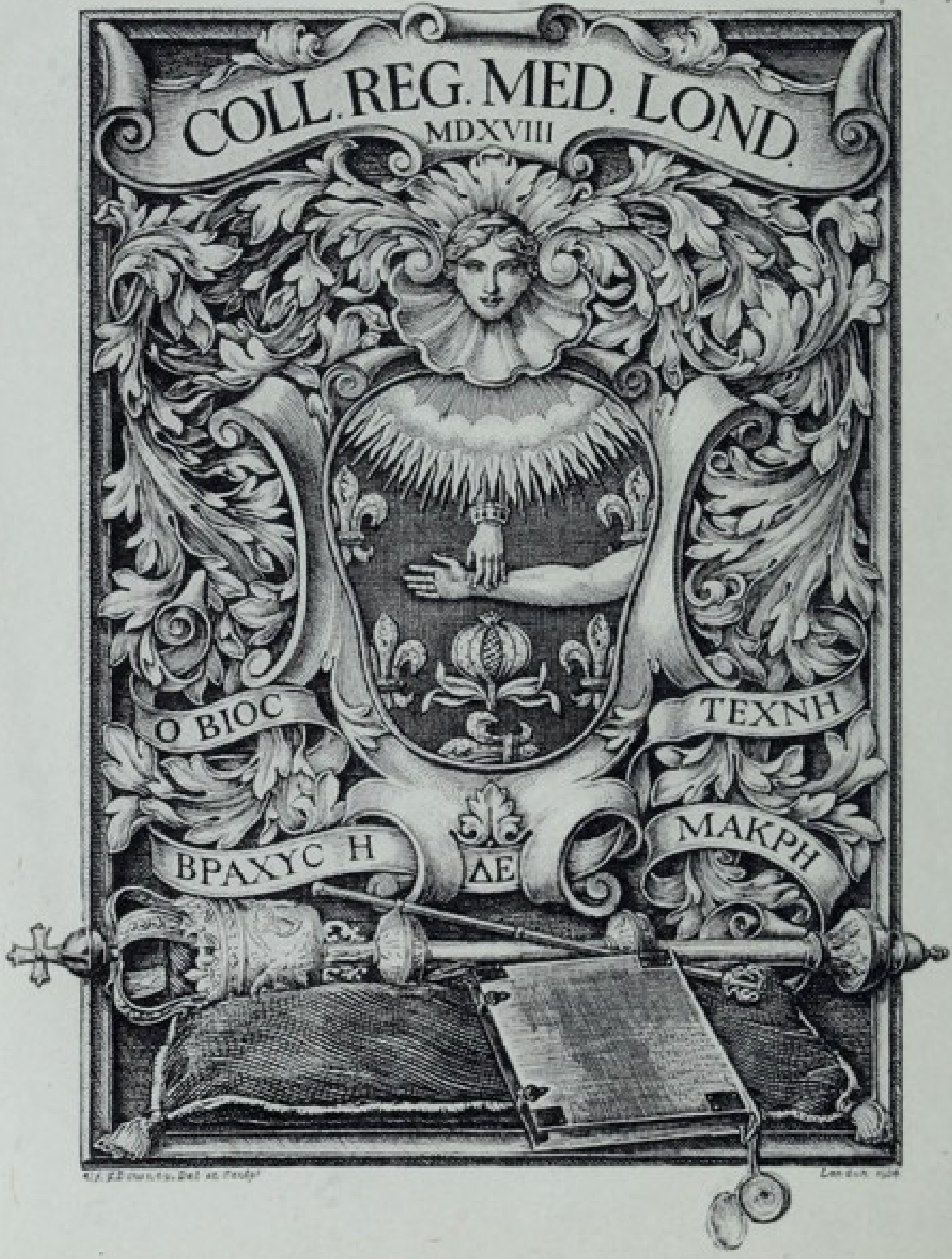
ON THE CIRCULATION AND THE ATTRIBUTES OF THE BLOOD

HARVEIAN ORATION

SIR R. DOUGLAS POWELL, Bt.


COLL. REG. MED. LOND.
MDXVIII
Ο ΒΙΟϹ
ΤΕΧΝΗ
ΒΡΑΧΥϹ Η
ΔΕ
ΜΑΚΡΗ

With the Author's compliments for the Library

The Harveian Oration

ON

ADVANCES IN KNOWLEDGE REGARDING THE CIRCULATION AND ATTRIBUTES OF THE BLOOD SINCE HARVEY'S TIME

"FOR THE LIFE OF ALL FLESH IS THE BLOOD THEREOF."

Delivered before the Royal College of Physicians of London on
October 19, 1914

BY

SIR RICHARD DOUGLAS POWELL, BART., K.C.V.O.
M.D., F.R.C.P., LL.D.

PHYSICIAN IN ORDINARY TO THE KING; CONSULTING PHYSICIAN TO
THE MIDDLESEX HOSPITAL AND THE HOSPITAL FOR CONSUMPTION
AND DISEASES OF THE CHEST, BROMPTON; EMERITUS LECTURER
ON MEDICINE AT THE MIDDLESEX HOSPITAL.

Reprinted from THE LANCET, *October 24 and 31, 1914*

The Harveian Oration

ON

ADVANCES IN KNOWLEDGE REGARDING THE CIRCULATION AND ATTRIBUTES OF THE BLOOD SINCE HARVEY'S TIME.

MR. PRESIDENT, FELLOWS, MY LORDS, AND GENTLEMEN,—Some of us may recall the picture by W. Yeames, R.A., portraying our great master Harvey absorbed in study whilst the battle of Edge Hill, timorously watched by his Royal pupils, is raging within a bowshot. So may we now. perhaps without reproach of cynicism, detach ourselves for an hour in contemplation of some of the beneficent gifts to medicine that have ensued from Harvey's work, whilst we with well-nigh the whole world are steeped to the skies in a war to which science has given the last touch of horror and carnage.

INTRODUCTORY REMARKS.

By the request with which, Mr. President, you have honoured me that I should give the Harveian Oration this year you have placed me under deep obligation, for you have put me in communication with the spirit of Harvey—a great man—as it shines out in his works, as it sheds light upon the thoughts of the centuries that went before, and as it illumines the paths of progress that radiate onwards from his time. And although, Sir, your command is the 258th that has reached the Fellows of this College, yet so numerous are the branches of thought and inquiry that have emanated from Harvey's discovery, as the spreading tree from a single pregnant germ, and so ever living and extending is each branch of that tree of knowledge, that year by year some advancement has been found with a freshness of interest worthy of record in this College. In my respectful response to your invitation I will endeavour to trace the progress and growth of one or two of those branches of knowledge that have emanated from Harvey's root, and have reached our time with their new buds of fresh development, each endowed with a spirit of further growth and increase.

Dr. Edmund Parkes, my revered teacher, in his Harveian Oration, the latest words of his beautiful life, which were read to this College by Sir W. Jenner, commences with the question, Will the name of Harvey be echoed down the stream of time with deathless fame? And his answer is, Yes. Harvey's discovery is a landmark for all time as "one of those cardinal discoveries which lie at the very foundation of physiology and medicine." Parkes proceeds to say: "The full interpretation of this great discovery is even now not given, for we are still painfully learning what the blood does in that marvellous circuit which never ends, yet ever recommences."[1] It is this theme of what the blood does that I would wish chiefly to pervade my address to-day.

Sir W. Church observes that although the knowledge of anatomy reached a considerable degree of perfection at the hands of Aristotle, Galen, and later in the sixteenth and seventeenth centuries, of Silvius, Vesalius, Fallopius, and Fabricius, yet, "from the time of Aristotle to that of Harvey no advance was made in physiological knowledge, if indeed it had not receded, and that as Aristotle must be regarded as the first of the biologists, so Harvey was the founder of physiology."[2] The late Dr. Ogle remarks: "And upon Harvey's discovery as a new 'primum mobile' rests, in fine, all our knowledge of pathology, and much of our knowledge of the action of remedies."[3]

[1] Harveian Oration, 1876, E. A. Parkes.
[2] Harveian Oration, 1895, Sir W. Church, pp. 14 and 15.
[3] Harveian Oration, 1880, John W. Ogle, p. 28.

The Master Mind and Scientific Discoveries.

The visitation of genius may in a sense be defined as a divine touch in a ready environment. We do not know at exactly what period Harvey attained the conception that quickened and directed his life's work. Dr. Ogle was very right in disputing the statement of Willis that the discovery of the circulation came fully from him. "This view," Ogle continues, "cannot be held. The discovery was, like all other scientific discoveries, the result of the growth of germs sown long before. It was not the work of one mind."[4] True; but it required the master mind of Harvey to collect and collate the numerous detached observations of his teachers and contemporaries to a discovery he had already adumbrated. Such is the case, perhaps, with regard to all epoch-marking discoveries: Newton's conception of gravitation, Priestley's oxygen, Simpson's anæsthetics, Lister's antiseptic system, Koch's discovery of the bacillus tuberculosis were all effected in an atmosphere of thought and experiment highly charged with expectation and speculation in the direction of the particular discovery.

It is said by the Psalmist, "When the breath goeth out of a man he returns to his dust and all his thoughts perish." But whilst the man may think no more, his thoughts live for good or evil to strive with other thought in the sentient atmosphere that gathers about the centres of civilisation and progress.

> Our thoughts are ours, their ends none of our own.[5]

Harvey's sentient atmosphere was shared by great anatomists and ardent pioneers of thought. Servetus had already described correctly the circulation through the lungs, although Harvey never saw his work. This fecundity of thought is finely

[4] Ibid.
[5] Hamlet, Act III., Scene 2.

expressed by Shakespeare in the words of King Richard—

> My brain I'll prove the female to my soul ;
> My soul, the father ; and these two beget
> A generation of still breeding thoughts,
> And these same thoughts people this little world ;
> In humours, like the people of this world,
> For no thought is contented.[6]

The Character of Harvey.

It is unnecessary again here to describe—as has often been done—the features and character of Harvey. It must be said, however, that he was a man dominated by an ardent and imperious spirit. His mind was naturally practical and forward looking—a mind educated by wide culture and reading from the old authors, especially Aristotle, Hippocrates, and Galen. He read all with his critical faculty well awake ; and in regard to physiology and medicine, which were the objects of his life's work, he accepted nothing on mere authority, but by logical analysis and by actual experiment tested all the conclusions which interested him. His outlook was ever onward from laboriously accredited or discovered facts to the conclusions to which they pointed and to the fresh inquiries and experiments they might prompt. In this respect he was in marked contrast to his great contemporary in this College, Sir Thomas Browne ; and I say this in no disparagement to Sir Thomas, who was indeed Harvey's superior in scholarship. The two minds were essentially different—the one contemplative, retro- and introspective, the other practical, inquiring, strenuously objective and forward-looking ; each is supplemental to the other, but perhaps an impetus was given to the objective order of mind with the revival of learning under conditions of increasing freedom from the restraint of ecclesiasticism. We are fortunate in having both classes of mind present with us to-day. We may in our own College recall the names

[6] King Richard II., Act V., Scene 5.

of Linacre, Sir Thomas Browne, Richard Mead, and Caius for their purity of language and enrichment of literature from the stores of traditional learning; whilst those of Harvey, Sydenham, Willis, Bright, Addison, Jenner, and Jackson may be especially remembered amongst the great pioneers and teachers of medicine.

Not only in medicine but equally in other sciences—including political science—may this characteristic, pregnant of the future, be observed. As instances of recent pioneers of action may be mentioned the names of Lord Strathcona, Cecil Rhodes, and Joseph Chamberlain, amongst others, who were "for ever moving forward with reverence for the past, with care to guard its great traditions, but ever seeking in the future something better, something nobler, something greater than that which we now enjoy."[7]

The Medical Profession and New Discoveries.

We hear it often said of the medical profession that new discoveries are met by captious criticism and ungenerous distrust. This has been the subject of comment by many Harveian orators. Sir James Alderson remarks in reference to the obstruction and neglect with which Harvey's work was greeted: "Yet it may be questioned whether difficulties in the establishment of any new truth ought to be esteemed a hardship. New knowledge must be proved; and too facile acceptance can be wished for only by promulgators of error."[8] Sir Edward Cook in his "Life of Florence Nightingale" makes the remark: "Controversy is perennial between those who ascribe the course of political or social history mainly to great men, and those who ascribe it rather to streams of tendency. It is less open to controversy to say that the great men who leave the more permanent mark upon history are those whose genius conforms to the spirit of their time, but who are yet a little in advance of their age."[9]

[7] Speech by Mr. Austen Chamberlain, Morning Post, July 10th, 1914.
[8] Harveian Oration, 1867, J. Alderson.
[9] The Life of Florence Nightingale, by E. T. Cook, vol i., p. 442.

Controversy quickens thought and strengthens understanding, and all great pioneers, like Harvey, Darwin, Spencer Wells, and Lister, have shown their recognition of this truth. This is the true attitude, especially for pioneers in medical science. No one in a grave and responsible profession can expect to promulgate a new doctrine carrying with it, it may be, fateful results to human beings, without being prepared to sustain with equanimity the ordeal of ardent criticism, to suffer patiently even the obstruction of fools, until he can convince by demonstration the minds of all. Harvey has given to us a great lesson on this patient striving with criticism, pursuing his arguments without bitterness, and strengthening them to conviction with sweet and laborious persuasiveness.

The Origin of Life.

Harvey speculated much on the immediate source of life. He recognised, however, its general origin in ova, and presumes that this may still be so in even the minutest organism far beyond his vision. "Let physicians therefore cease to wonder at what always excites their astonishment—namely, the manner in which epidemic contagions and pestilential diseases scatter their seeds and are propagated to a distance through the air, or by some 'fomes' producing diseases like themselves in bodies of a different nature and in a hidden fashion silently multiplying themselves by a kind of generation (until they become so fatal), and with the permission of the Deity spread destruction far and wide amongst man and beast; since they will find far greater wonders than these taking place daily in the generation of animals."[10]

He thus clearly recognises the generative elements in minutest nature, and he is not disposed with Hamlet at the same time to admit and to question "if the sun breeds maggots in a dead dog being a God kissing carrion," but frankly recognises the germinative edict of the Creator "as if it were said by the Almighty 'let

[10] The Works of W. Harvey, M.D., by Robert Willis, M.D., p. 322.

there be progeny' and straight it is so." "A superior mind and more divine agent than man," he later on observes, "therefore appears to engender and preserve mankind, a higher power than the male bird to produce a young one from the egg ...... to none can these attributes be referred save to The Almighty first cause of all things, by whatever name this has been designated—the Divine Mind by Aristotle; the Soul of the Universe by Plato; the Natura Naturans by others; ...... by ourselves, and as is seeming in these days, the Creator and Father of all that is in heaven and earth, on whom animals depend for their being, and at whose will and pleasure all things are and were engendered."[11]

Source of Cardiac Energy.

Since Harvey dispelled the views of Hippocrates, Aristotle, and Galen, which prevailed for 2000 years, that the operative force of the heart was in diastole, opinions have alternated as to the source of cardiac energy. Harvey did not discuss the matter, but observing the contractile spot as the motor force of the circulation at the fourth day of the life of the chick *in ovo* assumed it to be an intrinsic rhythmic function of the ventricle. Some observers, with Haller, agreed with Harvey's view that it was intrinsic in the cardiac muscle. Others, with Legallois (1812) and Remak, have regarded it as derived from nervous stimulation either from outside the heart or originating in ganglia first discovered by the latter observer within the heart in 1844, at about the time that the brothers Weber demonstrated the restraining influence of the vagus upon the heart. Gaskell in 1881 again demonstrated this myogenic activity of the heart, and he regarded the ganglia within it as inhibitive. This view was strengthened by the later researches of Engelmann, and it is now generally agreed that the ganglia and nerves of the heart with their corresponding centres are for the purpose of regulating the functions of that organ.

[11] Ibid., p. 402.

The Rhythmic Function of the Heart.

After careful observation on the hearts of tortoises Harvey concluded that the automatic rhythm of the heart's contraction commences at the venous end, spreading to the auricle and then to the ventricle in a very definite manner. Purkinje, Kölliker, Gaskell, Kent, Tawara, and Keith and Flack, with all the wealth of research at their command, would seem to justify this general view; and they have further shown that there are in the heart centres of neuro-muscular tissue more embryonic in character than the adjacent textures, and which are in continuity with a bundle of fibres, the band of His. This band, dividing above the septum, distributes branches throughout the subendocardium, the fibres of which are identical with those described by Purkinje and minutely examined by Kölliker and terminate mainly in the papillary muscles of the ventricles. Only the elaborate methods and instruments of modern physiology could have elucidated these important points.

It is then evident that the rhythmic function of the heart muscle is a coördinated neuro-muscular force still inherent in the sino-auricular and auricular nodal sarcoplasm and carried onwards by the auriculo-ventricular band; that it is a survival of the neuro-sarcoplasmic function of the heart which preceded any existing extrinsic nervous system and is exhibited in the first contractile spot of the chick noted by Aristotle and so closely investigated by Harvey; and that the extrinsic nervous mechanism of the heart has been gradually developed as the requirements of the organism have become more complicated. The continuity and incorporation of this more elemental neuro-muscular tissue with the striated fibres of the heart is beautifully shown in some of the illustrations in Tawara's monograph (Plate IV., Figs. 6 and 5). Thus the myogenic and neurogenic views of the heart's action have become, we may hope, finally merged and reconciled.

That the first beat of the heart is really ventricular, as concluded by Harvey from his observations of the chick at the fourth day, is not altogether improbable, although Harvey himself in later observations of the tortoise describes vermicular movement extending from the sinus venosus and completed by the ventricular systole. It is interesting to note in this connexion an observation by Dr. Pavy,[12] which is referred to in the late Professor Rolleston's Harveian Oration (1873), pointing out that in the dog a sudden impulse is given to the auricles by the violent contraction of the ventricles which appears to start their vermicular contraction. It may seem little more than a matter of account whether the heart's action commences with ventricular systole, the shock of which starts the mechanism of diastolic filling, or whether it is a vermicular action culminating in a powerful systole. A practical interest is, however, given to the question by comparatively recent observations with the electric cardiograph, which show that the auricles are not infrequently put completely out of action, as in the auricular fibrillation described by James Mackenzie and figured in the electrical tracings of Hill, Lewis, and others; and yet the circulation goes on by ventricular action alone, the auricles being converted into mere passive tubes.

Much valuable work from a therapeutical point of view was done in Ludwig's laboratory and by the late Dr. Ringer in discovering the effect of certain saline solutions, especially the chlorides of sodium, calcium, and potassium, in maintaining the irritability of cardiac muscle. A certain mixture of these salts for this purpose is still known as Ringer's saline solution.

The Reaction of Cardiac Muscle.

Amongst the differences in the reaction of cardiac muscle and skeletal muscles to stimulus there is one which is no doubt of some importance, but to which a misleading prominence is given in most text-books of physiology. It is known as the "all or nothing law" of Bowditch. It was found by Bowditch and Ranvier that a portion of muscle detached from the heart of a frog, when electrically

[12] Medical Times and Gazette, Nov. 21st, 1857, p. 521.

stimulated, contracts at once with its full power and that a stronger stimulus will not have any further effect, differing thus from the graduated force of contraction of skeletal muscle according to strength of stimulus, and the conclusion is drawn that if the heart contract at all its contraction is maximal, "for all it is worth."

Even if this observation be trustworthy it will not apply to the living heart under vital conditions of innervation. As pointed out in Howell's "Text-book of Physiology" (p. 573), "numerous observers have called attention to the fact that the vagus fibres may also cause a weakening in the force of the beat as well as a slowing in the rate, or, indeed, the two effects may be obtained separately." In no other organ of the body is there a more manifest reserve of functional power to meet the exigencies of varied conditions of effort, of arterial resistance, of emotion, of sudden or gradual valvular defect or other vicissitudes of life.

It is to be noted that later observations have disclosed another peculiarity of heart muscle unknown to Bowditch at the time of his experiments—namely, that at the time of contraction the heart muscle is "refractory" to further stimulus. It is possible that this fact may vitiate the conclusions drawn from electrical stimulation of heart muscle, and I do not know whether it has been allowed for.

Effect of Lung Elasticity on the Circulation.

In addition to the driving power of the ventricles, roughly recognised as equivalent to 6 and 3 inches Hg respectively, there are certain further aids *a tergo* to the circulation which may be briefly enumerated. They are partly sustaining and partly supplementary. The driving power is sustained and carried on with least possible loss (1) by the elastic recoil of the great vessels upon their closed valves; (2) it is said (Lauder Brunton and T. D. Lister) that there is a certain rhythmic or rather peristaltic contraction of the smaller vessels which has some slight effect in propelling the blood through the veins; (3) the larger veins being sheathed with their corresponding arteries are compressed with each arterial systolic expansion, and the blood restrained from back flow by the valves is thus propelled onwards towards the heart; (4) during exercise the contraction of the limb and trunk muscles compresses the venules and larger veins and similarly urges on the venous current; and (5) the compressing effect of abdominal, perineal, and diaphragmatic muscles under various twisting, bending, and straining movements has the same influence upon the great reservoirs of blood in the abdominal veins, the direction of all these forces being determined by valves.

It is a matter for great regret that Harvey's observations on respiration and the greater part of his observations on medicine have been lost through destruction by fire and the malice of a political mob. It is hardly likely that with his extraordinary perceptive powers he could have failed to note and to comment upon the *vis a fronte* aid to the circulation which is derived from the aspiratory traction of the lung elasticity upon the mediastinal space.

Physicians and anatomists before Harvey's time regarded the lungs as a power in the movement of the blood, but they erroneously thought that blood and air were impelled to the heart by the compression of the lungs in the act of expiration. Perhaps even modern physiologists and clinicians have not fully grasped the agency of the elastic traction of the lungs as a constant force of low tension, increased with every inspiratory movement, diminished but not wholly extinguished during expiration, tending always to attract blood through the central veins to the heart cavities, and thus steadily and perpetually aiding the venous return.

The Dynamics of Respiratory Movements.

Up to and at the time of Hutchinson's well-known paper read before the Royal Medical and Chirurgical Society in 1846 the dynamics of respiratory movements were not rightly formulated. Hyde

Salter, a Fellow of this College, who first pointed out in 1865 that the elasticity of the ribs was in ordinary breathing a factor in aid of, not against, inspiration, had had his attention especially drawn to the mechanism of respiration by his own sufferings from asthma. This traction of the ribs in aid of inspiration—as I have endeavoured to point out—is throughout the respiratory act never entirely lost in calm breathing, although it tends to become neutralised as the chest enlarges with inspiration. Salter pointed out that in the cadaveric position of expiration there was an outspring of the ribs when released from the traction of the lungs equal to 1/100 inch or 0·25 mm. Some experiments I made in 1876 led me to regard this outspring as equal to from 1·6 to 3 mm. Hutchinson, and later Burdon Sanderson, estimated thoracic expansion in ordinary breathing at about 1·6 mm. Hence practically the thoracic movements in ordinary breathing oscillate within the range of thoracic outspring, leaving this factor constantly on the side of the inspiratory forces. The diaphragm, attached like a bowstring to the elastic margin of the thorax, is similarly held in a state of arched tension by the traction of the lungs.

The result of this elastic mechanism is that the respiratory act in both directions commences with perfect automatic smoothness and imperceptibility. Another effect is to protect the lungs from pressure. There are several other important considerations that arise out of this mechanism in diseased conditions of the respiratory organs. But I am concerned now chiefly with the circulation, and especially as it is affected by these agencies having their root in lung elasticity.

The traction exercised upon the mediastinum and those contents of it which are not in communication with the outer air—the heart, arteries, veins, and lymphatics—is estimated as equal to from 4 mm. in expiration to 7 mm. Hg in inspiration.[13] (It has been stated that this effect is not wholly lost even in the peripheral veins, being appreciable in the small veins by the side of the

[13] Howell's Text-book of Physiology, p. 649. Professor Starling places it at 10 mm. Hg during expiration and even 30 mm. Hg on forcible inspiration.

tendo Achillis.[14]) The positive blood pressure within the great veins as they enter the thorax is well-nigh exhausted, and in the lymphatic currents it is still less, so that this *vis a fronte* equivalent to from 4 to 7 mm. of mercury, being in constant action, is of considerable value in drawing onward the sluggish venous current to refill the auricles and ventricles during diastole.

It is said that at the very commencement of diastole the ventricles have a certain suction power supposed to be due partly to recoil, partly to an erectile effect upon the muscle produced by the influx of blood through the coronary arteries. This aid to the refilling of the ventricles is, however, but momentary and slight and probably does little more than help to open the auricular valves.

Influence on the Heart in Disease.

In health the powerful muscular ventricles during systole can easily disregard any impedient to their contraction caused by the negative pressure in the mediastinum. Such impediment can only be noted by fine instruments as a slight lowering of the blood pressure during inspiration.[15] But in cases of failing heart power, and especially when attended with over-distension of the right cavities, the vacillation of systole with each inspiration becomes so marked that the respirations can be easily counted by the remissions of the pulse force.[16] In extreme cases complete failure of the pulse is observed with each inspiration. This phenomenon must be familiar to physicians. I have pointed it

[14] System of Medicine, Allbutt and Rolleston, vol. vi., Thrombosis, by W. H. Welch, M.D., p. 717.

[15] It must be here remarked that Professor Starling considers that the blood pressure is increased at least during the latter two-thirds of inspiration. He illustrates this view in a diagram, but I am not clear that the diagram represents an actual measurement and venture to think on the clinical grounds above stated that this view needs further verification. The view adapted in the text is upheld by Leonard Hill. (The Vascular System and Blood Pressure: Further Advances in Physiology, 1909, p. 145.)

[16] The subject of pulsus paradoxus, the singularly undescriptive name given to the phenomenon of inspiratory failure of pulse under certain conditions, is very fully discussed in an elaborate and interesting paper by Dr. A. W. Falconer and Dr. James M. McQueen which appeared in the Quarterly Journal of Medicine for October last.

out to students and practitioners for many years as an important and ominous sign of failing heart power. In certain conditions it would be an argument in favour of relieving the venous fulness of the right cavities by bleeding, whilst stimulating heart power by strychnia and oxygen.

We bear witness to the value of this *vis a fronte* force in the use of respiratory exercises as an aid to cardiac action and development in feeble, dilated hearts, especially in children, and for the fatigued hearts of adults. We witness clinically the embarrassment which arises in emphysema from the diminished aid from this force to the circulation. Only in extreme and dangerous fluid effusions and pneumothorax does the pulmonary tension, however, become wholly exhausted and the compression of the lung suggested by Galen and apparently accepted by Harvey operative.

The Right Ventricle.—Arteries after Death.

It may be noted that as the systolic work of the right ventricle is distributed within the thorax the pulmonary arterial pressure is not affected by the respiratory mechanism under consideration (except when possibly some fluctuations occur in the capacity of the pulmonary capillaries). The diastolic supply to the right ventricle is, however, greatly aided by aspiration through the great veins.

Although Harvey pointed out the fallacious inferences drawn by the old anatomists from the supposed occupation of the arteries by air during life he never seems to have denied that the arteries were so occupied after death or realised that only with the first division of an artery by the anatomist's knife is air admitted to them. It is possible that the extreme expiratory contraction of the chest so constantly observed at death is connected with the emptying and collapse of the great intrathoracic arteries and the attempt to restore atmospheric equilibrium. And it is in this connexion interesting to observe that after death the great vessels, when occupied at all by ante-mortem clot, are so occupied by a clot much smaller than their calibre.

Instrumental Methods.

It may be said that the great advances in knowledge respecting the circulation since Harvey's time have been made through the aid of instrumental methods. When the pocket lens of Harvey was replaced by the primitive microscope of Malpighi the capillary link of the circulation which could only generally be assumed by Harvey was demonstrated.

The systemic blood pressure was first roughly but very accurately estimated by the Rev. Stephen Hales (1773), and by simple experiments he also demonstrated contraction and relaxation of the vessels as influencing the output or blood pressure—no small feat in a man of his time and with but little medical training. Next to the general blood pressure the recognition of its local distribution according to the requirements of the different organs was an epoch-making event in the history of discovery, which was inaugurated by the memorable experiments of Claude Bernard upon the chorda tympani nerve in 1851.

The Local Distribution of the Blood.

The fact of such varied distribution of the blood to organs and tissues under conditions of emotional and functional stimuli had not altogether escaped Harvey. He commented upon the pallor or flushing of the face under the emotions of self-consciousness, fear, anger, or shame, and he observed that the ears might be red when the face was pale; he was, moreover, aware of some connexion of the nervous system with the local disturbances of circulation caused by irritation. He comments upon the fact in association with stomach and other abdominal irritations, and in his remarks upon the effect in his own person of a poisoned needle puncture clearly shows his appreciation of this agency. Having pricked his hand at one point with a clean needle and at another with one envenomed with spider poison, he remarks: "I could not by my simple sensation perceive any difference between the two punctures; nevertheless, there was a capacity in the skin to distinguish the one from the other; for the part pricked with the envenomed needle immediately contracted into a tubercle, and by-and-by became red and hot and inflamed, *as if it collected and girded itself up for a contest with the poison for its overthrow*."[17] The careful observations upon Alexis St. Martin perhaps first demonstrated the accession of blood to organs in activity. The importance of nervous control in regulating general blood pressure was more fully recognised by the discovery by Ludwig in 1866 of the depressor nerve as an afferent nerve of the heart which, when stimulated, as by excessive blood pressure within the heart and aorta, caused through the medium of the splanchnic nerve a dilatation of the abdominal arterioles with instant release of intracardiac pressure.

It would take more than one address to illustrate in detail the many results and conditions of flushing and restriction of circulation through the different organs and tissues as required for their individual functions. We now fully recognise how efficiently the blood is held in the grasp of the arterial system, to be distributed here or there in accordance with local needs telegraphed to the nerve centres from the several organs; and our knowledge of the details of this control with regard to individual organs is ever increasing, in witness of which I might quote Dr. Markwalder's and Professor Starling's recent researches showing how the coronary circulation of the heart itself is thus regulated by some local mechanism in accordance with the demands upon its functional capacity.[18] These observers find that the coronary circulation is intimately dependent on the general arterial pressure; that adrenalin causes dilatation of the coronaries, as it raises arterial pressure; that increase of CO_2 in the blood also causes coronary dilatation; and that non-volatile metabolites produced by the heart muscle are potent agents in causing a similar dilatation.

[17] The Works of Harvey, by Robert Willis, M.D., On Generation, p. 431, Sydenham Society, 1847.

[18] Journal of Physiology, vol. xlvii., Nos. 4 and 5. THE LANCET, Feb. 14th, 1914, p. 469,

The presence of the same neuro-vascular mechanism in the lungs and brain has long been conjectured by physicians as necessary to explain certain symptoms—apnœic, aphasic, convulsive—which are familiar in practice. Such mechanism has been long and even recently denied, but has been demonstrated to exist by the successive observations of Sir John Rose Bradford, Dr. Bokenham, Sir Lauder Brunton, Roy and Sherrington, Brodie and some others, and affirmed by Sir David Ferrier in his Harveian Oration (1902).

The Use of Instrumental Methods.

Up to recent times instrumental methods were mainly restricted to the laboratory and utilised for experimental researches upon animals. They are now largely employed in the clinical investigation of health and disease. The systematic examination of the urine for albumin and sugar, and still more the quantitative estimation of these substances and of urea, with microscopic examination of urinary and sputum deposits as clinical tests, are well within the time of many of us. The observations of Wunderlich, Ringer, and numerous others with the clinical thermometer have rendered exact the more crude recognition of the older physicians that the body temperature, so wondrously constant under all conditions and vicissitudes in health, is readily disturbed in definite ways by blood ferments and altered tissue metabolism in disease. It must be confessed that these instrumental aids have not always at first been received with the cordiality they deserved by clinical physicians. I can remember one of the pioneers of the clinical thermometer being somewhat petulantly snubbed by a very distinguished physician of that time on producing in a post-mortem room the temperature records characteristic of a case of tuberculosis.

Diseases of the circulatory system have been especially favoured by this combination of laboratory and clinical methods. Observations on the pulse—old as the history of medicine—have been supplemented by the refined methods of the sphygmograph. Again, such instruments as the capillary pressure gauge, the radiographic apparatus, the combined veno- and cardiograph and the electric cardiograph have given us, in association with the stethoscope, a comprehension of the cardiac mechanism and its perversions in disease which is almost complete. Greatly as we are indebted to laboratory investigation for exact knowledge and clinical insight, we must not forget how much has been and is being learned and suggested respecting vital processes by the older and less exact methods of clinical observation. Need I point to the laborious and minute clinical observations by Harvey himself, and his innumerable necropsies and dissections.

The Coördinating Control of Clinical Observation.

Whilst fully recognising and rejoicing in the value of instrumental aids we must be careful, then, not to weaken by disuse the coördinating control of clinical observation. The more deeply we study the human mechanism—and where shall we find a more profound lesson than may be drawn from the circulation and properties of the blood—the more we shall be convinced of the complete interrelation of its parts as they have become evolved from one comprehensive bioplasm. Instrumental methods deepen insight and observation at the bedside, whilst ever remaining in reserve for the more thorough investigation of individual cases of obscurity. Unless thus employed, however, in due perspective with the whole clinical phenomena of disease, any one method must prove full of the fallacies inherent in all isolated methods. I would urge, then, a steady maintenance in full efficiency of general clinical observation in correlation with all necessary laboratory and instrumental methods as essential to our right interpretation of disease; for it cannot be doubted that a want of coördination and perspective in the use of the two methods breeds bad physicians and tends to reckless and sometimes harmful treatment. In my humble opinion, Sir, and in this I agree with some previous orators, no institution of lectures has been more valuable to the profession and more in accordance with the spirit of Harvey than those founded by our distinguished Fellow, Dr. Oliver, in memory of the revered teacher of still some of us, Professor Sharpey. Clinical observation and teaching have been encouraged and the dignity of medicine enhanced by the able men who have given these lectures in successive years since 1904. We should never forget that the great physiologist and anatomist and Fellow of this College, whom we commemorate so proudly to-day, was also a great physician and an acute and laborious clinical observer.

Attributes of the Blood.

Harvey's life work was the demonstration of the circulation of the blood. He could speak and speculate only generally as to the composition of the blood itself. He recognises the blood as the medium in which "the life" dwells, as "the generative part, the foundation of life, the first to live, the last to die, and the primary seat of the soul" (or vital principle). He goes beyond Aristotle, whom he quotes as saying that "the blood is that alone which lives and is possessed of heat whilst life continues," and lays emphasis upon the fact that it "is the prime part that is engendered and the heart the mere organ destined for its circulation." He holds it also as primary to the vessels which are constructed to contain it. Harvey's views were thus, as we should expect, thoroughly sound so far as they could go, and, as we may see, he makes some shrewd speculations and divinations on the more subtle functions of the blood which could not be plain to him. I will endeavour very briefly to refer to the cardinal discoveries respecting the blood which have come to light since Harvey's time. Within half a century the red corpuscles were recognised and described by Malpighi, followed in more detail by Leeuenhoek.

Oxygenation.

In 1668, three centuries after saltpetre had been utilised in explosive combination for the destruction of human life, Mayow recognised "nitre air" as the essential agent of slower combustion, and its activity in respiration and other processes in the body. "The function of breathing," says Mayow, "is merely to bring air in contact with the blood to which it gives up its nitro-aerian constituent and from which it carries off the vapours produced by the heating of the blood." Again, "The blood carries the nitro-aerian constituents to the muscles (including the heart), and their motion results from the chemical reaction in the muscle with the combustible matter contained therein." The view thus expressed by Mayow nearly two and a half centuries ago may be said to epitomise what we now know of the oxidation side of the respiratory function, and was further confirmed by Boyle in 1670, who demonstrated that the presence of air was necessary for the existence of both land animals and water animals. Although the existence of oxygen was thus predicated by Mayow and Boyle, and especially by Mayow, as necessary to life, it was not actually isolated until a century later by Priestley (1774).

The fact that oxygen forms a loose but definite combination with the hæmoglobin of the red corpuscles, and the further important fact that carbon monoxide has a preferential attraction for the hæmoglobin, and forms a more stable combination with it, are discoveries of great importance in elucidating the processes of respiration both in the lungs and in the tissues, especially the muscular tissues.

The most recent observations of Haldane and Priestley, Loewy, Zuntz, and others upon the composition of alveolar air and of venous blood, especially as regards oxygen and carbon dioxide, bring the matter up to date, showing: (1) that whilst normal arterial blood as it flows away from the lungs is within 1 volume per cent. of being completely saturated with oxygen (19 c.c. oxygen to 100 c.c. of blood); (2) after passing through the systemic capillaries the oxygen is reduced to 12 volumes per cent. (3) In venous blood the tension or pressure of the two gases O and CO_2 has been estimated by Loewy and von Schrötter as 5·3 per cent. of an atmosphere (37·6 mm. Hg) for oxygen and 6 per cent. (42·6 mm.) for CO_2 respectively. In arterial blood the tension of oxygen is about 100 mm. Hg (or 15 per cent. of an atmosphere) (Howell), that of CO_2 5 per cent. of an atmosphere (35 mm. Hg.) (4) In the tissues the relative tension of oxygen and CO_2 is for oxygen *nil*, for CO_2 50 to 70 mm. Hg. (5) The oxygen is so loosely combined as oxyhæmoglobin and so readily displaced by CO_2 that practically these gases follow the law of diffusion through membranes.

It thus becomes evident that, coincidently with the circulation of the blood, there is a respiratory circuit in lungs and tissues of the gases it contains, oxygen entering the blood at the lungs and permeating the capillaries into the tissues; CO_2 entering the blood at the tissues and permeating the pulmonary capillaries of the alveoli. The respiratory process commences in the lungs and is completed in the tissues, the remnant of oxygen returning with the venous blood being replenished in the lungs, and the carbonic acid accumulated from tissue changes escaping through the lungs to gather again as the blood reaches the tissues through the systemic capillaries, the whole function being under the watchful regulation of the medullary nerve centre. The picture only differs in its more exact detail from that so ably sketched by Mayow 250 years ago.

The presence of oxygen and nitrogen in the blood plasma is but of slight collateral importance except in morbid conditions such as those found in caisson disease both in compression and decompression.

Coagulation.

The coagulation of the blood was a phenomenon familiar to physicians from all time, and innumerable observations were made on the characters of the clot resulting from venesection and what they might portend. In alluding to the phenomena observed we must bear in mind that all the earlier and much of the later observations relate to inanimate or shed blood, or *gore*, as Harvey brusquely speaks of it.

In 1770 William Hewson, a junior contemporary and for a time a co-lecturer with William and John Hunter, made some remarkable observations on the coagulation of the blood, recognising that it was due to changes in the plasma, was prevented by some action of the vessel wall, and that outside the body it was also prevented by the presence of a neutral salt (sulphate of soda). It was Schmidt, however, who in 1861 laid the foundation of the modern theories of coagulation by isolating fibrinogen and by the discovery of the fibrin "ferment" to which the name of thrombin was afterwards applied. Hammarsten confirmed and extended his observations, which were importantly added to by the discovery by Arthus and Pages that calcium salts played an important part in the coagulating process.

Thrombin is not naturally present in the blood, but is evoked by the action of calcium salts upon an inactive precursor called prothrombin or thrombogen. Whether thrombogen exists naturally in the blood is also questioned. The theory of coagulation accepted by Professor Halliburton is that thrombogen is a substance existing in the blood plasma which in association with an activating agent called thrombokinase (which does not pre-exist but is derived from the platelets, red corpuscles, and tissue elements) and in the presence of calcium salts is converted into the active enzyme or ferment. The thrombin thus produced reacts upon a protein substance, fibrinogen, which is present normally in the blood plasma and transforms it into the insoluble, stringy material, fibrin, which entangles the other elements of the blood to produce a clot. It is assumed that for the production of thrombokinase some disintegration of the platelets is necessary, or that it is washed in the flow of blood from the tissues. These observations, complex as they are and by no means as yet fully accepted, apply, let me repeat, to inanimate blood after it has left the vessels. They also apply with some reservations to the formation of post-mortem clots in the heart and great vessels.

It was observed by Wooldridge in 1886 that thrombin as prepared by Schmidt when introduced intravenously does not produce coagulation. This little difficulty has, however, been met by the supposition that the thrombin is neutralised by an antithrombin circulating in the blood. The nucleoproteins of tissue extracts which coagulate the living blood are supposed to do so by the thrombokinase they contain, but Wooldridge has shown that a larger quantity of the same extracts causes the blood to become less coagulable.

Intravascular Thrombosis.

The coagulation of living blood to form a thrombus in a vessel is a somewhat different process of which the formation of fibrin is a comparatively late phase. An accumulation and adhesion of platelets seems to be the first thing that happens at a portion of an artery or vein which from injury or disease, usually of an infective nature, excites the coagulation. Almost immediately leucocytes collect in the mass followed by fibrinous formation which penetrates the whole, entangling red corpuscles and other elements of the blood. Whether this formation of fibrin is the result of the reaction of platelets or white cell secretion upon fibrinogen does not seem to be settled, but both appear probable. More purely fibrinous clotting of the blood may be observed within the vessels over roughened surfaces and inflammatory areas. Pure leucocytes may collect to block small vessels. Again, under certain toxic conditions the red corpuscles may adhere to form thrombi, occluding small vessels.

The mode of extension, absorption and organisation of thrombi has been fully established. The initial reason for the occurrence of a thrombus is much more obscure. It would seem that slowing of the current of the blood tends to the accumulation of platelets which normally occupy the centre of the current to the sides in the outer and comparatively still zone of the stream, and the same is known to hold with regard to the white cells. It still requires a broken or a diseased inflammatory or degenerated surface of the vessel to attract the accumulation of platelets and corpuscles, and the ultimate formation of fibrin to form the thrombus. The so-called inflammatory thrombi, whether originating in phlebitis or arteritis, are now recognised as of infective origin, associated with such diseases as rheumatic fever, influenza, enteric fever, and the like.

It would thus appear that intravascular thrombosis is a vital and not a chemical or fermentative process such as obtains in inanimate blood. It is more like the reaction of a tissue to heal a breach of surface. The thrombokinase reaction resulting in thrombosis and the formation of fibrinous layers and reticula are secondary occurrences, although of great importance in building and consolidating the thrombotic mass. In due time the thrombus degenerates, is absorbed, or rather consumed in its effete parts by phagocytic action, whilst from the vessel side it is becoming organised by the penetration of new vessels. Like many vital attempts at repair, the process has its inconveniences and dangers, but in the closing of severed or ligatured vessels and the occlusion and consolidation of aneurysms we find its value, whilst the immediate isolation of a morbid spot in the vessel by the formation of a protective clot must be of importance in preventing general blood contamination.

In septic thrombi a new element is introduced which need not be discussed here. Given a breach of surface—e.g., a degenerated aorta or cardiac valve—and the presence in the blood of bacterial organisms derived from infected surfaces—colon, bladder, gums—or absorption from without, and there is now no mystery to be explained in the occurrence of infective thrombosis from the lodgment of such organisms on unprotected surfaces.[19]

Dr. Senhouse Kirkes[20] first drew attention in 1852 to embolism or blocking of the vessels from fibrinous

[19] Professor Welch's account of Thrombosis in Vol. VI. of Allbutt and Rolleston's System of Medicine is the most lucid and comprehensive, and although five years old, as yet, I believe, requires no material modification.

[20] Transactions of the Royal Medical and Chirurgical Society, vol. xxxv.

clots conveyed from the right or left cavities of the heart to the lungs and systemic organs respectively. And further developments of the observations have been far-reaching in pathology and clinical medicine.

Coördinative Attributes of the Blood.

In the fertilised protoplasm in which animal life has its beginnings there is a coördination of the formative, digestive, circulatory, and sentient functions under the ægis of nervous activation—if I may apply so modern a term to so old a service—that maintains the autonomous individuality of the organism. This coördination of process is sometimes spoken of as a species of chemiotaxis, using the term in its widest sense. In the course of evolution and in that brief epitome of it that proceeds *in utero* in the more advanced types of animal life separate organs representing each function are gradually differentiated. The same correlation of function, however, must still be maintained, and the *consensus partium*, as it has happily been expressed, by which this correlation is preserved under conditions of greater elaboration is effected through the medium of the circulation by means inconceivable at the time of its great discoverer, but still, as in the primitive plan, under the control of the nervous system. The principle of every cell being an individual organism was instilled into my mind in my earliest student days by a remarkable man, Professor Grant, of University College, who held the chair of comparative anatomy in the middle third of the last century. In 1846 Wharton Jones, another pioneer of blood biology, had discovered the amœboid movements of the white cells in fishes, and Davine soon afterwards found the same in human blood.

Many years before the doctrines of cellular pathology of Virchow, of the wandering cells of Cohnheim and their phagocytic function as discovered by Metchnikoff were under discussion, Professor Grant thus interested the young minds of the few who would attend his class in the cells of the blood. He pointed out that they were, as the other cells of the body, living entities, but carried here and there in the highways and byways of the liquid tissue of which they formed a part; that each cell earned its own livelihood within the limits of its environment, absorbing its own nourishment and secreting its own products; and that, moreover, these cells were, like Autolycus, "snappers up of unconsidered trifles," such as may be effete and strange in the vital stream—flotsam and jetsam of the tissues, or foreign bodies introduced from without.

These two conceptions—(1) that the blood is a liquid tissue the formed elements of which have their own autonomous vitality, and (2) that it is the chief means by which the *consensus partium*, so simple in the protoplasmic organism, is maintained in all the later complex developments of that organism—may be regarded as the main principles which underlay all the discoveries established by the brilliant researches of modern observers in the vital chemistry and biology of the blood. *Phagocytosis* is perhaps the factor around which the processes illustrative of the first principle centre; *internal* secretion that by which the second principle is best illustrated.

I can do little more than enumerate these discoveries. I cannot even name—except here and there—the workers who have brought them about; they are all well known and for the most part still living amongst us, many of them Fellows of this College, still searching out the secrets of nature by way of experiment in the topmost branches of the tree of knowledge rooted in Harvey's discovery. Some have suffered, but, like Harvey, have outlived the obloquy cast at them by ignorance and slander.

Chemical Attributes of the Blood.

The structure and function of the blood is a subject too vast to be touched upon save in a very elementary manner. It is a tissue of which the cellular elements, as with other tissues, are beings with their appetites and antipathies, earning their living "on their own" in their plasmic environment; the difference being that the environment of the blood cells is liquid, a vital, an ever-flowing stream, whilst the cells of the fixed tissues are dependent upon such portions of the plasma as are conveyed to them by the vessels of their connecting framework.

The blood thus contributes to and partakes of all organic function, and in the composition of its plasma there have been recognised, identified, and isolated—(1) substances called proteins destined for the body nutrition; (2) products of metabolism *en route* for removal; (3) salts which attend and facilitate both processes; and (4) certain other substances, neutral bodies, ferments, opsonins, antibodies, too numerous to speak of individually, some of which, as fibrinogen, can be identified and isolated; others—the opsonins, the antibodies, and some of the ferments—are discoverable only by their effects, some of them somewhat supposititious, like the meat-roasting quality in a jack, humorously alluded to by our quondam Fellow, Arbuthnot, in his amusing skit on the learned disquisitions of his time respecting the seat of the soul.

Harvey's tribute to the blood as the very essence of life is thus scarcely exaggerated; it is the tissue which has relations with every other tissue and process in the body by virtue of its fluidity and the pressure of its penetration. It gives and receives, and yet in health is ever the same. Its intimate concern in all the relations of life may be further revealed in the additional features I have yet very briefly to mention.

The whole subject of the chemical reactions of the blood and the means by which the uniformity of its reaction and quality are maintained has been most recently and fully discussed by Dr. F. Gowland Hopkins in the Oliver-Sharpey lectures of this year.[21] Its uniform reaction under the imbibition of large quantities of acid and alkaline fluids and acid and alkaline-producing foods is as truly remarkable as its constant temperature in health. It is suggested that whilst the lungs are chiefly concerned in controlling the hydrogen ions due to carbonic acid, the kidneys are concerned with those due to other acids, chiefly lactic acid, formed in the muscles, with

[21] THE LANCET, June 6th (p. 1589) and 13th (p. 1661), 1914

the result that the mean reaction of the blood is normally adjusted with great exactness.

Cholesterin is an important constituent of the blood, or rather an important agent circulating in it intimately concerned with cell life, which is now recognised as an essential and vivifying constituent of all cells. Its presence in the blood plasma may be only *en route* to its destiny in cell formation. With the disintegration of cells which takes place largely in the liver their cholesterin is set free to be reabsorbed and utilised in the generation of new cells.

Many of the ferments discovered—mainly by their effects—in the blood may perhaps be regarded, somewhat crudely from a physician's point of view, as to some extent contaminative, having their source as overflows from organic function (especially of the digestive cells) and of little or no importance in the vital mechanism, unless they should be in excess from accumulation owing to defective elimination, when they act as poisons.

Abderhalden draws attention to the protective action of certain ferments in defending the body from the injurious effects of organisms and chemical substances which are foreign or "disharmonious" to the blood and tissues. He finds that the introduction into the blood of disharmonious substances results in the appearance of ferments which were not previously present, but which possess the property of breaking down the foreign substances into simpler bodies with which the cells are accustomed to deal. He regards such ferments as modifications of the normal metabolic processes of the cells of the tissues or blood, and would thus seem to sanction the view I have been advocating that the cells of the body are equipped for their own defence as well as their own nutrition, and may be principally concerned in the secretion of "opsonins" and "antibodies" appropriate to their needs. The first and second lines of defence provided by the gastro-intestinal and hepatic cells are described by Abderhalden, and the plasma derives from the tissue and blood cells the ferments required for further dealing with disharmonious intruders and rendering them so far disorganised as to be amenable to phagocytic action.

Abderhalden pushes his argument to the formulation of a diagnosis of pregnancy, carcinoma, and some other diseases by the recognition in the blood of ferments antagonistic to the proteins yielded by the placenta and carcinomatous growths respectively. No doubt his work will be subjected to careful scrutiny and will stimulate new researches. The question of the production of antibodies to meet other extrinsic infections he has not discussed.

Internal Secretion.

With the recognition of the fact that nearly every glandular organ in addition to its proper secretion discharged through its duct yields also to the blood a secondary secretion peculiar to itself, a large field of interest and inquiry has been opened up to physiologists and many previously obscure phenomena have become more clear to physicians. Herein may be found an illustration and perhaps an explanation of the correlation of organic function which has been spoken of as the *consensus partium*, through the messages—mostly chemical—communicated by each organ to the controlling nerve centres; in a word, the "chemiotaxis" of the embryonic germ is maintained through the medium of the blood between differentiated and distant organs.

Professor Berthold, of Göttingen, in 1849, first showed the existence in the testicle of this second function of contributing of its essence to the blood, and it was Claude Bernard who in 1855 first applied the term "internal secretion." But Brown-Séquard's experiments upon the testicular internal secretion gave the impetus to all the physiological and therapeutic work that has followed. Brown-Séquard's experiments (1889) and the therapeutic measures to which they pointed led to false hopes and to abuses of an unworthy kind which for a time brought some discredit upon them. Their value in the treatment of premature senility, climacteric disturbances, and of some mental ailments was in a measure established, though with exaggeration, but their chief importance rested upon the further researches they initiated with regard to generative and other glands. The therapeutic measures they instigated are used extensively, though somewhat surreptitiously, at the present day.

Investigations on the Ductless Glands.

The ductless glands were the first objects of this further inquiry, and in rapid succession there appeared important results from the physiological experiments and clinical observations of Schiff, Sir W. Gull, Miller Ord, Kocher, Victor Horsley, and others upon the function of the thyroid gland and the parathyroids. In 1856 Schiff showed that the thyroid gland was essential to life. In 1873 Sir W. Gull described the condition which he named the "cretinoid state in adult life in women," which was further studied by Dr. Ord, who more fully described the clinical features of the disease, which he named myxœdema and associated with atrophous conditions of the thyroid gland. A swelling of the gland of a peculiar kind had long been associated with exophthalmic goitre, and in 1882 Reverdin and Kocher discovered that the removal of the gland for this disease resulted in symptoms described as those of "cachexia strumipriva," which were of the nature of myxœdema. Similar symptoms were artificially produced in monkeys by the removal of the healthy gland, by Horsley in 1891. In the same year Dr. Murray, then of Newcastle, introduced the injection of thyroid extracts for the successful treatment of this disease, on the same principle as Brown-Séquard had used allied extracts for senile affections. Thus, and by further researches at other hands, the relations of myxœdema, cretinism, Graves's disease, and operative myxœdema or cachexia strumipriva to the thyroid gland have been fully established, and a new era of therapeutic treatment invaluable for the relief of human suffering has been opened up. More complex relations have been found in the internal secretions of the parathyroids to other organs, especially the pancreas.

The relation of thyroid essence taken up by the blood to cardiac innervation and to general metabolism is being carefully investigated, and has been so far established as to instigate various measures of therapeutic value.

Another great Guy's physician, Addison, first discovered (1855) the importance of the suprarenal glands and described the symptoms of a certain diseased condition of them which is known by his name. This discovery led to a chain of observations by Brown-Séquard, by Kölliker, and others until, in 1894, Schäfer and Oliver established the connexion between the suprarenal essence, and especially that of the medullary portion, and blood pressure. Addison had recognised as a marked feature of his disease the notable depression in the pulse tension. Schäfer and Oliver discovered as a chief function of the suprarenal bodies the maintenance of blood pressure, and initiated an important and now well-known method of treating suprarenal disease and established the value of extracts derived from the gland as a sympathetic nerve stimulant. Further researches have shown that this extract especially affects circular organic muscle, including the heart and vessels, and there are many collateral effects still under investigation.

On similar lines interest attaches to the contribution of the pituitary body to the blood, its function in health, its effects under diseased conditions, and the therapeutic value of extracts derived from certain portions of it. The field of investigation has greatly widened, and the pancreas, the kidneys, the liver, and the gastro-intestinal cellular digestive tract have successively been found to yield not only their secretion into the ducts and channels with which they are properly connected, but a secondary internal secretion contributed to the blood.

Importance of Internal Secretions.

Professor Starling and Dr. Bayliss, to whose researches a large portion of our knowledge respecting the internal secretions of the digestive tract especially is due, have applied the term "hormone" to these secondary glandular products, and the term will probably soon be used to include all internal secretions. It is important to recognise

Professor Starling's distinction of hormones from other materials or influences in the blood, such as antigens arising from toxins, ferments, &c., each with its corresponding antibody. Hormones readily pass through the capillary vessel walls, and, having effected their purpose, they undergo rapid destruction by oxidation or otherwise and are known no more. It may be the condition of greater simplicity of composition, lighter specific gravity, and greater diffusibility attributed to these chemical essences that cause these hormones to get into the blood, whilst the more obvious organic secretions escape through ducts to their destination.

It would be difficult to exaggerate the interest and importance of these hormonic contributions to the blood from the different organs and tissues. Quite unobservable in their course, they yet convey messages and instructions to the nerve centres leading to vaso-motory relaxation or constriction of the capillary areas whence they proceed. In this way they correlate and regulate growth and function, at the same time preserving that *consensus partium* so comparatively easy in the simple amœboid structure. Here is a great function of the circulation, undreamed of by Harvey, in distributing these agencies, which is as imperceptible to our unaided comprehension as are the infinity of living particles in the clear atmosphere until illumined by a sunbeam, or the thought waves teeming in a crowded assembly. By their effects only can we gauge them, and only by the deepest and most subtle researches—by experiment upon their effects—can we learn these secrets of nature.

> Strange is it, that our bloods,
> Of colour, weight, and heat, pour'd all together,
> Would quite confound distinction, yet stand off
> In differences so mighty.[22]

The mental side of these phenomena is of great but at present, for the most part, speculative interest to the psychologist, the alienist physician, and the criminologist. In the phenomena of hysteria and its border-line manifestations, of insanity and of criminal impulses, as well as in the

[22] All's Well that Ends Well, II., 3.

controlled impulses that account for character and discipline, we may find interesting fields for the study of the effects of internal secretions as they here and there emerge to consciousness from their sphere of automatic action.

Defensive Attribute of the Blood.

The last attribute of the blood is that of defence against attacks, mainly infective, upon the organism, an attribute which eventuates in the establishment of immunity to infective diseases. After the experience of an infective illness the blood becomes more tolerant of that particular poison, whilst its defensive forces are strengthened and the poison influence is weakened or altogether neutralised. Thus immunity arises.

The Establishment of Immunity.

The methods of blood defence and the modes by which immunity is established are still matters of considerable controversy, and the various views expounded are often expressed with a vocabulary which obscures rather than renders more clear the arguments of the disputants. There are, however, two main contentions or schools of opinion: the one with which Professor Ehrlich is perhaps most identified, which regards the bactericidal influence of the blood as chemical and residing in the plasma; the other, held by Metchnikoff and his followers, regarding it as resident primarily in the cell elements of the blood and of certain tissues. It has been shown, mainly by the work of Sir A. Wright, that (as in most controversies) the essentials of both views enter into the truth of the matter.

From my earliest training to recognise the predominance of cellular over liquid plasmic processes, I must confess a strong prejudice in favour of the opinion of Metchnikoff that the leucocytes of the blood chiefly, and perhaps the endothelial cells of blood-vessels and serous spaces and the cells of the tissues to a greater extent than he would admit, are the source of such agents, doubtless mainly chemical, as are found in the blood plasma as alexins, ferments, antibodies, immune bodies, opsonins, or what not. These agencies, by whatever name they may be known, reinforce the general qualities of the blood serum in the attack upon living and for the digestion of dead foreign bodies, which are then consumed by the phagocytic action of the leucocytes and the other cells named. On the other hand, bacterial and protozoic organisms on their side, with their infinite productivity and the secretions they yield, may well be conceived to be capable in many instances of overwhelming the defensive action they at first excite. This is how the matter crudely presents itself to the mind of an average physician after labouring through as best he can the intricate and wonderful work of those numerous bacteriologists who have cast such brilliant light on the intimate biochemical processes of the blood. It is also readily to be understood how the local introduction of minute quantities of "disharmonious" substances, such as bacterial toxins, may excite the production locally of antibodies the absorption of which into the general circulation will reinforce the defensive qualities of the serum. We must not forget, however, that it is a natural process of defence, a tendency to immunity, which is excited by all bacterial and protozoic infections, the exact nature of which it has been the primary object of all these brilliant researches to show, and that it is the observation and study of this natural process which has prompted the use of artificial measures for its assistance.

Vaccine Methods of Treatment.

The immunity gained by an attack of certain specific diseases against further assaults has long been known to physicians: how mild attacks of small-pox, whooping-cough, scarlet fever, dissection wounds, will protect, at least for a time, often the lifetime, from further attacks. Lady Mary Wortley Montagu and Edward Jenner were pioneers in interpreting rightly this natural lesson in immunity, and the exact inquiries of modern observers have thrown so much light upon the processes concerned as to have established on scientific lines vaccine methods of treatment in many acute specific diseases and of analogous methods in some chronic diseases. It was Pasteur who, in 1880, revived the question of immunity on experimental lines in his observations on chicken cholera, and suggested the possibility of establishing artificial immunity in certain diseases. Within the lifetime of the youngest here diphtheria, enteric fever, tetanus, and plague have lost half their terrors.

The applicability of knowledge gained respecting immunity processes is now being utilised in certain chronic infective diseases, notably tuberculosis and perhaps arthritis. All practical physicians have long been aware of the fact that an attack of tuberculosis, or repeated attacks, having resulted in a chronic passive fibroid lesion, the patient if able to endure such lesion without fresh assault for a certain time acquires a very considerable, even a permanent, degree of immunity, and may die in later life from disease of a quite different kind. It is now recognised that such patients acquire and perhaps retain their immunity through the absorption of successive doses of tuberculin taken up by the blood in its course through their passive or indolent lesions. They are in possession of an inoculate, a source of vaccine, in the remnants of quiescent morbid tissue left behind by the acute disease. Thus are they in a measure fortified against fresh infection. This view, which would seem to hold good with regard to tuberculosis and perhaps syphilis, may in a more subtle manner hold good also with regard to remnants left behind by the acute specific fevers, as so coarsely illustrated by the effect of inoculation in small-pox; such a hypothesis is at least interesting in bringing into line the doctrine of immunity with the phenomena of internal secretion already discussed.

Advantage has been taken of this knowledge in the rational treatment of tuberculous patients by retarding or exciting the circulation through their lesions by regulated exercises. A warning must attend these observations—viz., that some of these people have their leucocytic functions sensitised by such autogenous stimulation, and are thereby rendered unduly excitable to further stimulation—they are anaphylactic—in a greater or less degree, and tuberculin inoculations are apt, unless given with the greatest caution as regards dosage and repetition, to induce a recurrence of negative phases or periods of paralysed resistance very inimical to the patient's prospects. I cannot say that I have ever observed tuberculin vaccine given three times a day after meals, after the manner of the Court physician in the "Doctor's Dilemma," but I have often seen it given on unsuitable occasions and in recklessly repeated doses in entire ignorance of the intimate history of the disease and with disastrous results. The necessity of a period of restful quietude after any administration of tuberculin is further emphasised by the above considerations.

We have seen how heart and pulmonary mechanism are subordinate to the circulation of a vital stream which, so constant in all its physical aspects, so infinite in its attributes and adaptations, dominates all the functions of life. Might not Harvey quote Leviticus—"for the life of all flesh is the blood thereof"—with even greater conviction to-day?

I have yet, Mr. President, one duty to perform, and that is to exhort the Fellows and Members of the College to continue their endeavours for the advancement of the College in learning and general prosperity. It is impossible to record the numberless gifts to the College since Harvey's time; gifts of learning, gifts to the library, gifts of valuable and interesting documents relating to the College, gifts for research, gifts for hospitality. In the past year such gifts have been continued and were recorded in your address recently published. Harvey's further exhortation to the Fellows was that for the honour of the profession they should continue "in mutual love and affection amongst themselves, without which neither the dignity of the College can be preserved, nor yet particular men receive that benefit by their admission into the College which else they might expect, ever remembering that *Concordia res parvae crescunt, discordia dilabuntur.*"

I gratefully acknowledge the kind help I have received from my colleague Dr. R. A. Young in the literature, especially that relating to the blood; and also my great indebtedness to Miss E. Parry for much assistance in revising the proofs and in verifying the references, only a small fraction of which are annotated in the text.

*** *With reference to paragraph 1 on page 5, see correspondence in* THE LANCET *of Oct. 31, Nov. 7 and 14, 1914.*

Printed at The Lancet Office,
423 Strand, London, W.C.