FUNCTIONS OF THE BLOOD

Edited by

R. G. MACFARLANE
M.A., M.D., M.R.C.S., F.R.S.

and

A. H. T. ROBB-SMITH
M.A., M.D., F.R.C.P., M.R.C.S.

1961
ACADEMIC PRESS, New York and London

ACADEMIC PRESS INC.
111 FIFTH AVENUE
NEW YORK 3, N.Y.

U.K. Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
17 OLD QUEEN STREET
LONDON, S.W.1

Library of Congress Catalog Card Number: 60-8051

PRINTED IN GREAT BRITAIN BY
SPOTTISWOODE, BALLANTYNE AND CO. LTD.
LONDON AND COLCHESTER

LIST OF CONTRIBUTORS

H. R. BIERMAN, *Institute for Cancer and Blood Research, Beverly Hills, California, U.S.A.*

J. P. BULL, *Birmingham Accident Hospital, Birmingham, England*

H. HARRIS, *Sir William Dunn School of Pathology, Oxford, England*

F. HAUROWITZ, *Department of Chemistry, Indiana University, Bloomington, Indiana, U.S.A.*

M. HEIDELBERGER, *Institute of Microbiology, Rutgers, The State University, New Brunswick, New Jersey, U.S.A.*

L. V. HEILBRUNN, *Zoological Laboratory, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.*

W. HOLMES, *Department of Zoology and Comparative Anatomy, Oxford University, Oxford, England*

R. G. HUNTSMAN, *Department of Pathology, St. Bartholomew's Hospital, London, England*

O. P. JONES, *Department of Anatomy, School of Medicine, University of Buffalo, Buffalo, New York, U.S.A.*

H. LEHMANN, *Department of Pathology, St. Bartholomew's Hospital, London*

R. G. MACFARLANE, *M.R.C., Blood Coagulation Research Unit, Churchill Hospital, Oxford, England*

A. E. MOURANT, *Blood Group Reference Laboratory, Medical Research Council, London, England*

O. J. PLESCIA, *Institute of Microbiology, Rutgers, The State University, New Brunswick, New Jersey, U.S.A.*

A. H. T. ROBB-SMITH, *Department of Pathology, Radcliffe Infirmary, Oxford, England*

D. S. ROBINSON, *M.R.C., Sir William Dunn School of Pathology, Oxford, England*

H. P. WOLVEKAMP, *Zoologisch Laboratorium der Rijksuniversiteit te Leiden, Leiden, The Netherlands*

FOREWORD

In biolog , as in most branches of science, the progress of knowledge is rapidly outstripping the power of the human mind to assimilate and view it as a whole. The result is the disintegration of something which was once generally understood into a growing number of isolated specialities, with their own techniques and language, and their own societies and journals—a situation reminiscent of the one which brought the building of the tower of Babel to an ignominous halt. At the present time a book on "the blood" which was at all comprehensive would cover a range of specialized subjects, each completely intelligible only to its own exponents; and in such a book morphologists, cytologists, geneticists, immunologists, biophysicists, protein chemists, coagulation workers and rheologists might find little to interest them outside their own particular field. A more restricted alternative would be a book on "haematology", a term which has come to refer to the clinical or pathological applications of specialized research. But there are already many books on haematology, and many advanced and factual reviews on its various subdivisions. In planning the book presented here, the editors have tried to find some unifying approach which would give a common interest to these diverse ways of studying the blood. The idea which seemed to provide most promise was the idea of function. Though one hesitates to ask such a teleological question as "What is the blood *for*?" it is perfectly legitimate to ask "What does the blood *do*?" Most of the divisions between the branches of biological investigation stem from differences in technical processes, and often from differences in the methods for determining the *structure* of living matter. If the idea of function were the predominant one, then structural differences become less important, since the same vital function can be adequately performed by chemically different substances (e.g. the respiratory pigments). This is, of course, a return to physiology in its widest sense, and to comparative physiology in particular, since the tracing of the evolutionary pathways by which functions are developed may reveal basic mechanisms which are difficult to discern in the complex systems of higher animals.

It is one thing, however, to have what seems to be a good idea, and quite another thing to put it into effect. Having mapped out a series of chapter titles which we hoped might be treated in this way, we tried to persuade our authors to orientate their ideas to the basic idea of function. But the habit of severely factual writing, acquired from years of painful scientific education dies hard. It is now very difficult to get a scientist to speculate in print, and some licence to speculate was particularly desirable here, since only speculation can connect much of what is known about function and make it intelligible. We wanted a review of ideas, rather than the dry reviews of undigested and disconnected facts which seem to occupy so much of the biological literature of today—a review of biological strategy rather than the tactics of research.

In some cases the subjects of the chapters have proved to be amenable to the treatment we hoped for, in others it has been difficult to achieve. Perhaps we asked too much of our authors; of this the reader must judge for himself. One effect, undoubtedly, has been that several years have elapsed since the inception of this book, so that some chapters received early may now appear somewhat dated, if the lack of quotation of 1959 and 1960 references in the text is taken as a guide. But, in a book of this sort, this "up-to-the-minute" criterion applies much less validly than it would to a collection of abstracts or the conventional review article. Ideas move more slowly than facts; most of the ideas, for instance, on which modern blood coagulation work is based, were current a century or more ago. A 1960 reference is not necessarily more valuable than an 1860 reference just because it is newer; often, in fact, a recent reference is essentially similar to some earlier and neglected work, and a better knowledge of the latter would prevent the endless rediscovery and republication of the same facts which so burden the literature and those expected to read it. The editors must, of course, take the responsibility for the leisurely pace of production, but they hope that readers of the book, and the authors, who have contributed to it will understand the reason and consider that the result has justified any imagined disadvantage.

THE GROWTH OF KNOWLEDGE OF THE FUNCTIONS OF THE BLOOD

A. H. T. ROBB-SMITH

Department of Pathology, Radcliffe Infirmary, Oxford, England

---

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 so created the earliest anatomical picture. It is generally believed that these drawings were part of the rituals of sympathetic magic and that, before a hunting expedition, prehistoric man performed some mystic rites deep in these caverns, surrounded by the images of the animals he hoped to vanquish; spears were thrown at the painted symbols in the belief that this would give the hunters the magic power to strike down the mammoth, bison or red deer.

If the dark red mark on the shoulders of the Pindal mammoth does represent the heart, we have here the earliest evidence of the understanding that came to primitive man of the heart and the blood; its rhythmic beating continued as long as there was life and 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. Whether paleolithic man had these beliefs cannot be known, but certainly they are held by primitive races at the present day and with them, this interplay of magic and religion. It is from Ancient Egypt that we can first trace a historical 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 these writings we can see the two sides of medicine, the magical and the natural, but only traces of physiology and pathology; it is somewhat doubtful how much, if at all, these theories influenced medical practice. 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 interrelationship of the four elements,—air, water, fire and earth, was influenced in his thinking by both Egyptian and Babylonian philosophies. Our knowledge of Sumerian biological thought is tenuous, but it would seem that to them it was the blood that was the actual vital principle, having the liver as its central organ, and being of two sorts, day and night blood (red arterial and dark venous), while the heart was the seat of understanding. The major fabric of Babylonian medicine, however, was a compound of astrology and mysticism.

Empedocles was a Sicilian aristocrat who lived at Acrages about 470 B.C. In his poem "On Nature" he epitomizes his philosophy

"Listen first, while I sing the fourfold root of creation,
Fire, water and earth and the boundless height of the aether,
For therefrom is begotten what is, what was, and what shall be."

Empedocles also put forward 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 (pituita), black bile (melancholia) and yellow bile (choler), which made up the body, but 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. and is attributed to Polybus, the son-in-law of Hippocrates. 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 it 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, and was in active use by the Hippocratic school.

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 sanguinis, inflammatoria or 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 sub jugation 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 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 (jaundice) or melancholic.

The other dogma—that of the innate heat—related to the humours and yet distinct from it, was to survive until the 17th 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 in its broadest sense, recalls this ancient idea of the creation of life. To

Aristotle (384–322 B.C.), 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 for 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, for palpitation occurs when the emotions are stirred; 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 which 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 a systematist, whereas his physiology was a compound of philosophy and the view of others, as he had never dissected a human body; however, his views were far from being accepted by his contemporaries or the later Alexandrian School. For example, Diocles (*c.* 350 B.C.) the last of the Hippocrateans, and the first physician to write in Attic Greek, was more concerned with the mechanism of digestion than respiration. He likened digestion to fermentation and saw in the abdominal viscera a source of animal heat; he believed that the liver was the factory where blood was formed from food and that the heat there generated, but reinforced by some vital spark, was carried to the heart, which was the heat centre of the animal system; furthermore Diocles believed that the arteries contained some blood together with pneuma.

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, and the latter is of importance in relation to the functions of the blood, for he came near to a discovery of the circulation.

Erasistratus (330–250 B.C.), after an active life as a court physician at Antioch and elsewhere, devoted his later years to anatomical and physiological research; his ideas evolved from the pneumatic and peripatetic doctrines, but were checked by anatomical dissection and experiments. He considered that the body was compounded of atoms, vitalised by warmth derived from the outside. The foundations for 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 (the cerebellum was its particular seat, based on experimental observation of the fatal result of injuries in this site) 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; the alternating action of the valves in the right heart preventing regurgitation of the blood passing to the lungs through the pulmonary artery. Arteries and veins were related through ultimate venous ramifications—synanastomosis—which opened into the arterial terminations. Under physiological conditions 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. Plethora gave rise in the first instance to distension of the vein walls, then to rupture, and then to forcible penetration of the blood, through the synanastomosis, into the arteries, with consequent interference with the action of the pneuma; this might cause an inflammatory reaction, or fever, which could be recognised by a rapid pulse. Normally the bile was separated from the blood in the liver, as the narrow bile ducts only allowed the thin bile to pass, not the viscous blood; dropsy arose if the movement of the blood was impeded in the liver, so that the unpurified blood poured into the abdomen as a watery secretion.

As can be seen, Erasistratus largely rejected the humoral hypothesis, replacing it by his concept of plethora, which in a modified form, was to persist until the 18th century and form a justification for blood letting. Erasistratus himself opposed phlebotomy—so much so that Galen called him a "haemophobist",—for the Alexandrian believed that opening a vein allowed the pneuma to escape, and so do harm; he preferred to bandage the part affected, so as to impede the opening of synanastomosis and apply local remedies in the region of the lesion. Unhappily, Erasistratus maintained that scientific research, admirable for its own sake, was of little value in practical medicine and so the successors in his school happily resorted to empiricism, and no new physiological 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 that impeded progressive thought until the 16th 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. He held that 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, by the arteries to all parts of the body, where it ebbed and flowed and could be felt to pulsate. The arteries to the brain, carrying blood charged with vital spirits, dividing into minute channels, the rete mirabile, and passing into the brain 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's synanastomoses, so he rejected his plethora pathology, 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 phase of the moon and stars; thus arose the science of judicial astrology, which so much occupied the minds of the mediaeval physicians; indeed when printing was invented, the first medical texts to appear 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 are his ponderous works or commentaries upon them, Syriac, Arabic and Hebrew, suffocating the intellectual world with authority. 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, and themselves commented on the early writers so that the Galenical corpus provided a complete review, as seen through Galen's eyes, of ancient biology and medicine; secondly, and perhaps more important, he was a teleologist and of such a sort that his views conformed with mediaeval theology, whether Christian, Moslem or Jewish. To Galen, everything which exists and displays activity in the human body, originated in, and is formed by, an Intelligent Being, and on an intelligent plan, so that the organ, in structure and function, is the result of that plan.

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 with authority 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 storm in the faculty, and Brissot was banished and betook himself to Spain. The controversy followed him and raged still more fiercely after his death with the publication of his "Apology", in which he defends the Greeks, and attacks the Arabists with much learning. The Arabists appealed first to the University of Salamanca, when it decided against them, then to the Emperor Charles V, claiming that the diversionary doctrine was as flagitious as Lutheranism; unfortunately a relative of the Emperor had died as a result of bleeding by the Arabic method, so he also decided for the Greeks. Meanwhile the Italian Physicians, like the English, supporters of the derivative method, attempted to settle the matter by holding a synod, on the theological model, at Bologna, under the presidency of Pope Clement VII and once again the Arabists were worsted.

These disputes on the site of venesection, caused anatomists to pay more attention to the veins and as a consequence the valves in the veins 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 (1514–1564), 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, overtly, to contest a doctrine accepted by both church and medicine. In writing of the heart in the first edition of the "Fabrica" (1543) he says: "Therefore the septum of the ventricles, as I said formed from the thickest substance of the heart, abounds in pits impressed into both sides of it; for this reason the surface which faces the ventricle is uneven. None of these pits (at least insofar as may be observed) penetrates from the right ventricle into the left, so that we are compelled to wonder at the industry of the Creator of all things, by which the blood sweats from the right ventricle into the left through invisible passages."

But in the second edition, published in 1555, after twelve years of traversing Europe as court physician to Charles V and, four years after receiving a polemic from his old master Sylvius, he writes more openly: "In considering the structure of the heart and the use of its parts, I have brought my words for the most part into agreement with the teachings of Galen: not because I thought that these were on every point in harmony with the truth, but because, in referring now and again to a new use and purpose for the parts, I still distrust myself. 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. . . . When these and other facts are considered, many points concerning the arteries come forward about which doubts may reasonably arise. We may note too that almost no vein goes to ventricle, intestines, or spleen without an accompanying artery, and likewise the portal vein has an accompanying artery almost throughout its course."

Though Vesalius was never averse to a quarrel, the romantic picture of the young anatomist slashing through the impenetrable galenical jungle is over drawn. In the "Blood Letting Letter" of 1539, when he had already determined to write his own anatomy, finding that it was not enough to correct the errors in Galen's osteology, which he was editing in the great Giunta edition, he writes: "For this opinion of mine on venesection in pleurisy, conceived by no one previously, I might strive to extract from the statement of Hippocrates in the second book of The Regimen on Acute Diseases, except it too pointedly contradicts the authority of Galen, which I am afraid of disputing almost no less than if in our very sacred religion, I were secretly to doubt the immortality of the soul."

Fourteen years later, for openly questioning the authority of the Church, a doctor 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 interventricular septum to form the vital spirit, when nourished by the inspired air, "but by a very ingenious arrangement the subtle blood is urged forward by a long course through the lungs; it is elaborated by the lungs, becomes reddish yellow and is poured from the pulmonary artery into the pulmonary vein. Then in the pulmonary vein it is mixed with inspired air and through expiration it is cleansed of its sooty vapours. Thus finally the whole mixture, suitably prepared for the production of the vital spirit is drawn onwards from the left ventricle of the heart by diastole."

It is clear from this paragraph that in a theological disputation, setting out the Unitarian viewpoint, Michael Servetus (1509–1553) had revealed his recognition of the pulmonary circulation, gained perhaps as a student, in Paris, with Sylvius. It is equally certain 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, either by the Inquisition or the cautious publisher; only three copies have survived and Servetus's account was unknown to science until it was revealed by William Wotton in 1694.

It is one of those insoluble priority wrangles, beloved of medical historians, as to whether Servetus's observation was known to his contemporaries or not, and whether he had read the arguments that a 13th-century Arabian, Ibn an-Nafis, had adduced against Galen's view as to the porosity of the interventricular septum, whether the account of the pulmonary circulation, published in Spanish by Juan Valverde de Homusco in 1556, or that of Realdus Columbus published in Venice in 1559, first revealed to the scientific world, this fundamental change in physiological outlook. Certain it is that it was the writing of the vain Cremonian, that informed Harvey of the pulmonary circulation, however much it may be questioned as to whether Columbus 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 (1578–1657) 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 on the thoracic organs, may not have grasped the significance of his conclusions "unde perpetuum sanguinis motum in circulo fieri pulsu cordis", 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 their 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. We find Martin Wall (1747–1824) an able physician, in 1781, in his inaugural lecture as Reader in Chemistry at Oxford, saying, "But the attention of the learned in England to Chemistry was considerably interrupted by Harvey's discovery of the circulation of the blood, and by the doctrines and controversies to which it gave rife; but still more by the wonderful progress of Sir Isaac Newton in the investigation of the laws of the planetary system.

"Hence the studies of astronomy and geometry were introduced most justly into general repute in England: but unhappily, while these sciences were cultivated with the greatest advantage and success, many others were excluded and neglected, as unnecessary to the perfection of a liberal education.

"Medicine in a very particular manner felt the influence of this system. The doctrines of Chemistry were rejected. Not only the theory, but even the practice of physic, was conducted and explained upon mechanical or geometrical principles. Chemistry was of course disregarded and uncultivated, except by a few retired persons for their amusement."

In 1759, Richard Davies (d. 1762), a Cambridge scientist, whose original work on the blood has not received the credit it deserves, wrote to Stephen Hales 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 principles 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 recognised 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; indeed, in one of his later letters, speaking of Riolan's attempts to disprove the pulmonary circulation "bringing all the blood through the septum, and so vaunts himself as having upset the very foundation of the Harveian circulation (although I have nowhere laid that down as a foundation for my circulation; for the blood fetches a circuit in very many red-blooded animals in which no lungs are to be found)". As Curtis says, in his admirable study of this whole problem, "Harvey's own clinching statement that the heart drives into the aorta at least one thousand drachms of blood in half an hour, this reduction *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."

Perhaps it would be best to display the problem in Harvey's own words, firstly from "De Motu Cordis" and them from "De Generatione", written in his old age. It will be noted that, by that time, he had departed from Aristotle's view that the primary nutritive soul must be located in the heart, which governs the region, which is intermediate between that which food enters and where excrement is discharged: Harvey had placed the heart second in dignity to the blood "for in it life and the soul first show themselves and last become extinct. I maintain against Aristotle that the blood is the prime part that is engendered and the heart the mere organ for its circulation".

Thus did he write in the eighth chapter of "De Motu Cordis": "And so in all likelihood, does it come to pass in the body, through the motion of the blood; the various parts are nourished, cherished, quickened by the warmer more perfect vaporous spirituous, and, as I may say, alimentive blood; which, on the contrary, in contact with these parts becomes cooled, coagulated, and, so to speak, effete; whence it returns