The Harveian Oration ON CARDIO-VASCULAR DISEASES SINCE HARVEY'S DISCOVERY.

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BY

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INTRODUCTION.

THE President's command to deliver the 272nd Harveian Oration in the tercentenary year of the publication of the *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* is an honour to be prized with humble gratitude, but with a due sense of its heavy responsibility, by any man, especially by one whose father obeyed the call to this high duty fifty-five years ago.

The tercentenary of the publication of Harvey's immortal discovery was appropriately and splendidly commemorated by the celebrations organized by this College. In no way could its significance have been more suitably and graphically shown than by the remarkable cinematograph films of Harvey's original physiological experiments as repeated by Sir Thomas Lewis and Dr. H. H. Dale, Fellows of the College, who have been eminent in obedience to Harvey's exhortation "to search and study out the secrets of nature by way of experiment." Further, the historical aspect of the tercentenary has been permanently assured by the publication by the College of a facsimile of the first edition of the *De Motu Cordis*, and by the appearance of two other Harveian books, a reproduction of the first English translation in 1653 of the *De Motu Cordis* (Nonesuch Press), and *A Bibliography of the Writings of William Harvey, M.D.* (Cambridge University Press), both due to the pious devotion of a licentiate of the College, Mr. Geoffrey Keynes.

John Freind, the elegant scholar and eminent physician, when commenting on the history of the circulation, wrote in 1725:

"From this discovery of our great countryman [Harvey] many improvements, even in the cure of distempers, might be made: he had thoughts of composing such a work himself, to show the advantages of this doctrine, in relation to practice, but was prevented by sickness and death: the design of the Architect was very noble, and I with some of his successors might finish it. At present I shall hint only at two or three particulars, which will convince us, of what use a perfect knowledge of the circulation may be to us, if rightly applied, in the practical part of our profession."

If more than two centuries ago the learned author of *The History of Physick from the Time of Galen to the beginning of the xvi Century* apparently thought the task difficult and accordingly acted with wise discretion, it is now obviously, from limitations of both time and capacity, impossible to attempt more than the barest outline of the accumulated knowledge of the diseases of the circulatory system since Harvey's time. An attempt to piece together the history of the various forms of cardiac disease is attended by no small difficulties: the same ideas often occur to several minds at the same time, but simultaneous and identical solutions are not published synchronously, thus making it far from easy to decide who really deserves the rather barren crown of priority. Another obvious objection to such a subject is that it entails lists of men and dates; but as many of these names are those of Fellows of this College it will surely be in obedience to Harvey's injunction to commemorate these benefactors of the College, for can any benefaction be more welcome than new and true knowledge?

The knowledge of cardio-vascular disease, which was very slight at the time of the discovery of the circulation,

has since come through several channels: (1) the accumulation of data provided by anatomical observation, normal and morbid; (2) unaided clinical observation; (3) as the result of the application of instruments of precision to the examination of patients; and (4) the information derived from physiological and pathological experiments. Though these four headings are attractive as a means of sketching the advance of knowledge, it is in practice difficult, and indeed somewhat inconvenient, to follow them out rigidly or attempt to make them absolutely watertight; there will therefore be much overlapping, as will at once be only too obvious.

ANATOMICAL OBSERVATION.

Anatomy is an indispensable step to the more complex science of physiology, which explains the vital forces of the body, and this, though it may be helped by anatomy, demands observation of, or experiment on, the living organism. Fabricius's description of the valves in the veins stimulated Harvey to find out their use by the experimental method. Gaskell's physiological demonstration of the muscular continuity between the auricle and the ventricle was made on reptiles, and was supposed to be confined to them until 1893, when the auriculo-ventricular bundle was described in mammals by Stanley Kent and by W. His, junior; in 1906 Tawara gave a full account of the junctional system, including the auriculo-ventricular node and the bundle previously described by Kent and His, the fibres of the bundle being continued into the Purkinje fibres which line the interior of the ventricles and communicate with their muscular fibres; this was followed in 1907 by Keith and Flack's discovery of the sino-auricular node, the normal pace-maker of the mammalian heart; the later anatomical observations were subsequent to, and directly stimulated by, the needs of the new cardiology, for Mackenzie's epoch-making book on the pulse was published in 1902. Thus it may be noted that, just as medicine is deeply indebted to the experimental method, so also science owes a debt to medicine, and that they two "according well may make one music as before."

The Capillaries.

The tercentenary of the birth of Marcello Malpighi, the father of histology, on March 10th, 1628, and that of the *De Motu* appropriately coincide, for in 1661 he provided the final proof of Harvey's discovery by recognizing the capillaries in the frog's lung. He also saw the red blood corpuscles in the mesenteric vessels of a hedgehog, but as he regarded them as fat cells, Antony van Leeuwenhoek, who described them fully in his *True Circulation of the Blood* in 1686, has the credit of their recognition. Johannes Swammerdam, however, had actually noted the presence of red blood cells as early as 1658, but his observation was not made public until 1738, when Boerhaave brought out Swammerdam's *Biblia Naturae*.

After the discovery of the capillaries there was a long interval before this most essential part of the circulatory system received due attention. Thomas Young in 1808 had the foresight to assume as probable variation in the size of the capillaries. The view that the capillary circulation was a mere passive communication between the arterioles and the venules was definitely modified by Stricker's observation in 1865 that the capillaries became constricted from swelling of the endothelial cells. In 1873 Rouget observed on the surface of capillaries the cells which bear his name, and described their contraction. In 1879 Roy and Graham Brown showed that the calibre of the capillaries is constantly changing without corresponding alterations in the arteriolar pressure. The study of the capillary circulation then languished; but the invention of capillary microscopy by Lombard in 1912 again stimulated investigation, and it has now been proved that the walls of the capillaries have independent powers of changing their calibre.

The capillary circulation, thanks to the experimental labours of Dale, Laidlaw, Richards, Krogh, and Lewis, has been placed in a new light. It appears that the capillary area as a whole is in a constant state of flux; while the great portion is relatively empty, various parts of it open for a time, so that with a constantly changing

condition of the constituent portions the average total path remains about the same and maintains the peripheral resistance. Normally only a very small proportion of the whole available capillary area is open, for if it were universally open all the blood would stagnate there. The varying dilatation of the capillaries corresponds, as Krogh demonstrated in muscle, with the needs for it.

The question whether the circulation in the nervous system, the lungs, and the coronary vessels is under the same nervous control as the rest of the general systemic capillaries has been exhaustively investigated and is referred to briefly elsewhere; the effect of adrenaline on the vessels—constriction or its absence—has been employed as a criterion of the presence or absence of vasomotor fibres, but can hardly—for example, in the case of the coronary arteries—be regarded as devoid of exceptions due to a species difference in the nerve supply and reactions.

Morbid anatomy must also be supplemented by clinical observation or by experiment; the example set by Harvey of always submitting to the test of physiological proof the explanations suggested by anatomy, which is completely instructive only when elucidated by physiological experiment, was followed with regard to morbid anatomy and its correlation with symptoms by Morgagni, Corvisart, Laennec, Hope, and later the experimental results obtained by Claude Bernard, Cohnheim, Roy, Starling, and many others were brought to supplement the teaching of the *post-mortem* room.

It was not until the eighteenth century, with the publication of observations on morbid anatomy made by Raymond Vieussens (1715), Lancisi (1718, 1740), and Morgagni (1761), and the first treatise dealing specially with diseases of the heart by J. B. de Senac (1749), that cardiac disease was really recognized. Theophilus Bonetus, in the first volume of his *Sepulchretum* (1679), collected a number of observations on palpitation and cardiac pain during life associated with polypi in the heart, calculi in the myocardium, inflammation of the heart, acute inflammation, effusion, and adhesion of the pericardium, and aortic aneurysm, and thus prepared the way for Morgagni and others. Vieussens and Morgagni recorded a number of valvular lesions, and Lancisi in 1718 described vegetations on the valves and noted dilatation and hypertrophy, but applied the term "aneurysm" to the former; in his posthumous book (1740) syphilitic lesions of the heart were outlined. De Senac described ulceration, abscess, and inflammation of the heart, "the hairy heart" of acute pericarditis, and, in a short chapter, malformations.

Corvisart and his pupils, Laennec and Bouillaud, carried on the anatomico-clinical investigation of cardiac affections, and among the Fellows of this College James Hope (1801-41) set a fine example in this respect.

[The Orator then considered in some detail the anatomico-clinical history of various cardio-vascular diseases.]

UNAIDED CLINICAL OBSERVATION.

Under the heading of unaided clinical observation the use of the stethoscope may perhaps be included, as it is artificial to separate the employment of this instrument of precision from that of direct auscultation. In this section the history also is outlined of some cardiac disorders—dyspnoea, angina pectoris, coronary thrombosis, the Stokes-Adams syndrome—which give rise to characteristic clinical pictures. As would naturally be anticipated the history of cardiac diagnosis shows that in the main recognition and correlation of symptoms came first and the invention of physical methods of examination later. Albertini of Bologna laid stress on palpitation and dyspnoea as evidence of cardiac disease, and ascribed the latter to venous stasis in the lungs. He also made use of palpation, which was little employed before his time, or indeed for a hundred years after, until Corvisart revived it and drew attention to thrills.

Percussion was described by Leopold Auenbrugger of Vienna in a pamphlet of twenty-two pages in 1761, the year in which Morgagni's great work on morbid anatomy, *De Sedibus et Causis Morborum*, appeared, and so should have been a means of correlating physical signs with gross structural changes. But though praised as worthy of all attention by his senior contemporary Albrecht von Haller

of Berne, and translated into French by Rozière de la Chassagne, and published in Paris in 1770, the conservatism responsible for opposition to Harvey's discovery delayed the acceptance of Auenbrugger's percussion. It was thus long before its time and did not receive any recognition until, in 1808, the year before the author's death, J. N. Corvisart translated it into French for the second time.

Auscultation, though in practice and in our minds dating from Laennec and the invention of the stethoscope, was not an absolutely new idea in 1819. The story of the invention of the stethoscope by Laennec has often been told: in 1816 he noticed boys in a court of the Louvre at play with the ear applied to long pieces of wood listening to the transmitted sound of a pin scratch at the opposite end. He immediately put this hint into practice, as he says, by applying a rolled-up quire of paper to the chest of a stout girl with symptoms of heart disease, and was electrified by finding that the heart sounds were more audible than to the direct ear. He keenly practised this method at the Necker Hospital, where, however, Granville, as an onlooker on September 16th, 1816, states that the original birth of mediate auscultation actually occurred on the chest of a male patient. Laennec then devised a wooden cylinder $1\frac{1}{2}$ inches in diameter, a foot long, and perforated longitudinally by a bore three lines wide; this he regarded as too simple to require a name other than "the cylinder" or "bâton"; but eventually, as somewhat barbarous names, such as "sonometra," "pectorilogue," "thoraciscopie," "cornet de papier," and "cornet médical," appeared on the horizon, he suggested, if it must have a name, "stethoscope." With his knowledge of morbid anatomy he correlated the local lesions with the corresponding physical signs, like his teacher Corvisart, thus advancing the anatomico-clinical method and the special pathology of the organs; and in the extraordinarily short time of three years his classical work *Auscultation médiate* appeared, about August 15th, 1819. While correcting the proofs he had been busily making stethoscopes so that every buyer of his book might be properly equipped; in fact, it is probable that at the time of his death every existing stethoscope was the work of his hand (Thayer).

Though the stethoscope has some obvious advantages over the naked ear, the enormous advances that followed its introduction were not so much due to the stethoscope as a mechanical instrument as to the psychological effect that this new method exerted on Laennec, who otherwise would not have so ardently pursued auscultation as a means of diagnosis. It was much the same with regard to the pleximeter introduced by P. A. Piorry in 1828, which in itself, apart from its temporary influence in stimulating investigation, is inferior as a method of eliciting physical signs to Auenbrugger's direct percussion, which it was intended to supersede.

Laennec's original stethoscope underwent modifications by him, by Piorry, who reduced the thickness of the stem to that of the finger, by C. J. B. Williams, and others. The invention of the binaural stethoscope was the subject of some dispute as to priority, as is shown in the pages of the *London Medical Gazette* for 1840-41; Sibson used one in 1838, Burne in 1840, and Golding Bird stated that Babington at Guy's Hospital had used one for some time. In America, where it was introduced in 1850 by Cammann, its vogue became general much earlier than in this country. Auscultatory percussion, or a combination of the two methods enabling the vibrations produced by percussion to be directly transmitted to the ear by the stethoscope, was advocated by Cammann and Clark in 1840. More modern developments are the phonendoscope and the differential stethoscope.

Until auscultation had become somewhat elaborated the diagnosis of heart disease depended on general symptoms, such as dyspnoea, palpitation, a weak and irregular pulse, and there was not any discrimination in diagnosis. In the posthumous edition of Matthew Baillie's *Morbid Anatomy* (1825) it is stated that "no observations have yet been made by which practitioners can ascertain with any precision what set of valves is diseased." But Laennec's *Auscultation médiate* stirred the waters to much purpose. Bouillaud, Hope, Williams, and Elliotson became

extremely active in tabulating the physical signs with the valvular lesions and accumulating data—the time, propagation, and characters—so as to determine the significance of murmurs. Hope's *Treatise on Diseases of the Heart and Great Vessels* (1832), though somewhat marred by his disputes with Bouillaud, chronicled a most notable advance; having carried on experimental research he was able to apply physiological principles to unravelling the haemodynamic problems of cardiac disease.

During the latter half of the last century an exaggerated importance was attached to cardiac, and especially systolic, murmurs as evidence of heart disease. With "the passing of morbid anatomy," or the overshadowing of gross morbid changes by the renewed attention to symptoms and physiological efficiency, there has now resulted a diminution in the importance attached to the physical signs of cardiac disease. But the traditional stress laid on the presence or absence of a murmur as the criterion in determining whether the heart was or was not seriously affected, though qualified by the warnings of W. T. Gairdner (1862), Thomas Watson, Andrew Clark, G. W. Balfour, and others, did not become fully discounted until after the war, and then largely by Mackenzie's insistence.

CARDIAC DYSPNOEA.

As a result of work done during and since the war, cardiac dyspnoea may be divided into (1) simple, in which there is increased irritability of the respiratory centre from oxygen want brought about by diminished blood supply to the centre; in these cases, occurring in the young, especially with mitral stenosis, and comparatively early, the cyanosis being bright, Fraser, Ross, and Dreyer found a definite alkalaemia; and Lewis and Barcroft noted the absence of acidaemia; (2) cases of a more complicated nature, often arterio-sclerotic or cardio-renal, in older people, with myocardial degeneration, dyspnoea occurring later and the cyanosis being of a leaden hue (Fraser). In these cases there is acidaemia (Lewis and Barcroft) and stimulation of the respiratory centre by the increased hydrogen-ion concentration, the fundamental idea that acidaemia causes breathlessness being directly deducible from Haldane and Priestley's work (1905). These cases manifest true cardiac asthma with a sudden onset, which was ascribed by Lewis, Ryffel, Wolf, Cotton, and Barcroft (1913-14) to sudden waves of acidaemia. The attacks are probably much allied to those long known as renal asthma, which, as pointed out by Loomis (1873) and Stephen Mackenzie (1889), are greatly benefited by hypodermic injection of morphine. These paroxysmal attacks of cardiac asthma were mentioned by Heberden, who eliminated from his picture of angina pectoris the symptoms of breathlessness; but there is a close relation between the three conditions of angina pectoris, oedema of the lung, and cardiac asthma (Pratt), which may be combined or confused with each other. Hope in 1839 gave an account of cardiac asthma, but rather confused the issue by bringing in ordinary cardiac dyspnoea and Cheyne-Stokes respiration. Clinically James Mackenzie drew special attention to the true cardiac asthma about which scepticism had been expressed. The value of morphine hypodermically in the paroxysmal dyspnoea of cardiac asthma has recently been emphasized (Fraser); and it may be noted that, on more general grounds, Clifford Allbutt in 1869 recommended morphine in cardiac disease by the then comparatively new method of hypodermic injection, the syringe having been invented by F. Rynd in 1845 and Alexander Wood in 1855.

ANGINA PECTORIS.

Angina pectoris was first described on a good basis of cases, twenty in number, by the British Celsus, William Heberden the elder, in a paper entitled "Some account of a disorder of the breast," read before this College on July 21st, 1768. In the text he says: "The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly called angina pectoris," and his posthumous *Commentarii de Morborum Historia et Curatione*, 1802, show that altogether he had seen a hundred cases. Isolated cases had been reported before this: Seneca in his epistles to Lucilius recorded his

own sufferings, which may well have been those of angina sine dolore, and at any rate were by his medical attendants called a "Meditatio mortis"; the Earl of Clarendon described the sudden death of his father, Henry Hyde, in 1632, and Morgagni the case of a woman who died in 1707 with a characteristic distribution of the pain and was found to have a dilated and calcified aorta. Hoffmann recorded another single case "de spasmo praecordiali a motu corporis" in 1734; Rougnon, professor of medicine in the University of Besançon, wrote a letter to M. Lorry dated February 23rd, 1768, earlier in the same year as Heberden's more complete account, describing a case of angina with a necropsy, and accordingly in France a claim for priority was made for him by Huchard. On November 17th, 1772, two further communications on the subject were made to the College; Heberden read a letter addressed to him by a man signing himself "Unknown," who, having seen an abstract of Heberden's original paper in *The Critical Review*, recognized the resemblance to his own experiences, gave an account of them, considered by Osler as one of the best extant, and expressed a wish that in the event of his death there should be a necropsy; this, when performed by John Hunter, did not reveal anything save slight calcification of the aorta, but Edward Jenner, who was present, wrote to Caleb Hillier Parry, "I can almost positively say the coronary arteries of the heart were not examined." The other, though less dramatic, communication made at this meeting, by John Wall of Worcester, has perhaps hardly received its due meed of attention; for in his letter to Heberden describing the *post-mortem* examination of a case of aortic stenosis with angina, the first inch of the aorta is stated to have been partly ossified, and the spasm of the pectoral muscle is ascribed to "an irritation on the nerves of the thorax and heart," and the following comment is added: "Perhaps it may throw some light on this affair to consider that the nervi intercostales or sympathetici distribute many branches to the heart, arteria pulmonalis, and aorta." He thus, perhaps, in the first place anticipated James Mackenzie's view that the pain of angina is partly due to spasm of the intercostal muscles and Charlton Briscoe's suggestion that the spread of pain depends upon irritation of one of the expiratory muscles, and in the second place suggested Corrigan's and Clifford Allbutt's conception of the aortic origin of anginoid pain. The association of coronary disease with angina was first recognized by Edward Jenner from *post-mortem* examination, though it is possible that John Hunter, on whose account, as his anginal symptoms dated from 1773, Jenner kept silence, knew or suspected it in 1776, when John Fothergill published a fatal case of angina in which at the necropsy Hunter found that "the two coronary arteries from origin to many of their ramifications on the heart were become one piece of bone." Jenner, who is said to have diagnosed angina in Hunter in 1777, never directly published anything on this subject, but he communicated his opinions to C. H. Parry, who in 1788 read a paper—"An inquiry into the symptoms and causes of the syncope anginosa, commonly called angina pectoris; illustrated by dissections"—to a small medical society in Gloucestershire of which Jenner was a member, and came to the conclusion that coronary disease was the cause. In this paper, not published until eleven years later, he quoted the case of ossification of the coronary arteries published by Black of Newry in 1795, and pointed out that he and Jenner had independently come to the same opinion in 1788.

The explanation of the causation of angina pectoris by coronary disease was, as pointed out by Osler, given by Allan Burns, the Glasgow anatomist and surgeon, who in 1809 ascribed the symptoms to anaemia—or, as it might now be expressed, anoxaemia—of the heart muscle resulting from coronary obstruction. This conception is now known as intermittent claudication—a term introduced by Bouley in 1831 in regard to horses and applied to man by Charcot in 1858—and perhaps more intelligibly as intermittent limp (Erb). Benjamin Brodie in 1846 explained angina pectoris on these lines rather more fully, and Potain in 1870 expressed the same opinion. The view that disease of the base of the aorta was one of the causes of angina pectoris, perhaps dimly foreshadowed by Wall (1772) and

Baumes of Montpellier (1808), was put forward by Dominic Corrigan in 1837, and independently by Allbutt from 1894, with confirmation from our Honorary Fellow, K. F. Wenckebach, in the special lecture he gave in this library on May 5th, 1924, when he accordingly advocated division of the depressor nerve. James Mackenzie considered that angina is due to cardiac failure, a revival of the view held by Parry (1799) and supported by Stokes (1854), and Daniélopoulu put forward the slightly different explanation that myocardial intoxication by fatigue products is responsible for angina.

The syndrome of angina pectoris, ascribed to various factors, has been divided into (1) true organic or major, and (2) functional, pseudo, mock, false, vasomotorial, or minor. John Latham (1813) described a spurious form as angina notha; Laennec (1818), who had two attacks, did not accept coronary disease as the cause, considered mild cases as common, and described it as neuralgia of the heart; Desportes (1813) had previously expressed a similar view; Forbes, the translator of Laennec's *Auscultation médiate*, spoke of organic and of functional angina, subdividing these two main categories. Lartigue (1846) and Walshe independently introduced the term "pseudo-angina," which has not escaped criticism from Allbutt and Mackenzie; Nothnagel in 1867 brought in the term "vasomotor angina"; and toxic angina, especially that due to tobacco, was described by Huchard. Angina sine dolore, a form of true or major angina, was so named by W. T. Gairdner (1877). The distribution of pain and cutaneous tenderness was investigated by James Mackenzie (1892) and Henry Head.

Excision of the cervico-thoracic sympathetic containing the sensory nerves of the heart and aorta as a means of relieving the pain of angina was suggested in 1899 by François-Franck, the physiologist, but not put into practice until 1916 by Jonnesco of Bucarest. The treatment by amyl nitrite was initiated in 1867 by Lauder Brunton, when a house-physician, on the grounds that he found the blood pressure high in an attack and, having heard from Arthur Gamgee that amyl nitrite lowered the blood pressure, logically and successfully employed this drug.

In the tercentenary year of the publication of the *De Motu Cordis* it is interesting to find that the coronary circulation, on which R. Lower, R. Vieussens (1706, 1715), and Adam Christian Thebesius (1708) worked, has been investigated after the Harveyan manner. Wearn finds that the blood in the coronary arteries may pass into the Thebesian vessels and so into the ventricles or auricles without entering the capillaries, there being either a direct communication between the coronary arteries and the Thebesian veins, or more probably between the arteries and large veins, and thence into the cavities of the heart. Further, he argues, from observations on two cases of gradual complete obliteration of the orifices of both coronary arteries, that the Thebesian vessels may take on the new function of supplying the heart muscle with blood from the cavities of the heart, a view to some extent previously expressed by Pratt. The coronary blood flow depends on the arterial pressure, but opinions differ as to the relative importance of the diastolic and systolic blood pressures in the aorta. In this year Anrep and King have shown by experiment that the coronary blood flow is not determined by either the diastolic or the systolic pressure in the aorta singly, but follows closely changes in the arithmetical average of the diastolic and systolic aortic pressures, which in most cases is a sufficiently accurate measure of the true mean pressure.

CORONARY THROMBOSIS.

The syndrome of thrombosis of the coronary arteries, long included in angina, has quite recently been isolated, though Harvey's description of Sir Robert Darcy's case, in his second Disquisition to J. Riolan, in which the wall of the left ventricle was ruptured apparently as the result of "an impediment to the passage of the blood from the left ventricle into the arteries," has now been recognized as an early example (Wearn). The syndrome, first described in 1910 by Obrastzow and Strachosko, and again in 1912 by J. B. Herrick, is, now that its characteristic features have been pointed out, obviously a frequent event;

this year Parkinson and Bedford published one hundred clinical cases and in addition eighty-three *post-mortem* cases. Isolated cases had been reported in 1884 by Leyden and even diagnosed by Hammer in 1878, and it is now easy to wonder why coronary occlusion, long recognized pathologically, had not been correlated earlier with a clinical picture. Cases of angina with pericarditis had been recorded (Steell), and the occurrence of the status anginosus, or pain lasting for hours or days, in contrast to the pain of angina, which is a matter of minutes, was noted by Huchard. Both these phenomena belong to the syndrome of coronary thrombosis. Rapid and sudden death may be due to ventricular fibrillation or to rupture of the infarcted area as in Harvey's case; recovery may occur, but myocardial failure, cardiac aneurysm, rupture, or recurrent thrombosis may follow.

STOKES-ADAMS SYNDROME.

J. B. Morgagni in 1761 mentioned two men aged 68 and 64 years with slow pulse rates, one "twenty-two within one-sixtieth part of an hour," dating from the time they were "first attacked with epileptic paroxysms, beginning from the belly"; Heberden in 1768 described a pulse seldom above thirty associated with torpidity; Andrew Duncan described the same events in 1793; Bright in 1831 recorded the clinical features of a case with a necropsy showing a much enlarged heart. The condition was called "maladie de Stokes-Adams" by Huchard after the two Irish physicians, Robert Adams and William Stokes, who gave accounts of it in 1827 and 1846 respectively and laid much stress on fatty degeneration of the myocardium; indeed, they transferred to that condition many of the symptoms of complete heart-block. This, of course, was long before Gaskell's physiological explanation (1883) of heart-block, which is usually, but not invariably, primarily responsible for the syndrome. Galabin in 1875 first published tracings of the independent contractions of the auricles and ventricles, and ten years later Chauveau's tracings also showed this in a man with an auricular rate of sixty to sixty-five and a ventricular rate of twenty-one to twenty-four. Osler pointed out the various forms of the Stokes-Adams syndrome, especially the rare cases with gross extrinsic lesions exerting pressure on the medulla or the vagus, such as those of Holberton, Lépine, and Boffard, and to his writings the general recognition of the syndrome is due in no small degree. Recently it has been shown that the ventricle may pass into fibrillation, and that the direct injection of adrenaline into the heart will start the circulation again even if it has stopped for four or five minutes. Subcutaneous injection of adrenaline has been found to arrest the syncopal attacks (Phear and Parkinson), but not to prevent them. For this purpose Cohn and Levine had recourse to barium chloride by the mouth, which, by increasing the irritability of the ventricle, was successful in preventing the attacks. An interesting account of his own experiences during the last seven years of his life was given by W. T. Gairdner.

EXAMINATION OF PATIENTS WITH THE AID OF INSTRUMENTS OF PRECISION.

Sphygmomanometry.

The history of blood pressure really begins with Stephen Hales, minister of Teddington, who, with a sound training in Newtonian physics, applied this knowledge to biology and physiology. Before 1723 he tied tubes into the arteries and veins of animals and estimated the pressure in the capillaries, thus being far in advance of his time. In a mare he found that the blood pressure was equal to a column of blood of eight to nine feet. Nearly a century passed before the subject was further investigated, and then Poiseuille (1828) employed a U-shaped mercurial manometer (haemodynamometer). The clinical estimation of blood pressure by instrumental means was first attempted by Vierordt in 1855 by measuring the weight necessary to stop the arterial pulsation; but von Basch, in 1880, invented a sphygmomanometer on this principle, which was applied locally over an artery and was widely used. This underwent modifications; among others by Potain, Marey, Mosso, and Hürthle. Attention should be drawn to F. A. Mahomed's laborious observations on blood pressure made between 1874

and 1881, not with a sphygmomanometer, but with his own form of Marey's sphygmograph, which led him to anticipate much that is now known and far more easily verified—for example, he described a pre-albuminuric rise of blood pressure in Bright's disease, which, with von Basch's conception of "latent arterio-sclerosis" and Huchard's pre-sclerosis, led up to the recognition of primary or essential high blood pressure or hyperpiesia. The present sphygmomanometric methods became generally available as a result of Riva-Rocci's modification of von Basch's instrument. The publication of Korotkoff's auditory or auscultatory method in 1905 has made estimation of the diastolic pressure both easy and accurate for all conditions except some cases of aortic regurgitation.

The general use of the sphygmomanometer in this country was largely due to Clifford Allbutt, Brunton, and G. Oliver. The greater stability of the diastolic than of the systolic pressure, and therefore its greater diagnostic value, the importance of the pulse or differential pressure, and a correct estimation of the significance of abnormal pressures have gradually become established. Allbutt described the occurrence of high blood pressure without renal disease, and introduced for this the word "hyperpiesia." He also insisted that long-continued high blood pressure may cause, but is not due to, arterio-sclerosis.

The *sphygmograph*, first invented by K. Vierordt in 1855, and improved by Marey (1860), who did so much to popularize the method of graphic registration, Mahomed (1872), Burdon-Sanderson (1867), R. E. Dudgeon (1882), Pond, von Jacquet, and others, was much used; though the information it provided was somewhat limited, it was the first step in the application to cardiology of the graphic method of record, which has since thrown so much light on haemo-dynamics. By means of his clinical polygraph (1902) James Mackenzie, then of Burnley, correlated the arterial and venous pulses with those of the heart, and thus brought order out of the chaos of cardiac irregularities, distinguishing the unimportant, such as the extrasystoles of sinus arrhythmia, from those, such as *pulsus alternans*, pathognomonic of grave organic disease of the heart muscle.

The *Electro-cardiograph*.—The potential bearings of investigating the electric currents produced by the cardiac contractions, recognized in 1843 by Matteucci of Pisa and in 1856 by Kölliker and Müller, were examined with the capillary electrometer by Sanderson and Page (1878), Gaskell (1881), Starling and Bayliss (1890), and A. D. Waller. In 1903 Willem Einthoven of Leyden first described the string galvanometer, which was a great advance on the capillary and other galvanometers, and utilizing Waller's observation that curves of the cardiac contractions can be obtained from the limbs of animals without opening the chest, he, as Sir Thomas Lewis says, laid the foundation of human and experimental electro-cardiography, and by papers published in 1907 and 1908 led to modern electro-cardiography and the final analysis of the arrhythmias. The fundamental knowledge thus acquired by methods demanding delicate instruments it has fortunately been possible to correlate in many instances with simple indications which can be employed at the bedside. Wenckebach, Thomas Lewis, and their followers have thus exactly localized the site of disorders and morbid changes in different parts of the heart muscle, and particularly in the junctional system, such as lesions of the right or left branch of the auriculo-ventricular bundle, and the Purkinje arborizations, thus providing evidence of myocardial degeneration and impending cardiac failure earlier than can be detected by other means of examination.

Auricular flutter was described as long ago as 1887 by MacWilliam as the result of weak faradization of the mammalian auricles. Clinically, however, it was not recognized until much later by W. T. Ritchie and by Hertz and Goodhart. A healthy auricle responds to a single stimulus by a single contraction; but if the refractory period of a ring of muscle, as in the auricles, is shortened, the wave of contraction travels round continuously and is spoken of as a circus movement. This physiological observation of G. R. Mines was further elucidated as the condition in auricular flutter by Thomas Lewis and his co-workers. The

auricles contract extremely rapidly—200 to 300 or more times a minute, the ventricular rate being usually half that. The treatment consists in the production of a certain degree of heart-block by digitalis, or more radically by directly acting on the muscular tissue of the auricle by quinidine sulphate.

The development of knowledge about *auricular fibrillation* illustrates the close interdependence of clinical medicine and experimental work. Auricular fibrillation, long familiar to physiologists, was first recognized in man by Cushny and Edmunds in a case under their care in 1901 and published in 1906, the fibrillation being ascribed to vagal inhibition; but their diagnosis of fibrillation was received with doubt. In 1902 Mackenzie had recognized the complete irregularity of the pulse now known to be characteristic of auricular fibrillation, and on the ground of the absence of the auricular wave in the jugular tracings argued that the auricles had ceased to contract and were paralysed. In 1907 he abandoned the idea of paralysis, as in some cases, at any rate, the muscular fibres of the auricles were found by Keith to be hypertrophied, and argued that the auricular and ventricular contractions occurred simultaneously as the result of irritability of the auriculo-ventricular node, and called this "nodal rhythm." In 1910 Rothberger and Winterberg, and Lewis, by means of the electro-cardiograph, proved that the auricular condition was one of auricular fibrillation. The condition of nodal rhythm or simultaneous contractions of the auricles and ventricles due to the stimulus starting in the auriculo-ventricular instead of in the sino-auricular node occurs, but is uncommon.

Auricular flutter and auricular fibrillation are closely related, and in the same heart one may be transformed into the other; thus under quinidine fibrillation returns through impure and occasionally pure flutter to a normal rhythm (Lewis, Drury, Ilescu and Wedd). They are both due to circus movement in the auricles depending on shortening of the refractory period in the muscle fibres. But in auricular fibrillation the refractory period of the muscle is shorter, and as a result the path taken by the circus movement is shorter and more irregular than in flutter (Lewis, 1921). The muscle fibres of the auricle contract independently of each other, and much more rapidly than in flutter. The auricle fibrillating at the rate of 450 times a minute overwhelms the conducting capacity of the auriculo-ventricular bundle, so that some only of the impulses reach the ventricle, and these are so irregular that the characteristic pulse results.

Quinidine sulphate and digitalis relieve the subjects of auricular fibrillation in different ways; Mackenzie showed the value of digitalis in auricular fibrillation while recognizing that it did not restore the auricular contractions, and Cushny and others proved that it acted by inducing a certain amount of heart-block. An enormous amount of experimental work has been done upon the action of digitalis on the heart of cold- and warm-blooded animals, the effects on the two being different. In the mammalian heart contractility and inhibition are increased and then conduction is impaired. The observations of Lewis and his co-workers upon the action of certain drugs upon fibrillation of the auricles, in 1922, showed that quinidine sulphate lengthens the refractory period, and so, by closing the gap between the wave and the advance of the circulating wave, tends to abolish auricular fibrillation; but in addition it has the antagonistic effect of slowing conduction and so widening the gap between the successive waves. Successful treatment therefore depends on the first effect being predominant, and so enabling the normal pacemaker to regain control.

Paroxysmal tachycardia was described by Cotton (1867), called tachycardia by Gerhardt (1881), received its full title from Bouveret (1889), and was critically considered by Herringham (1897). The polygraph and the electro-cardiograph in Mackenzie's and Lewis's hands have thrown much light on this clinical syndrome, showing that it is not simply an acceleration of rate, but that the rhythm is abnormal as a result of the stimulus originating not in the sino-auricular node but elsewhere. The ectopic stimulus may start in the auricle, so that transient attacks may

be due to accelerated nodal rhythm (Lewis), to auricular flutter, to auricular fibrillation, or may even originate in the ventricle.

PHYSIOLOGICAL AND PATHOLOGICAL EXPERIMENT.

Essential in all branches of medicine, in none, except perhaps in neurology, has experimental physiology been more inseparably connected with progress than in the cardio-vascular system. Clinical observation alone, though in the hands of the greatest intellects, has laboured long and often ineffectually, but when aided and corrected by experimental control has rapidly brought about an advance in cardiological knowledge. This difference in the results given by these two ways—clinical observation and experiment—of obtaining new knowledge in medical science, which is so disappointing to the pure clinician that he may not unreasonably contest the statement, depends on the inherent potentialities of the two methods; in clinical observation the conditions cannot be arranged to meet the exact requirements as can be done in a laboratory. The clinical ward has been called "the physician's laboratory," but obviously this phrase does not confer the same opportunities for exact determination of questions as are provided by the experiments of the physiological laboratory. On the other hand, some care must be taken in transferring the results on animals to the more complex conditions in man. As disease, according to Claude Bernard's definition, is a physiological reaction in altered circumstances, it is obvious that the laws of these reactions can be much more surely established and the modifying circumstances varied and controlled by well-considered animal experiments. Further, animal experiments prepare the way for the application of somewhat similar methods to man—thus Stephen Hales's experiments on blood pressure find their clinical representatives in the modern sphygmomanometers, Marey's tambours, and Mackenzie's polygraph; the observations of electrical changes in muscular contraction eventually led up to the electro-cardiograph. Gaskell proved that the cardiac contractions arise in the muscular tissue independently of the nerves and ganglia, and that the auricles and ventricles have their own automatic rhythm, though normally obedient to the influence of the sinus. This was to some degree foreshadowed by Harvey's observation that if the ventricle of an eel or of various fish is cut into several pieces contractions continue in the several portions. It must not be forgotten that the recognition in 1672 of muscular irritability by Harvey's fellow Caian, Francis Glisson, which was revived by Albrecht von Haller, who in 1757 stated that the cardiac contractions originated in the muscle, was the first step in the recent elucidation by Gaskell in physiology and in pathology by Lewis and others of cardiac problems.

Although in his second letter to Riolan in 1649 Harvey showed that he was familiar with local disturbances in the character of the cutaneous circulation, it was not until long after the great conception of the circulation as a whole was established that its local characters received special consideration. The effects of embolism, studied by Virchow (1846-56), and independently in this country by W. Senhouse Kirkes (1852), led, from the resulting lesions, to the realization of end-arteries in the kidney and brain on the one hand, and on the other hand to the recognition of the peculiarities of the circulation in the spleen, lung, and liver, the two last having nutrient arteries (bronchial and hepatic) in addition to the vessels (pulmonary artery and portal vein) conveying blood to be modified in those viscera.

Nearly fifty years ago Roy pointed out that the *splenic circulation* differs from that of other organs in the important particular that the force which drives the blood through the organ is not the arterial blood pressure, but chiefly, if not exclusively, the rhythmic contraction of the muscular fibres in the splenic capsule and trabeculae. Barcroft's observations suggest that in the spleen there are alternative circulations, and that the blood of the large splenic artery may either (1) when not required elsewhere, as it is in the emergencies of exercise or haemorrhage, accumulate in the splenic pulp, there to undergo changes, or (2) rapidly traverse a by-pass, and incidentally, like

the bronchial arteries to the lungs and the hepatic artery to the liver, maintain the nutrition of the viscus. The blood stored in the spleen may contain as much as a quarter of the red cells, and, as shown by Barcroft's experiments with CO poisoning, be practically cut off from the general circulation, and so remain free from a poisoned state ruling elsewhere. Anoxaemia stimulates the smooth muscle fibres in the spleen and so drives out the resting blood; it thus, as Henry Gray (1854) pointed out, regulates the quantity and quality of the circulating blood. While serving as a reservoir the spleen also acts as a metabolic refinery for the red blood cells and a manufactory for the white cells. The resting blood in the spleen deposits any foreign matter, such as bacteria, protozoa, and cells of malignant growths, which may either be destroyed, the process being an immunological asset, or remain and by multiplying there account for the splenomegalies of chronic diseases, such as malaria, kala-azar, "splenic anaemia." As an important storehouse of reticulo-endothelial cells the spleen is concerned with the destruction of the red blood corpuscles, increasing their fragility by what Botazzi (1895) called its haemokatonistic function, and plays an important part in the first stage of the transformation of effete haemoglobin into bilirubin.

Wearn's even more recent evidence that the blood in the coronary arteries has alternative circulations, either through the capillaries into the coronary sinus, as usually considered, or directly into the Thebesian or other veins and so into the cardiac cavities, is of obvious importance in connexion with angina pectoris.

These data have a bearing on the question of the reserve power of the organs, which in the past has been regarded as mainly or entirely quantitative in character. Now it would appear that the reserve power may also depend on the utilization of potential alternative courses of the circulating blood, and that in pathological conditions compensatory processes may maintain the reserve of an organ, as has been mentioned in the case of the heart in coronary obstruction, and is perhaps also shown in the increased size of the hepatic artery in cirrhosis of the liver. The variations in the state of the capillaries—full or empty—in different areas of the body, which Thomas Young clearly anticipated in his forgotten Croonian Lecture before the Royal Society in 1810, have been recently brought out by the work of Krogh, Lewis, Dale, and others.

A more accurate knowledge of the unit blood supply of the kidney and liver is important so as to understand the mechanism and distribution of changes likely to result from blood-borne toxæmias or septicaemias and from chronic vascular disease. With the help of x rays and radio-opaque injection mass, normal and pathological kidneys have been investigated, with results encouraging as regards further knowledge about differences between arterio-sclerotic and glomerular nephritis (R. S. Graham).

The *coronary arteries* are provided with vaso-constrictor nerves from the vagus, and vaso-dilator from the sympathetic (Anrep). Adrenaline undoubtedly dilates the coronary arteries of animals usually employed in laboratory experiments; accordingly Büdingen, at the suggestion of Morawitz and Zahn, treated cases of angina pectoris with hypodermic injections of adrenaline, but the results were negative. Barbour (1912) found that the action of adrenaline causes vaso-constriction of rings of human coronary artery, thus differing from its effects in laboratory animals, and with Prince showed that in the monkey this difference also holds good, the coronary arteries of these two species being presumably supplied with constrictor fibres from the true sympathetic. Reference has already been made to Wearn's observations on the alternative courses in the coronary circulation.

Pulmonary Circulation.—The questions whether or not the branches of the pulmonary artery (1) are under the control of the vasomotor nerves, and (2) are acted upon by drugs in the same manner as the systemic vessels, are obviously of practical importance in connexion with the causation and treatment of haemoptysis and pulmonary oedema. The need of an authoritative lead from physiology on these points was very clearly expressed by James Andrew in his Harveian Oration of 1901. Vasomotor innervation of the pulmonary vessels was

denied until 1871, when C. E. Brown-Séquard, on experimental grounds, argued that lesions of the pons caused haemorrhages, and injuries of the medulla oblongata oedema of the bases of the lungs as a result of impulses transmitted through branches of the sympathetic leaving the cord in the upper dorsal region. Rose Bradford and Dean (1889, 1894) found that in the dog vasomotor nerve fibres derived from the upper dorsal nerve supply the pulmonary blood vessels, though the pulmonary vasomotor mechanism is poorly developed as compared with that regulating the systemic arteries. They also concluded that the pulmonary circulation is comparatively independent of the systemic, and that alterations in the blood pressure of the latter must be so considerable as to interfere with the action of the cardiac valves and produce regurgitation before affecting the pulmonary blood pressure. On the other hand, Brodie and Dixon, in 1904, denied the vasomotor control of the pulmonary circulation, and in 1928 Dixon and Hoyle confirmed this. In the meanwhile Fühner and Starling, using the heart-lung preparation, found a considerable degree of pulmonary vaso-constriction and a rise of pulmonary arterial pressure with adrenaline, and in 1905 François-Franck came to a similar decision. In a critical review of the extensive work on the subject Wiggers, in 1921, concluded that reflex vasomotor effects on the pulmonary circulation must be regarded as probable rather than proved.

The *intracranial circulation* is remarkable for the rigid cranial cavity and the water-bed of the cerebro-spinal fluid. Whether or not the nerves accompanying the cerebral vessels exert a vasomotor function has been repeatedly investigated, but with discordant results; Roy and Sherrington (1890), L. Hill (1896), and more recently Florey (1925) who found that the cerebral arteries and the cerebral ends of the capillaries react to mechanical, thermal, electrical, and chemical stimuli by contraction and dilatation, agree that there is not any evidence of nervous

control over the cerebral vessels. On the other hand, the existence of active functional control of the cerebral vessels by vasomotor nerves has been supported by Claude Bernard (1858), Nothnagel (1867), Wiggers (1915), Forbes and Wolff (1928), and others. The experimental observations are of much interest in connexion with the belief held by many clinicians that transient paralyses, such as occur without evidence of a gross lesion, may be due to spasm of the cerebral arteries analogous to that in Raynaud's disease. Osler (1911), in describing transient attacks of aphasia and paralysis in states of high blood pressure and arterio-sclerosis, accepted the view put forward by Peabody (1891), W. Russell (1909), and others that they were due to transient spasm. Florey has thrown out the suggestion that possibly in pathological conditions, such as arterio-sclerosis, an abnormal metabolic product which has not any effect on normal blood vessels may produce spasm of damaged arteries.

The influence of the conditions of the cerebral circulation on the general blood pressure has been much discussed. Starling and Anrep (1925) showed that when imperfectly supplied with blood the vasomotor centre brings about a compensatory rise of blood pressure, thus confirming Cushing's earlier demonstration in 1901 that the vasomotor centre exerts a regulating influence whereby anaemia of the medulla oblongata is prevented when the intracranial pressure is increased above that in the cerebral vessels. This was supported by Bordley and Baker's (1926) observation that in arterio-sclerosis a high blood pressure was definitely associated with sclerosis of the arterioles of the medulla; this, however, was contested by Keith, Wagener, and Kernohan, and Cutler's observations showed that gross vascular changes in the blood supply to the medulla were not responsible for blood pressure changes. Experimentally Florey, Marvin, and Drury (1928) found that lowering the blood pressure in the circle of Willis has not any influence upon the general blood pressure.

ON RECOVERY FROM SYMPTOMS OF INTRACRANIAL TUMOUR.

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THAT an intracranial tumour can exist without distinctive symptoms, and even without suggestive symptoms, is a proposition that has for its warrant the sure teaching of experience. Again, it is well recognized that even when symptoms of tumour are present there is often, in the course of one and the same case, a wide variation in the degree of their severity, and, indeed, a period of quiescence may be so prolonged and so pronounced as to cast suspicion on the accuracy of the diagnosis. The explanation of such experiences is that for the most part the symptoms associated with intracranial tumour are due less to the mass of the tumour than to circulatory disturbances (congestions, anaemias, oedemas, haemorrhages, softenings) liable to occur in its neighbourhood, and to interferences which the tumour may exercise on the circulation of the cerebro-spinal fluid. Grant the absence of these accidents, and cerebral events and symptoms, in spite of the presence of a tumour, may be slight, non-suggestive, and even non-existent.* With these positions admitted, may it not be possible that symptoms, and even pronounced symptoms, of intracranial tumour may disappear, not merely for a more or less brief period, but completely and permanently? For if in an individual case the intracranial accidents or complications, and the symptoms which result from these, may after a period of activity subside, the possibility that such quiescence may be permanent can at least be contemplated. Assume that the tumour ceases to grow or perhaps shrinks in size, and that in this or in some other fashion it no longer causes the intracranial disturbances on which the

clinical evidences of tumour mainly depend, and it is no violent proposal to suggest the possibility of a clinical record in which the symptoms of intracranial tumour disappear completely and the patient regains a level of good health. The clinical history, unfortunately, marches usually in the opposite direction, but there is nothing in the nature of things to render exceptions to this rule impossible, and the principal object of this communication is to suggest that such exceptions do actually occur. This suggestion has for its support case records (admittedly exceptional) marked in the earlier stage by symptoms regarded as conclusive of intracranial tumour, while later these symptoms disappear and the patient succeeds to good health. Such experiences, of course, call for an explanation, and the explanation here proposed is cessation of intracranial disturbances consequent on quiescence or shrinking of the tumour growth.

That recovery from symptoms of intracranial tumour; except for blindness due to optic atrophy, actually occurs there can be no doubt. Records of patients who in earlier years have suffered a severe illness characterized by headache, vomiting, and optic neuritis, and who, but for loss of sight, have later made a good recovery, are well established. It may be suggested that these cases are not cases of tumour, and it must be admitted that in exceptional instances the symptoms just quoted have existed and yet no tumour has been found on *post-mortem* examination;¹ such conditions as hydrocephalus,² serous meningitis,³ or sinus thrombosis⁴ may perhaps be advanced as alternatives to tumour. On the other hand, in many patients who are blind from optic atrophy after an illness distinguished by cerebral symptoms, competent clinical observers present at the time of the original illness have felt no doubt that the symptoms meant intracranial tumour; and now and again in the brain of a patient included in this group, and dying years after the primary illness, a tumour has been present to *post-mortem* demonstration. Thus it is certain that within the natural history of intracranial tumours room must be found for cases in which all active evidences of the presence of a tumour disappear, the former cerebral disturbances being

* A recent example is reported by Professor Sydney Smith, *British Medical Journal*, January 22nd, 1927.