.

Ten years later Richard Lower performed two transfusions on dogs, one of which was successful and as Pepys wrote:

it gave rise to many pretty wishes as of the blood of a quaker to be let into an archbishop and such like; but as Dr. Crone says, may if it takes, be of mighty use to man's health for the amending of bad blood from a better body.

The following year Jean Baptiste Denis performed the operation on a man in Paris and on 23 November 1667, Drs. Lower and King, at the Royal Society, transfused the blood of a sheep into one Arthur Coga, a simple minded clergyman. Jean Denis' patient requested a further transfusion and it is not altogether surprising that 'his arm became hot, the pulse rose, sweat burst out over his forehead, he complained of pain in the kidney and was sick at the stomach. The next day the urine was very dark, in fact, black'; a third transfusion was given with the inevitable result, and Denis was charged with murder, but was ultimately released. However, the Paris medical faculty prohibited transfusion, and in England, the Royal Society quietly discouraged these experiments and nothing was heard of transfusion for over a hundred years.

In 1781, Dr. Martin Wall, the Reader in Chemistry at Oxford, said that the attention of the learned in England to chemistry was considerably interrupted by Harvey's discovery of the circulation and by the doctrines and controversies to which it gave rise and in a sense he was right for it did, for a while, deflect men's minds from the chemical theories that were evolving, to a more mechanistic approach.

It was Paracelsus who translated the early alchemical concepts into human physiology, but it would be impossible in the compass of this paper to explain the complexities of his philosophy; however, it is necessary to consider the outlook of Paracelsus' spiritual descendant, Jan Baptiste van Helmont. Van Helmont is

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remembered for the creation of two neologisms, 'Gas' and 'Blas', of which only the former has survived, although to its creator it was the less important. 'Blas' was almost equivalent to the Archeus, a concept of Paracelsus to describe the exalted invisible spirit, which determined all the functions of the human body; there were a hierarchy of minor Blases all subject to and ministering to the Chief Blas and responsible for individual functions—movements, digestion, etc.

It was, however, Van Helmont's concept of ferments which was to influence the minds of medical experimenters.

He believed that there were six stages of fermentation involved in the conversion of food to flesh; in the stomach food was turned to an acid chyme, then in the duodenum, with the aid of bile, to a saline chyme which was absorbed into the mesenteric vessels. Blood formation started in these vessels and continued in the liver. In the heart the dark blood of the vena cava was charged with vital spirits and became lighter and more volatile.

The sixth and last digestion took place in:

> the kitchens of these several members, for there are as many stomachs as nutritive members, a ferment in each place cooked the food for itself and the blood vessels brought aliment prepared for the kitchen of the tissues, but it is not their kitchen. Each tissue maintains its own individual kitchen within itself. [He goes on to say] I make no distinction between vital and animal spirits. The same blood with the same vital spirits, vitalized blood, is carried to all the tissues. The boat has only one rudder, each tissue lives upon that blood, exercising its own functions, the brain and other nervous tissues behaving in this respect like the rest of the tissues.

It would not be difficult to postulate that this Belgian mystic, a contemporary of Harvey's, had described the oxygenation of the blood, the metabolic transport function of the blood, enzyme and substrate specificity; but it must be remembered that this account has been over-simplified and the innumerable Blases surveying each operation have been omitted. Nevertheless, as the founder of the iatro-chemical school, Van Helmont's concepts, shed of their mystical trappings, were to influence men's mode of thought in subsequent centuries. Van Helmont was also interested in the theory of mumia, or magnetic force, upon which the sympathetic cure of disease was based, and as Osler points out, his theories suggest not only the mechanism of wound infection but also the doctrine of immunity.

> For he who has once recovered from that disease hath not only obtained a pure balsamical blood, whereby for the future he is rendered free from any recideration of the same evil but also infallibly cures the same affliction in his neighbour . . . and by the mysterious power of magnetism transplants that balsam and conserving quality into the blood of another.

One of Van Helmont's disciples, Franciscus Sylvius, was of a very different calibre, the introducer of clinical bedside teaching and of the first chemical laboratory into Europe. He followed, but simplified, many of Van Helmont's ideas and he fully accepted Harvey's demonstration of the circulation of the blood.

Sylvius assigned a prominent part in the production of disease to the state of acidity or alkalinity of the humours. A common cause of fever was an acrid element which irritated the heart. Inflammation of the blood was dependent on its stagnation in the vessels, so that its more volatile and subtle parts, which commonly dilute the acid or alkaline portions, evaporated. These humours became more acid, induced a fermentation, and the blood might be so inflamed that it turned into pus; this purulent material might be deposited on the throat or angina or the lungs in pleurisy. This could be diagnosed from the shed blood by the buffy coat, which although it resembled pus, was not identical with it. There is little doubt that the lay expression 'inflammation of the blood' can be traced back to Sylvius, but it is more doubtful if one is justified in claiming Sylvius as the discoverer of acidosis and alkalosis.

It would be well to turn away for a while from these intriguing, but so easily misinterpreted, metaphysical concepts and consider a fundamental discovery in the morphology of the blood.

There is a dispute as to who first invented the microscope, but certain it is that by the middle of the seventeenth century, men were peering at this and that and could scarcely believe their eyes. One of these early microscopists was Jan Swammerdam who, in 1658, was the first to see the red blood corpuscles; three years later Marcello Malpighi, the founder of histology, discovered the capillary circulation in the lung, so converting Harvey's logical necessity into a histological certainty; his account was addressed to his brilliant but cantankerous colleague at Pisa, Giovanni Borelli, who founded the iatro-mechanical school, by his studies on the haemodynamics of the circulation, showing amongst other things, that the steady flow of blood from the arteries through the capillaries into the veins was the result of the elastic reactions of the arterial wall and thus the indirect, not the direct, result of the heart beat.

However, it was not until 1674 that the little Dutch grocer Antony Leuwenhoeck gave an accurate account of the erythrocyte.

He described the red cells as globules, and showed that they were circular in mammals and oval in birds and fishes, and that the red colour of blood was due to the corpuscles and not to the fluids. He even measured their diameters and did it surprisingly accurately. He also regarded the blood as a valuable indication of his own health, and examined it every day. A darker colour than usual he ascribed to an excessive congregation of the globules; if this were so, he drank four cups of coffee for breakfast instead of two, and six of tea in the afternoon instead of three. He discovered this thickness usually after he had supped too freely of an evening and found his method of treatment admirable.

Having displayed the capillary circulation, it still remained to determine the necessity for respiration; the facts were provided by that group of Oxonian Sparkles, who added so much lustre to the early days of the Royal Society, but unhappily, the theorists obscured the observations and it took a further hundred years to unravel the mystery. Robert Boyle was the first to produce matter of note. He took infinite pains to show that respiration cannot cool the blood. He did not see how it could apply to cold-blooded animals which respire by the lungs. Further, he suggested that it was against the economy of nature to make the blood of so excessive a heat that it needs to be perpetually cooled. Again, to his touch the heat of the heart of an animal did not feel burning but gentle, and finally he noted that the systole and diastole of the heart were not synchronical with those of respiration, the fact which had eluded Aristotle and misled everyone up to this time, so that even Harvey did not realize the great importance of this.

However, Boyle felt that there was more in respiration than ventilation and purification of blood, and thought that 'there is a little vital quintessence (if I may call it so) which serves to the refreshment and restauration of our vital spirits'.

He then showed that if a candle and a mouse were placed in the exhaustion chamber of his air pump, the animal died and the candle went out, almost simultaneously, as the air was gradually withdrawn. This fundamental experiment in the physiology of respiration proved that the animal and the candle depended on the air itself and that the two were not extinguished because of the accumulation of fulginous vapours, incident to combustion. The next step was taken by Robert Hooke, a universal genius who was the curator of experiments for the Royal Society. In 1667 he performed an experiment on artificial respiration before the Society, and showed that it was possible to keep an animal alive with the lungs motionless but distended with air, which could escape through small punctures on the parenchymal surface. This proved that it was the passage of air, and not the movements of the lungs, which was the essential factor of respiration, and that the concussion which it had been supposed was given to the blood, had nothing to do with it.

Two years later, Richard Lower observed that the blood going to the lungs was dark in colour and as it entered the heart from the pulmonary vein was bright red and he deduced 'that the blood imbibes the air as it passes through the lungs and that its red colour is entirely due to the admixture'. Lower believed that it was the whole air which was taken up by the lungs, but about the same time a young countryman of his, John Mayow, cognizant of Hooke's and Boyle's experiments, provided the real clue to the problem but his achievements were largely ignored, until 1790, when Thomas Beddoes called attention to his work.

Mayow showed that nitre, which had long excited the chemists, was formed in part from the air, which was not a simple elementary body, but contained an ignoaerial spirit which was essential for combustion or a breathing animal and that the air lost something of its elastic force with its absorption. Mayow was fascinated by this elastic force, and so his chemical discovery of oxygen was ignored, as it was in advance of contemporary thought, while attention was paid to the physical properties of his igno-aerial particles.

But the question still remained as to the purpose of these particles and Mayow suggested that:

> nitro-aerial particles, derived from the inspired air, supply the one class of motive particles which excites that effervescence which gives rise to the muscular contraction.

One of the reasons why Mayow's work was forgotten was that a new and attractive theory was propounded in 1697 by George Ernest Stahl, court physician and professor of medicine at Halle.

Stahl reintroduced the concept of the sensitive soul which controls all bodily actions, in opposition to the mechanistic physiology of Descartes, and for some curious psychological reason, a vitalistic theory is always acceptable.

He held that in the composition of a body, there intervened as a constituent part, a principle of fire, though not fire itself, which he called phlogiston. When such a body underwent combustion, the phlogiston departed from it, it became dephlogisticated and suffered a loss. It was Stahl's monster, phlogiston, which held chemistry back for a hundred years.

It will be necessary to leave the problem of respiration and animal heat on one side and turn to a consideration of the general ideas as to the function of the blood in the eighteenth century.

It is right that one should look to Herman Boerhaave, for as a great clinician and teacher, his influence spread throughout the world, and it is no exaggeration to say that the beginnings of formal instruction in physiology occurred at Leyden. In 1708, in an inaugural address he said:

> When the eye examines through the microscope the vital fluid, oh how simple is it what he observes; there the salted fluid carries the red globules. . . . From now on Harvey's discovery of the circulation will mean that medicine may be calculated aloof from any sect, because of definite discoveries in the field of anatomy, botany, chemistry, physics, mechanics and facts of practice.

Unfortunately his optimism was somewhat discredited by his own theory of the error loci.

Boerhaave held that there were four orders of capillary vessels, the largest carrying the red cells, the next the serum, the third the lymph and the smallest the most tenuous fluids. Having examined blood, diluted with water, and seen the formation of haemolysed ghosts, he believed that each red cell was formed by six yellow globules of heat-coagulable serum; the globules of the lymphatic juices which were six times smaller and also heat-coagulable, formed the serum and lastly there were the limpid humours, not coagulable by heat, such as urine, etc. If the blood ceased to move, it coagulated, due to the natural tendency of the particles to cohere one with another.

The chyle derived from the food entered the superior vena cava and was mixed in the right ventricle. The lungs were the site of blood formation, in that the compression of the air caused the particles of serum to be pressed together to form red cells, hence the difference in colour between the blood in the right and left heart, and the size of the red cells was limited by the diameter of the pulmonary capillaries. Animal heat was produced by the frictional effect of the red cells, in relation to the contraction of the vessels and although this occurred throughout the body, it took place principally in the lungs; the lungs both heat and cool the blood, the latter being achieved by the outside air. When the blood left the heart and was forced around the body, there was a segregation of its various constituents in relation to their size and also a gradual breaking down,

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so that red cells, formed of serum in the lungs, were broken down to serum, which entered capillaries of a size which would not admit red cells, and a similar process took place to allow the lymph to separate from the serum, even down to the most subtle juice or spirit of the nerves. These various fluids, having nourished the body, were consumed and expelled in the form of an invisible vapour, principally from the lungs.

Boerhaave was well aware of the experimental work of the English school of Philosophy, and propounded arguments against their observations; for instance the fact that air can be drawn out of blood by a vacuum pump did not prove that the air was taken up during respiration, but merely that air is taken in with the food and contained in the chyle and hence enters the blood. However, in spite of refuting these experiments, Boerhaave does reveal a sneaking doubt:

In the meantime it is certain that the air communicates or performs something more in the lungs than what we have yet discovered; for if it be not perpetually renewed it kills the animal, not from it being heated, rarified or condensed, but from some other latent change. Query whether it is not from the destruction of its elasticity? and whether this is not the secret Pabulum of Life in the Air, so much talked of by the Alchemists?

Consequent on this physiological concept, Boerhaave believed that disease was due to a stagnation and coagulation of the blood in one of the four types of capillaries, either due to an alteration of the capillaries themselves, or of the blood, so that the normal partition did not take place. The arteries proximate to the obstruction became distended, due to the force of the heart's action, so that redness and pain developed and in the adjacent non-obstructed vessels, the increased speed of blood flow resulted in local heat; thus all the phenomena of inflammation were easily explained. The coagulated material might be restored to a fluid state and carried away in the blood, or it might be converted to pus, or gangrene might develop; a special form of error loci occurred in the glands, when the matter was especially solid and tough, and formed a solid tumour called a scirrhus, which could in time develop into cancer.

It will have been noted that although Boerhaave recognized that both serum and lymph were heat coagulable, yet he believed that the blood clot was formed primarily by a coherence of blood cells with some intermixed serum.

Another of Boerhaave's errors was to assume that the character of coagulation in the bleeding bowl reflected the state of the blood in the body and it must be confessed that it is an assumption frequently made by the modern blood coagulationist.

Francis Quesnay attacked this idea in 1750 and showed that the 'humeur glaireuse' which collected at the top of withdrawn blood, before coagulating into the buffy coat, was in reality lighter and more freely flowing than the blood as a whole; this glairy humour or lymph was formed from the red corpuscles destroyed and reduced to a glaire by the action of the blood vessels; in some diseases this might be so marked, that the number of red cells were diminished, and so should be regarded as a process of dissolution rather than a thickening of the blood. However, if this fluid developed to excess, as a consequence of disease, it might coagulate in the large vessels, especially in the vessels of the lung and brain and so cause a fatal outcome.

Quesnay's views, although in part erroneous, are significant in revealing two changes of viewpoint towards disease; the first, that disease might be associated with a diminution in the amount of red blood cells, and secondly and far more important, the recognition of disease associated with a location in a particular organ, rather than as a consequence of a general humoral disturbance—an idea to be propounded in full, in 1761, by Morgagni, in his epoch making *De Sedibus et Causis Morborum per Anatomen indagatis*.

One of the last of Boerhaave's supporters was John Huxham and he is illustrative of the paradox, so often to be seen in medicine, of the sound clinician, who insists on propounding a fantastic philosophical theory to support his excellent observations. In 1755 Huxham gave a very careful and clear account of the different forms of infections, distinguishing their clinical features, but maintained that in fever, the red cells were altered by too rapid movement, and were torn and broken into small portions which entered the smaller capillaries and so escaped, forming purpuric rashes. As the blood became thicker and stickier, the increased friction and heat in the blood vessels separated off the thinner components, and so the blood remaining, became thicker still and as a result of this vicious circle, the heat was still further increased. The buffy coat was a layer of serum coagulated by warmth and the local symptoms were due to this serum sticking fast to the walls of the capillaries.

Nevertheless it was just at this time that the beginnings of modern ideas on the function of the blood became apparent, though there were to be many and curious byways of thought in the intervening two hundred years.

Joseph Lieutaud, a physician of Versailles, who first described the leucocytes in the blood, published in 1759 a *Précis de la Médecine pratique* which rightly became very popular on the Continent for it deals with disease on the lines of the modern textbook. Lieutaud has a chapter devoted to 'Anaemia'—an exhaustion of the blood vessels—which he says is quite common, although little attention has been paid to it, as it can usually only be recognized at post mortem examination; it is a condition which may arise after obvious blood loss or prolonged starvation, but sometimes it is to be found in persons who have not suffered in this way, when it must be attributed to a disorder of the organs of digestion or blood formation, and he has seen this in cachetic persons and in girls with long standing chlorosis; he then described the symptoms of anaemia, and the striking pallor and lack of blood in the vessels at post mortem. As to treatment, he says it is not worth describing all the drugs used in the cases that died, and it is difficult to be sure that the cases that recovered had in fact been suffering from anaemia, but in the few cases in which he was confident of the diagnosis, he believed that the good results could be attributed to some extent to iron and other tonics, but principally to a liberal diet.

Lieutaud's observations are of great importance, for he was the first to set down clearly the clinical features of anaemia and also to regard chlorosis as related to anaemia, but it should be appreciated that he used anaemia in the sense of a deficient quantity of blood, the converse of plethora rather than a deficient quality of the blood which is the modern use of the word.

William Hewson has rightly been regarded as the first haematologist, for his experimental observations advanced our knowledge of the nature of the blood in many directions, although he added little to our understanding of its functions. He is principally remembered for his work on coagulation, but his studies on the erythrocyte and leucocyte were almost as important.

Hewson's interest in blood coagulation had been aroused by the nature of the buffy coat, and having shown that it was the plasma alone that clotted and some of the factors that control this, he concluded that:

> the buffy coat is nothing else but a form of variation of the usual product of coagulation which appears when the blood corpuscles nearest the surface have had time to subside before the blood coagulates.

John Hunter did not add any significant observations to our knowledge of the blood in his *Treatise on the Blood, Inflammation and gunshot wounds*. He took the view that the blood was alive—the blood's consciousness of its being a useful part of the body—and that the contraction of the blood clot was a vital act analogous to the contraction of a muscle. He suggested that the occurrence of the buffy coat was not so much an indication of an inflammatory process, but of the body's protective reaction.

From the days of Van Swieten, observers had been puzzled by the fact that in pregnancy, the blood invariably showed a well marked buffy coat, which under ordinary circumstances was regarded as indicative of ill health. Van Swieten himself proposed that it was due to a stagnation of the blood in the uterine arteries, but to Hunter the explanation was simple, it was merely an expression of an increase of the life power of the blood acting on the foetus.

On 16 October 1793, while John Hunter was struggling in his death agony outside the Board Room of St. George's Hospital, the tumbril was taking Marie Antoinette to her execution, and six months later, the selfsame guillotine claimed as its victim Antoine Lavoisier, who led the revolution of physiology, and provided the answers which Harvey had been asking a hundred and fifty years before.

But it is necessary first to go back to 1754, when Joseph Black, a young Scottish chemist, showed in his graduation thesis that chalk on heating or being treated with acid gave out a gas—fixed air, and that quicklime on exposure took up this fixed air and became slaked; this was the reverse of the phlogiston theory, which held that chalk took up phlogiston on being heated and quicklime lost phlogiston on being slaked. Further, Black showed that expired air contained fixed air and was irrespirable. Stahl's phlogiston had received a mortal wound, but its vital principle was strong and fantastically enough, Joseph Priestley, who by his preparation of oxygen in 1775, struck the final blow, yet struggled in his discovery to perpetuate the phlogiston theory. Priestley was trying to render expired air once more respirable, and he found that vegetation had this property; he then found that various metallic oxides, though of course they were not thought of as that, would give off a gas on being gently heated and that this gas not only caused a flame to burn more brightly but a mouse lived well in it, and dark venous blood became bright arterial blood. To explain this in terms of phlogiston, Priestley decided that common air was partially dephlogisticated and so could only take up a certain amount of phlogiston whereas his new air had all the properties of common air in much greater perfection and so he called it dephlogisticated air.

Thus Priestley, dominated by a theory, propounded a mirror image of the truth and it was Lavoisier who saw the truth and totally destroyed phlogiston by a pair of scales. Metal when it was burnt to the oxide did not give up phlogiston to the air but took something from it. Venous blood absorbed 'oxygine' as he called it, from the air and so became bright and bright blood absorbed 'aeriform calcic acid', for he had shown that Black's fixed air was a compound of carbon and oxygen, and became dark like venous blood. He almost interpreted the function of respiration correctly, but was confused by his physiological colleague Sequin, and though they recognized that digestion supplies the blood with the carbon and hydrogen necessary for combustion, which is oxidized by the respiratory process, thus producing heat and that the products of combustion were disposed of through the skin and lungs, yet he thought that a humour, principally composed of carbon and hydrogen, was secreted from the blood into the bronchi and that the whole oxidative process occurred in the lungs. The idea of this hypothetical hydrocarbonaceous fluid was accepted as an essential part of the theory of respiration until 1837, when Gustave Magnus, by the use of a vacuum pump, showed that venous and arterial blood both contained oxygen and carbon dioxide though in different proportions. It might well have been that Lavoisier would have corrected his erroneous idea, but his paper on respiration was read before the Academy of Sciences in April 1790, in the early days of the Revolution, and Lavoisier, though probably in sympathy with some of the aims of the Revolution, had been a successful administrator, under Louis XVI. On 14 November 1793, he was arrested for his activities as a tax-collector and later executed, the President remarking 'La République n'a pas besoin des savants'.

The early part of the nineteenth century revealed a definite regression in the study of the function of the blood and many of the eighteenth century achievements were forgotten. This was partly due to a misdirected enthusiasm for chemistry, which inferred that anything related to the humours could be ignored. In its place came the vitalistic philosophies and in medicine it was the ruthless François Broussais who led the field, behaving as he did when a sergeant in the Republican Army. Broussais modified the Brunonian theory by maintaining that life depends upon irritation and in particular heat, which excites the chemical processes of the body. Disease was due to a localized irritation of some viscus and should be treated by a powerful antiphlogistic or weakening regime, which consisted of starvation and blood letting. This arbitrary doctrine was overthrown by the statistical arguments of Louis, the sarcasms of Laennec and

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Hahnemann's homeopathy. Phlebotomy as a part of therapy slowly but steadily disappeared, but it is interesting to note that as late as 1920, there was a serious discussion at the Royal Society of Medicine on this subject at which many of the older physicians recalled its value and regretted its passing.

It was Jean Cruveilhier, the first professor of pathological anatomy in Paris, who restored interest in the blood in 1837 by his famous doctrine 'La Phlébite domine en quelque sorte la pathologie tout entière'. It stemmed from John Hunter's vitalistic views of inflammation, but Cruveilhier was more precise, as he believed that inflammation was characterized by hyperaemia with capillary stasis and a secretion from the capillaries themselves which could be fibrin, pus or caseous material. He distinguished adhesive phlebitis (although the word 'thrombosis' was coined by Galen, it did not come into popular usage until about 1856) from suppurative phlebitis, but he failed to recognize the possibility of embolism or the nature of pyaemia.

Far more important were the achievements of his contemporary, Gabriel Andral, who laid the foundations for an accurate assessment of the quantities of the various constituents of the blood in health and disease, by determining the relative proportion of corpuscles, fibrin, serum, albumen and solids; he showed that there was a diminution of fibrin in fevers, scurvy, after haemorrhage, and an increase in pneumonia and that it was possible to distinguish primary anaemias from those secondary to blood loss.

Andral described the changes in the blood in anaemia, jaundice and gout and he pointed out that there was invariably a diminution of the albumen in the blood before renal dropsy developed and a similar change was observed in nutritional oedema. He came to no definite conclusions as to the reasons for this association, asking:

> Is it the change effected in the physical qualities of the serum, by the loss of albumen, which assists the former through the vascular porities? Is this then a case of endosmosis favoured by the diminution in density of the fluid?

It was Starling who finally provided the answer, but it is obvious that Andral had an inkling of the truth.

Not only was there a revival of interest in the blood in disease, but also as to its general functions. One of the problems was the nature of the red colouring matter. Robert Boyle had noted that the blood residue, after ashing, was red, and Menghini in 1747 showed that iron was present, separating it from the ash with the aid of a magnet, and he maintained that iron preparations were absorbed rapidly from the stomach into the bloodstream, and could be detected there.

However, William Charles Wells, the medical philosopher, showed in 1797 that the colouring matter in blood was not iron but a complex organic substance; such a substance was isolated by Chevreul and was in fact haematin; it was soon realized that this was not identical with the colouring matter of the blood, which was called haematoglobulin, by Simon and other chemists, but could not be isolated in the pure state.

Franz Simon, a brilliant German chemist who died at the age of thirty-six, propounded the following ideas of the function of the blood in 1840. The nutrition of the organs is provided by the albumen, fibrin and fat of plasma and the cells of the organs possess an inherent power of selecting proper material for nutrition, or forming it from non-homologous matter, at the same time secreting breakdown products, which are chiefly lactic acid and non-protein nitrogenous material. The erythrocytes which are formed from leucocytes, as Hewson suggested, take no part in cellular nutrition, except in so far as they form fibrin, but are the source of animal heat; they absorb albumen and fat, and oxygen from the lungs, and in the course of their production of animal heat are broken down, largely in the lungs; hence they have to be constantly replaced; the products of their breakdown are carbon dioxide, urea, fibrin and bile. In this hypothesis one can see the vitalistic idea persisting, though clothed in chemical terms, and the belief that the red cell formed fibrin was based on a whole series of anomalous theories which cannot be pursued here.

Two years later, Justus von Liebig communicated his important paper on 'Chemistry in its Application to Physiology and Pathology' to the British Association, in which he introduced the concept of metabolism into physiology. His views show a great advance on Simon's hypothesis, and it is illustrative of the ferment of men's minds at this time, that two great physiological chemists, both of about the same age and with a similar background, should handle the facts so differently. To a minor extent it was Priestley and Lavoisier again; Simon was hampered by the theories of others; Liebig was a materialist, who would not look down a microscope and did not believe in such vital agencies as bacteria and living ferments. Liebig starts with the idea that red cells contain a compound of iron which can combine with oxygen or carbon dioxide, and that this is reversible, and is not associated with a breakdown of the basic compound but, as he puts it, 'the compound they form with carbon dioxide is destroyed by oxygen'. Accordingly he suggested that red cells leave the lungs with the iron compound saturated with oxygen, and this oxygen is given up to the tissues in the capillaries to play a part in their metabolism, and having lost oxygen, the red cells take up carbon dioxide from the tissues (produced as a result of tissue oxidation), and the venous blood then gives up the carbon dioxide in the lungs owing to the high oxygen content of the inspired air. Accordingly oxidation is taking place in two places in the body: in the lungs and in the capillaries, and the animal heat is provided by the latter.

There was considerable resistance to the acceptance of this hypothesis, largely because haematin would not do the things that Liebig had suggested his iron compound would do. However, in 1849, Reichert obtained haemoglobin crystals in the guinea-pig and in 1862 Hoppe-Seyler showed that haemoglobin had in fact the properties of Liebig's hypothetical iron compound.

William Addison, a general practitioner of Malvern and so far as we know unrelated to his more famous contemporary, Thomas Addison, was the first to reveal something of the function of the leucocytes. He recognized the granulocyte, observed diapedesis in inflammation and the identity of pus cells with

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granulocytes; he also emphasized the protective and reparative function of the leucocytes, and the functional significance of the inflammatory reaction, but like so much of the English work of this period, it was all forgotten and ignored, to be fought over again by Cohnheim and his adversaries in the 1870s. Addison was also the first to see the platelets, for which there are innumerable rival claimants, but more important, he recognized their relationship to the formation of fibrin which is usually attributed to Bizzozero.

In the field of blood coagulation proper, Andrew Buchanan, in 1845, revealed the enzymic nature of blood coagulation by some beautifully performed experiments, which were also forgotten, only to be confirmed by Schmidt in 1872.

Another problem that began to be explored was the source of the erythrocytes; it was generally agreed that the leucocytes were formed in the lymphoid organs and Hewson believed that the red cells were derived from them; this view in one form or another was generally upheld and when Zimmerman observed the platelets in 1845, he believed that they were the source of the erythrocytes, a view maintained by the great French haematologist Georges Hayem until his death in 1833. Thomas Addison, in his clinical account of pernicious anaemia, confused it with the other condition which he described—adrenal insufficiency—and suggested that the adrenals:

> hitherto mysterious in function, might be either directly or indirectly concerned in sanguinification, and that a diseased condition of them may interfere with the proper function of the body generally or the red particles in particular.

In 1838 Weber had observed nucleated erythrocytes in a human foetus and two years later Reichert saw them in the embryonic liver and suggested that this might be the site of blood cell formation.

In 1845, Kölliker agreed with this but thought that the spleen might also play a part; he had examined the bone marrow and found it consisted of fat and medullary cells of unknown function. So the matter remained until 1868 when Ernst Neumann demonstrated that the mammalian red corpuscles arise throughout life from colourless nucleated elements in the bone marrow. Claude Bernard hailed this epoch making discovery with delight, while Charles Robin, a distinguished histologist, considered that Neumann was encumbering science with this new theory.

However, this period was not lacking in theories to encumber science, and the most famous was Rokitansky's revival of the humoral hypothesis. Rokitansky was a magnificent descriptive morbid anatomist, but not content with observations, he propounded a theory to explain the changes. He seized on Andral's work on the varying fibrin content of the blood and Cruveilhier's concept of phlebitis and suggested that all diseases were derived from a primitive affection of the whole blood mass, probably of chemical nature, which he termed a 'crasis' and which was characterized by a hypothetical variation in the type of fibrin, each of which had a specific affinity for a particular localization; it was a theory susceptible to infinite refinements of classification and inter-conversion.

A Berlin graduate aged 26, who had only been qualified three years, and had just been appointed prosektor at the Charite Hospital, reviewed Rokitansky's book ruthlessly, in which, after tearing it to pieces bit by bit, the extravaganza of crasis was described as a monstrous anachronism. It is said that after Rokitansky had read Virchow's criticism, for he was the young man, he could never look at his book again, and certainly no mention of crasis appears in later editions.

Rudolph Virchow had already attacked Cruveilhier's concept of phlebitis, and being of a critical rather than a constructive turn of mind, it was a problem after his own heart. He first of all studied blood coagulation and the nature of the fibrin clot from a chemical point of view; he decided that there was only one type of fibrin, which could only be detected by the act of coagulation, and that most of the fibrin in the body was fibrinogen (Virchow coined the term), which was formed in the lymphatic and connective tissue, and was activated or converted into fibrin by the presence of oxygen. Virchow then went on to study obstruction of the pulmonary artery, and observing the frequent association of infected venous thrombi with pulmonary abscesses, introduced the revolutionary doctrine of embolism in 1846.

Virchow's concepts of thrombosis and embolism were of the first importance from the point of view of general pathology, yet their mechanistic simplicity deflected attention, as far as clinicians and pathologists were concerned, from the process of coagulation which initiated the thrombus and this became the exclusive prerogative of the physiologists; this segregation of interests was a harbinger of the isolationism in the study of the functions of the blood which has impeded research and a proper understanding of its nature and is only in recent years beginning to be broken down.

The next two decades saw the introduction of Virchow's concept of cellular pathology, the development of bacteriology and immunology, the introduction of mensuration into haematology and the characterization of those conditions now regarded as diseases of the blood. It was also the period when Claude Bernard was enunciating his views on 'general physiology' which were largely ignored, and with advancing techniques and increasing specialization there were increasing divisions between clinicians, pathologists and physiologists, and within each speciality the great systems such as the circulation, kidney, respiration, were studied in water-tight compartments with no attempt at correlation. As a result it is impossible to discourse on the views as to the functions of the blood in the last hundred years for there was no community of views and a list of the individual observations could but be confusing.

This isolationism can well be illustrated by examining the contents of the sixty odd editions of that ultra centenarian *Kirkes' Handbook of Physiology*. From the first edition in 1848 until the 12th edition of 1888, the chapter on the blood describes its physical and morphological characters and powers of coagulation, but the account of its functions are scattered through other chapters. The next edition, edited by Morant Baker and Vincent Harris, does not alter this arrangement but an opening sentence is added to the chapter

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on the blood, that its function is the direct and indirect nourishment of the tissues; this segregation continued during the forty-six years that this book changed to *Halliburton* and then to *Halliburton and McDowell*, but in 1944, when it became *McDowell's Textbook of Physiology*, the chapter on the blood was, for the first time in ninety-six years, completely re-written and now contained a comprehensive account of the many and various functions of the blood.

In studying the history of science it is often hard to determine where a change of viewpoint arose, but there is no difficulty as to the source of the reorientation which views the functions of the blood as a whole.

It was in the Department of Physical Chemistry of Harvard Medical School, where Professor Cohn and his colleagues devised the method of fractionation of the various constituents of the blood, based on the precipitation of proteins from alcohol-water mixtures at low temperatures, as part of a wartime plan for the provision of plasma and other blood products. By this method it was possible to separate the blood into a large number of fractions which maintained their functional activities and it was inevitable that this array of bottles standing together on one laboratory shelf, should raise the question: What is it all for?

Naturally the isolated knowledge which this work integrated and the technical achievements which made it possible have many and various sources which can only be touched upon. It was Boerhaave who recognized the existence of albumen in blood, and likened its function to the white of an egg; Mulder who, in 1820, named these substances proteins because he believed they were of first importance; Prosper Denis who, in 1859, isolated globulins by the process of salt precipitation, a method perfected in this century by Gowland Hopkins and Sørensen. In 1899 Sir William Hardy, having abandoned histology for a study of the molecules of which tissues were composed, in his development of colloid chemistry, characterized proteins as amphoteric electrolytes and so opened the way to electrophoresis. These were some of the foundations on which Professor Cohn and his colleagues built their achievements. In 1944 Cohn provided a masterly review of the whole subject in which he said:

> The mysteries that have always been ascribed to the blood have not been entirely solved by modern science. Blood performs more functions than we have learned to ascribe to the substances in it that we recognize. We now recognize many substances in the blood whose functions are not yet understood. We may hope, however, to resolve these mysteries by increasing our knowledge of this 'juice of rarest quality' which is the circulating fluid of the body.

This survey can best be concluded by two other quotations, one from Harvey, the other from Robert Boyle.

> It is thus demonstrated that a perpetual motion of the blood in a circle is brought about by the beat of the heart. What shall we say? Is this for the purpose of nutrition? Or is it for the better preservation of the blood and of the members by imparting heat to them, the blood by turns losing heat as it warms the members?
>
> It is highly dishonourable for a Reasonable soul to live in so Divinely built a Mansion as the Body she resides in, altogether unacquainted with the exquisite structure of it.

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This paper is based on a lecture given to the Faculty of the History of Medicine of the Society of Apothecaries on 2 December 1960, and is an abridged version of an introductory essay appearing in a volume 'The Functions of the Blood' edited by R. G. Macfarlane and myself (by the Academic Press 1961); in order that the lecture might not be intolerably long, it was necessary to omit many steps in the argument, so that the sequence of ideas may, in this account, appear obscure.

It would be an affectation to give the references of all the books and papers that have been mentioned in this essay but it would be churlish not to acknowledge some of the authors who have influenced its writing and the principal of these are:

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