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THE RESPONSE OF THE HEART IN HEALTH AND DISEASE.*

The George Alexander Gibson Memorial Lecture.

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THE first duty incumbent upon me is to express my most sincere and most grateful thanks for the high honour conferred on me by the Royal College of Physicians in inviting me to deliver the third of the series of lectures which have been founded in memory of George Alexander Gibson. To me it is a pious privilege to pay my homage to the memory of the great man who was my revered teacher and friend.

Nearly a decade has passed since the first of these Memorial Lectures, "An Appreciation of George Alexander Gibson, the Man and his Work," was delivered in this hall. No place could furnish a setting more fitting for these lectures than the hall of this College, of which Gibson was a most distinguished Fellow and which he served for twenty years, first as Secretary and subsequently as a Member of Council.

Throughout the history of Medical Science intellectual advance has often been intimately related to the influence of some world-wide agency, such as the fall of Constantinople, whereby the knowledge of the East became diffused throughout western Europe, or to the genius of a Harvey, a Jenner, a Pasteur, or a Lister. Gibson's life-work was accomplished at a time when progress in the science of Medicine was so rapid that it may truly be regarded as an era of discovery. The new science of bacteriology was being applied not merely to the elucidation, but also to the treatment, of disease; researches in physiology were disclosing the secrets concerning the beating

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of the heart; the careful study of disease was revealing to physicians the functions of the brain and the endocrine glands; the application of the discovery made by the genius of Röntgen was permitting a new insight into the human frame. Gibson's name will not be immortalised as that of a discoverer of a new world in medical science, but he was ever foremost in appreciating the significance of each new discovery and in applying it to the advancement of Medicine.

A successor of many famous men, from Cullen to Gairdner and Balfour, who had made Edinburgh pre-eminent as a School of Clinical Medicine, Gibson was an eminent physician, an eloquent teacher and a learned writer. The aspects of Medicine which he illumined by his pen extended over a wide field. His writings were enriched by his wide knowledge of the historic aspects of the subject and by felicitous quotations from the works of ancient and modern writers, from Hippocrates and Lucretius to Stevenson and Kipling.

It is in relation to the heart and its disorders that Gibson's name will indissolubly be associated. His monumental treatise, *The Diseases of the Heart and Aorta*, was published in 1898. His contributions to the study of blood-pressure were of the first importance.[1] His observations on the relation of the systolic blood-pressure to the pulse-rate in pneumonia form the basis of the law which bears his name.[2] His Morison Lectures on "The Nervous Affections of the Heart," delivered in this hall twenty years ago, and his masterly *Life of Sir William Tennant Gairdner* would alone entitle him to a permanent niche in the temple of fame.

The graphic method of studying the contractions of the heart which he had employed in association with Malet in 1879 and 1880, and his communication[3] on "The Action of the Auricles in Health and Disease," given to the Medico-Chirurgical Society of Edinburgh in 1882, heralded the dawn of the new era in the clinical study of the heart, which was fully developed in 1902 by the appearance of Mackenzie's epochal work, *The Study of the Pulse*. Then a new sphere of enquiry was at once laid bare; our knowledge of the structure and functions of the heart was found to be defective; the action of drugs on the heart had to be studied anew. In the search for truth there was much work to be done, and among those in all parts of the civilised world who entered on the quest none was more earnest than Gibson.

His life's-work brought him gratitude, distinction, and honours. It was the man himself, big-hearted, generous, and full of courage who was beloved. Those who knew him best admired and loved him most. I was privileged to be associated intimately with him in his work during the last ten years of his life. I cannot give you a better picture of the man than by a quotation from one of his own addresses.[4] "In all our doings," he said, "we must spend our lives in truth, faith, hope, love—clinging to that mood of mind, bent on winning to the very heart of everything; believing in real work as the means whereby, in its own good time, what is now hidden will be laid bare; trusting that the end of our quest will be the furtherance of knowledge, and the good of mankind." He was one who, to quote his own words, "entered into the lives of others in the fellowship of suffering, as well as into the brotherhood of happiness." He was one for whom "life is—to wake, not sleep, rise and not rest," to the very end inspiring others to look, as he did, up, not down.

In an address which Gibson delivered to the Medical Society of London in 1903, he showed that disturbance of function might result in disturbance of structure, and that both might be met by processes of adaptation and compensation. He illustrated his theme by original observations on acromegaly, on polycythæmia, and on diseases and disorders of the circulation of the blood. In none of the vital functions are the processes of adaptation and compensation more evident than in the circulation of the blood. The chief function of the heart is to maintain the arterial pressure, and thus cause the onward flow of blood through the vascular system. The circulation permits the continuous interchange of oxygen and nutrient materials, of carbon dioxide and other waste products of metabolism, between the blood and the tissues through which it flows. Were it not for the circulation of the blood which renders this interchange possible, the life of the cells, of the organs, and of the body would cease.

In the introductory chapter of *Diseases of the Heart and Aorta*, it is pointed out that a purely mechanical apparatus cannot maintain an efficient circulation because the metabolic processes are subject to great fluctuations, and because the interchange between the blood and the tissues is inconstant. The circulation, said Gibson, has constantly to be adapted to the wants of the tissues. The same fundamental fact has

recently been emphasised by Haldane,[6] who says: "It is not the heart nor the bulbar centres which govern the circulation rate, but the tissues as a whole . . . the heart and vaso-motor system are only the executive agents which carry out the bidding of the tissues. . . . The problem of the regulation of the circulation under normal conditions seems in the main to resolve itself into that of the regulation by the tissues of the amount of blood supplied to the heart." During physical exercise, for example, the heart is called upon to perform more work, because the skeletal muscles, needing more oxygen and having to get rid of more carbon dioxide and other waste products of metabolism, need a more ample blood supply than during a period of rest. Similarly, the heart has more work to accomplish when the metabolic rate is increased, as in the febrile state or in hyperthyroidism. Again, an increase of work on the part of the heart may arise because one or more of the valves of the heart are diseased, notable examples being incompetence of the aortic or of the mitral valve. Thus in health and disease the demands made upon the heart are constantly subject to change. The first theme that I shall submit for consideration is the nature of the heart's response, and the modifications which it undergoes in accordance with physiological requirements. Thereafter we shall consider cardiac responses which are essentially abnormal, and consider how they may be modified by therapeutic means.

Firstly, let us consider briefly the **Anatomical Structures** which are intimately concerned with the initiation of the stimuli, to each of which the heart responds by contracting, and with the transmission of those stimuli from one part of the heart to another. In the mammalian heart the sinus node or sino-auricular node, representing the sinus venosus of the primitive heart, lies beneath the epicardium at the junction of the superior vena cava and the right auricle. This node is pear-shaped, and is composed of slender muscle fibres, nerve cells, and nerve fibres. In this node the stimulus for each contraction of the heart arises. The stimuli are formed rhythmically at a rate which, though subject to great variation, is usually about 70 per minute in man. From the sinus node each stimulus is transmitted to the muscle fibres in the walls of the auricles, and is also transmitted, by means of a special neuro-muscular conducting system, to the ventricles. This system consists of the auriculo-ventricular node, the bundle, its branches and their

terminal filaments, the Purkinje fibres. The auriculo-ventricular node and bundle are situated in the septum of the heart, the former lying on the right side of the interauricular septum in front of the orifice of the coronary sinus, and above the line of insertion of the medial cusp of the tricuspid valve. The bundle, passing forwards and downwards from the auriculo-ventricular node, lies below and behind the membranous portion of the interventricular septum, at the lowest part of which it divides. The right branch passing downwards on the right side of the interventricular septum is slender and long, the left branch spreads out fanwise on the left side of the septum, and both ultimately branch out to form a fine arborisation of terminal filaments in the subendocardial layers of the ventricular walls. In contrast to the ventricular muscle fibres, those of the auriculo-ventricular node and bundle are slender and their striation is less pronounced. This system—the auriculo-ventricular node, bundle, branches, and terminal filaments—affords a path by means of which each stimulus emitted from the sinus node reaches every part of the two ventricles almost simultaneously.

The property of stimulus production is probably inherent in every part of the heart, but in the normal state the capacity for producing stimuli for contraction is more highly developed in the sinus node than in any other part. It has been estimated that the rate of stimulus production in the auriculo-ventricular node is 67 per cent. that of the sinus node. The rhythm of the heart is therefore dominated by the sinus node; the pace of the heart is set by that node; its activity however, is strictly subordinate to the balance of activity of the sympathetic and parasympathetic systems and to the metabolic activities of the tissues. The heart usually maintains its normal sinus rhythm tenaciously in all the varying conditions of life, awake and asleep, working and resting, in health and usually in disease.

In all other parts of the normal heart the property of stimulus production is meanwhile dormant. The auriculo-ventricular node, the bundle, and its branches are mainly concerned with the conduction of impulses—in other words, their chief attribute is conductivity. It has been estimated by Lewis that the rate of conduction is 4000 mm. per second in Purkinje fibres, 800 mm. per second in auricle, 400 in ventricle, and 200 in the auriculo-ventricular node. It is

interesting to observe that the property of conductivity is most highly developed in those muscle fibres of the heart in which the property of stimulus production is known to be low, and that the property of stimulus production is high in those cardiac muscle fibres which are least concerned with the conduction of stimuli.

For many years Gibson was interested in the electromotive changes which accompany the heart's contractions. His earliest investigations on this subject were made by means of Lippmann's capillary electrometer. I recall the enthusiasm with which he studied a remarkable instance of heart-block by means of that instrument, and the electroscopic demonstration of dissociated action of the auricles and ventricles which he gave to the Pathological Club in 1905.[7] When Einthoven introduced the string galvanometer as an electrocardiograph, Gibson was one of the first to grasp its significance and importance in relation to Clinical Medicine. When an anonymous donor presented him with a gift of £3000 for the purpose of founding a Research Laboratory in the Royal Infirmary, Gibson was enabled to instal an electrocardiograph in close proximity to the medical wards. The Royal Infirmary of Edinburgh was, so far as I am aware, the first hospital in this country to be thus equipped with the means whereby our knowledge of the heart in health and disease has been, and is still being, greatly extended.

The electrocardiograph, consisting essentially of a fine moving conductor or fibre, suspended between the poles of a powerful electromagnet, yields very accurate and delicate photographic records of the changes of electric potential or action currents which accompany each beat of the heart. The currents are led off to the electrocardiograph from the moistened skin surface of the limbs or chest. Normal electrocardiograms, although varying in detail according to the site from which the action currents are led off, present certain constant features. With each beat of the heart the fibre of the instrument is subjected to a number of upward and downward deflexions, which are indicated by the letters *P*, *Q*, *R*, *S*, and *T*.

P, the presystolic deflexion, signifies a co-ordinate contraction of the auricular muscle fibres. It is usually a simple upward deflexion which begins 0·01 second after stimulus formation starts in the sinus node. The summit of *P* coincides with the beginning of auricular systole. The ventricular

complex, representing ventricular activity, consists of an initial group of deflexions, *Q*, *R*, and *S*, or *R* and *S*, for *Q* is inconstant, and a terminal deflexion *T*. During the initial period of the ventricular complex, the ventricular muscle is being activated by a stimulus passing to it along the neuro-muscular system. The muscle fibres of the two ventricles begin to be in active contraction while the deflexion *R* is falling, for it is then that the first cardiac sound begins; the contraction ends synchronously with the end of *T*. Time will not permit of my describing in detail the variations in form of normal electrocardiograms. It will suffice to mention that the electrocardiogram of a healthy person, provided it is recorded in a constant manner, remains remarkably constant.

The means whereby the heart's activity is controlled, regulated, and adapted to the varying demands made on the organ have been the object of manifold enquiry. Although the heart is not under the control of the will, it is under the control of the autonomic nervous system, nervous influences reaching the heart from the sympathetic and from the para-sympathetic or vagal portions of the autonomic nervous system. No more masterly presentation of the modifications of the cardiac response by nervous influences is to be found in our own or any other language than in the Morison Lectures delivered in 1902 and 1903. The researches of the last twenty years have filled some gaps in our knowledge.

The effects of vagal stimulation, which are essentially inhibitory, are exerted mainly through the sinus node, thus causing slowing of the rate of the whole heart. A prolonged diastolic arrest of the whole heart may be induced by stimulation of the vagus, either reflexly or by direct compression of the nerve. Infrequent cardiac action, or bradycardia, as a result of vagal stimulation is not very rare in the human heart; whilst vagal stimulation of greater intensity and duration may cause the whole heart to stand still for so long a period that fainting, or even fatal syncope, may ensue. Vagal stimulation also lessens the contractility of the auricular muscle, depresses its excitability and shortens its refractory period. The vagi have also a powerful inhibitory influence on the auriculo-ventricular node and bundle, whereby transient auriculo-ventricular block may be produced. The vagi have probably no direct action on the ventricles. The ventricular effects of vagal stimulation and vagal paralysis are probably

entirely secondary to the effects exerted on the nodes, the auricles, and the bundle.

In contrast to the vagus, the sympathetic increases the frequency and force of the cardiac contractions, the effects being exerted on the ventricles and also on the auricles. The actions of the vagus and sympathetic on the heart are therefore in large part antagonistic. Overaction of the sympathetic in relation to the heart is well exemplified in the cardiac action, rapid, forcible, and rhythmic, so often observed in those who are under the influence of emotional stress. One episode in *The Master of Ballantrae* vividly depicts the palpitation of intense anger and hatred; that of a child's terror pervades the lines, "Now my little heart goes a-beating like a drum, with the breath of the Bogie in my hair."

Electrocardiography has taught us much, but it does not give us any information regarding the amount of work performed by the heart either in health or in disease. The development of our knowledge in this matter has been extended greatly of recent years by biochemical research. It is generally accepted that the amount of blood expelled at each contraction of a healthy man's heart, namely the output per beat, is from 100 to 120 c.c. While he is resting and the cardiac rate per minute is about 70, the heart's output per minute, namely its minute volume, therefore amounts to 7 or 8 litres. The oxygen intake meanwhile is about 320 or 350 c.c. per minute. During physical exercise, however, the oxygen intake has to be raised greatly in order to meet, as far as is possible, the demands of the tissues. Hill and Lupton[8] calculate that while a man is running his oxygen intake may be raised to 3000 or 4000 c.c. per minute. The faster he runs the greater becomes his oxygen requirement and, up to a point, the greater becomes his oxygen intake. This enormous increase of oxygen intake denotes an enormous increase of work on the part of the heart, and this organ has, indeed, a big reserve of power upon which to draw when the need arises.

It has long been thought that the increase of work accomplished by the heart during physical effort was attained partly by increased frequency of rate, and partly by an increased strength of contraction. That there is an increase of rate is a well-established fact. The change even from the recumbent to the erect posture raises the pulse-rate. The rate increases notably under the influence of physical exercise, as is shown

in the lower curve of Fig. 1, which represents the ventricular rate in a healthy young man before and after exercise.

Acceleration of the heart during physical effort is a salutary, beneficial process. In its production a number of factors are concerned, the most notable being an increased venous inflow from the actively contracting skeletal muscles, a lessened vagal

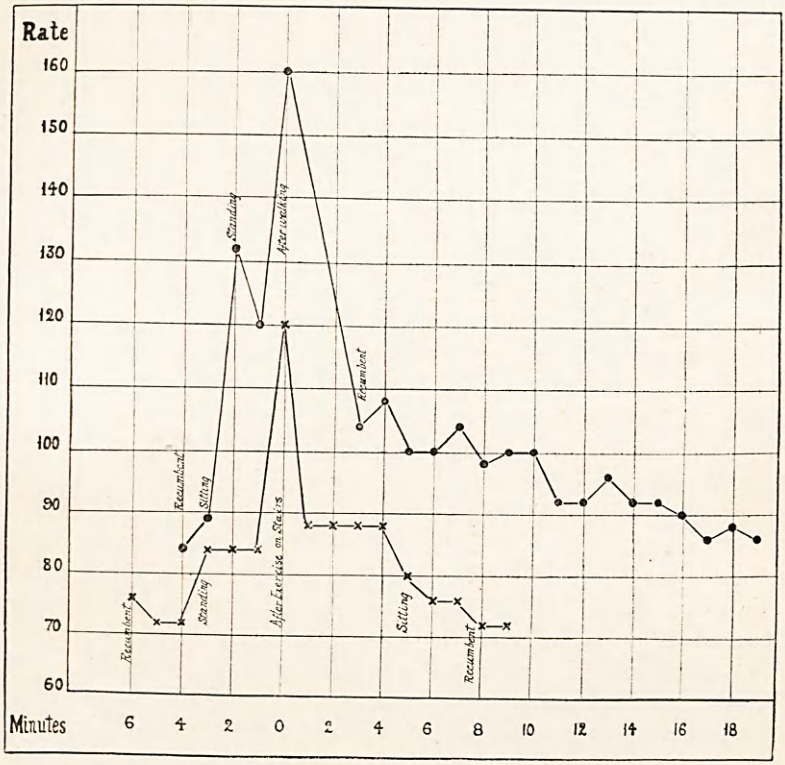

FIG. 1.—The cardiac rate before and after physical exertion. The upper curve shows the acceleration of cardiac rate produced by change of posture and exercise in a case of valvular disease of the heart. The lower curve shows the corresponding changes of cardiac rate in a healthy young man.

tone, an increase of sympathetic tone, an increased adrenaline content of the blood, and probably an increased hydrogen ion concentration of the blood. In respect of the last named factor we know that in health the reaction of the blood—in other words, its hydrogen ion concentration—is kept remarkably constant by means of three regulating mechanisms, those of the lungs, the kidneys, and the liver. Any tendency to acidosis on the one

hand, or to alkalosis on the other, is thus obviated or corrected. A temporary increase of hydrogen ion concentration whether due to excess of carbonic or other acid in the blood, raises the respiratory rate, and thus any excess of carbonic acid is washed out of the blood and the alveolar carbon dioxide pressure is kept approximately constant. Analogy between the respiratory rate and the cardiac rate suggests that an increased hydrogen ion concentration of the blood may be one of the factors increasing the rate of the heart during physical exercise.

The actual degree of cardiac acceleration in response to the same amount of physical effort, and the subsequent decline of rate vary materially in different individuals. By contrast with the lower record of Fig. 1, the upper record shows the ventricular rate before and after exercise in the case of a man who was affected with valvular disease of the heart. The curve starts from a higher level, attains a greater height and falls more slowly. Apart from actual disease of the heart, lungs, or blood, the degree of training and the man's ability to co-ordinate his muscles for the particular effort are important factors in determining the cardiac rate that will be attained. A man may be capable of performing, with ease and relatively little cardiac acceleration, physical effort to which he is habituated, yet he may fail to accomplish a lighter but unaccustomed task.

The problem regarding an increase in force of the cardiac contractions during physical exercise is more obscure. The observations of Starling and his co-workers showed that in heart-lung preparations the output of the heart was proportionate to the venous inflow. An increased venous inflow caused a greater cardiac output; the amount of blood discharged from the heart at each contraction was increased, the rate of cardiac contraction remaining unaltered. The conclusion was therefore drawn that, a greater venous inflow having caused a physiological dilatation of the heart, the muscle fibres of the heart were stretched to their optimal length, and consequently their contractile force was rendered maximal. Although these experiments undoubtedly show that the output per beat of the heart is not necessarily constant, but that it may vary in accordance with the venous inflow, it is doubtful whether those conclusions based on artificial experiments apply to the human heart.

The observations of Yandell Henderson in 1906 indicated that in the dog the volume of blood discharged per beat was

approximately the same whether the heart were beating faster or slower. Further light has been shed on this problem by the biochemical researches of Haldane which show that although the output of the human heart may rise during exercise from 7 or 8 to 30 or 40 litres per minute, the output per beat nevertheless remains practically constant, the increased general circulation rate being attained by an increased rate of the heart's contraction. Haldane's observations are being confirmed and amplified by other investigators, notably by Meakins and Davies,[9] who found that, while the circulation rate in health rose from 7·75 litres per minute at rest to 17·25 litres per minute during exercise, the output per beat remained constant.

Whether these observations are universally applicable is a problem not yet fully investigated, but they raise the question as to the significance of the expression "the reserve power of the heart." Is the force of each contraction variable, now weaker and now stronger, or is it always maximal? If an organic valvular lesion is adequately compensated by hypertrophy, or hypertrophy and dilatation, the output per beat, even although constant, and the minute volume may be sufficient, without any undue cardiac acceleration, for all the needs of the individual. The oxygen saturation of the arterial blood is kept at its normal level, the exercise tolerance is well maintained, and the present capacity for physical exercise is unimpaired. But organic valvular disease, even in its least harmful form, implies a damaged heart, and it is an error to consider the man whose heart is thus damaged as being physically equal to the Class A man in respect of military service, or to a first class life in respect of life assurance. If the valvular or myocardial disease is more serious, the output per beat of the heart is lessened. For example, in mitral stenosis Meakins and his collaborators[10] have found the output per beat to be as low as 32 c.c., with a cardiac rate of 90 and a minute volume of less than 3 litres. Under these circumstances the call of the tissues on the heart during exercise has to be met by a greater acceleration of cardiac rate than if the output per beat were normal. Despite a very marked acceleration, to 150 or 160 per minute, the minute volume may still remain below that which is requisite, oxygen desaturation of the blood ensues, the respiratory centre is exposed to anoxæmia, and the patient suffers from dyspnœa on exertion. If, the tone of the ventricular muscle being depressed,

the output per beat falls still lower, increase of rate fails to compensate; even while the patient is resting he is breathless, because his minute volume is inadequate; the oxygen desaturation of the blood is pronounced, and cyanosis, venous congestion, and œdema develop.

A man, aged 56, who was recently under my care, furnishes an illustration. By occupation he was a pavior, and on occasions it had fallen to him to set in the causeway of our High Street the stones which mark the site of the Heart of Midlothian. Professor Meakins and Dr Whitridge Davies kindly undertook the estimation of his cardiac output in January, and again three weeks later when the patient had become more dropsical and more breathless. In the interval the pulse-rate had risen from 76 to 94 per minute, the output per beat had fallen from 57·3 c.c. to 30 c.c., and the minute volume had fallen from 4·36 to 2·96 litres.

Biochemical research on the alkaline reserve, the gaseous content of the blood and the respiratory exchange, is affording us a new and clearer insight into the abnormal processes that may arise as a result of cardiac failure. As some of these processes are compensatory, it is fitting to mention Gibson's observations[11] on the compensatory polycythæmia of cyanosis, and the effects of oxygen inhalation thereon, and his researches on microbic cyanosis.[12]

To those modifications of the heart's action which are directly associated with alterations of metabolism, I shall refer very briefly. Acceleration is, as might be anticipated, more frequent than retardation. An increased metabolic rate, as in acute infective diseases and in hyperthyroidism, is attended by a pulse-rate of increased frequency, the heart meanwhile maintaining its sinus rhythm. Any exception to this general statement is rare, and indicates the operation of some unusual factor, for example, powerful vagal stimulation with resultant infrequency of the pulse in the early stages of enteric fever, or a particular liability to auricular fibrillation in diphtheria and exophthalmic goitre. Conversely, a low metabolic rate is accompanied by relative infrequency of the cardiac rate. A comparison of the rate of the pulse in exophthalmic goitre, with high metabolic rate, and in myxœdema, with low metabolic rate, furnishes a very beautiful illustration of the adaptation of the heart's response to the metabolic needs of the tissues.

Turning to cardiac responses which are wholly abnormal, I do not propose to discuss the morbid anatomical conditions of the heart which may arise in the course of disease, notably acute rheumatism and syphilis. The relation of the former to disease of the heart has long been recognised[13]; the significance of the latter is daily being more fully appreciated. The curves in Fig. 2 show the age incidence of aortic incompetence in a series of 189 persons of the male sex. The curve showing all the cases of the series is a complex

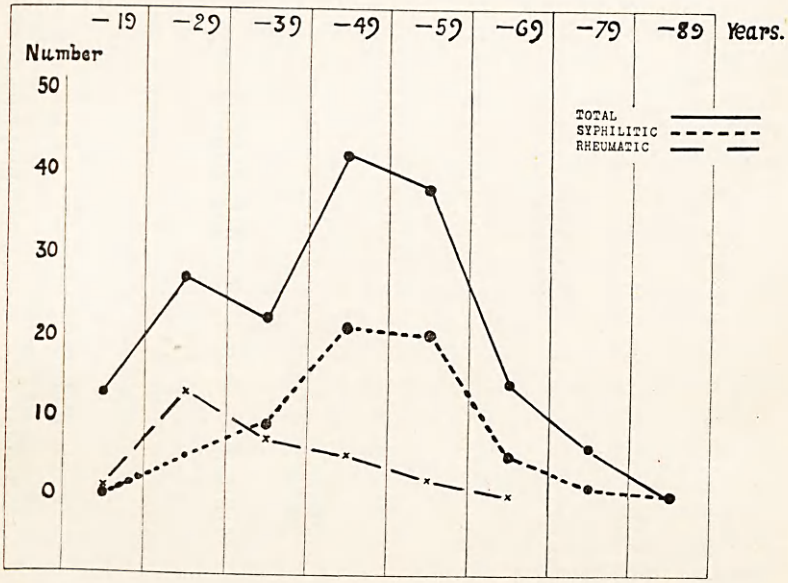

FIG. 2.—Curves showing the age incidence in 189 male cases of aortic incompetence.

curve, indicating the operation of more than one etiological factor; a second curve shows the age incidence of the cases which were due to acute rheumatism; a third shows that of the cases due to syphilis. The relative ages at which men begin to suffer from aortic incompetence of rheumatic and of syphilitic origin is clearly shown in this illustration.

Defective Conductivity.—A defect in the transmission of stimuli from the sinus node may occur in various parts of the heart. The defect is often due to organic lesions, namely to inflammation, degeneration, calcification, and occasionally tumours. The defect, however, may be functional. Thus, it may be caused by vagal stimulation, by drugs such as digitalis

and strophanthus, which are known to stimulate the vagus, by asphyxia, or by fatigue of some part of the conducting system. The various forms of defective conductivity are differentiated from one another according to the site and degree of the defect. If the defect is between the sinus node and the auricles, an occasional stimulus fails to be transmitted, or is, in other words, blocked. This condition is known as sino-auricular block. Each time the block recurs the whole heart misses a beat. Owing to the free communication between the sinus node and the auricles it is difficult to produce sino-auricular block experimentally, and it is a disorder seldom observed clinically. In nearly all clinical instances, sino-auricular block is probably due to functional causes, of which the chief is vagal stimulation. It is significant that the disorder is most apt to arise when the heart is fully digitalised, and that the block can be abolished by means of atropine.

By his communications[14] to Medical Societies in Edinburgh, London, Toronto, and elsewhere, Gibson did much to define and to extend our knowledge of defective conductivity in the auriculo-ventricular node and bundle. A slight defect of conductivity in this region is revealed merely by an undue lengthening of each auriculo-ventricular interval. In electro-cardiograms this interval is represented by that between the auricular deflexion, *P*, and the initial ventricular deflexion *R*. In health the *P-R* interval does not exceed 0·15 second. When the conductivity of the bundle is depressed the duration of the *P-R* interval exceeds 0·15 second and often amounts to 0·20 or 0·30 second.

When the defect is of greater degree, the transmission of an occasional stimulus to the ventricles fails, or every fourth, third, or second stimulus may be blocked, the condition being then that of partial auriculo-ventricular block. If no stimulus be transmitted to the ventricles, as occurs when the bundle is severed by disease, there is complete auriculo-ventricular block. What are the results which follow severance of the bundle? The rate and rhythm of the auricular contractions remain virtually unaffected; the ventricular contractions, though still rhythmic, are now very infrequent, and there is complete dissociation of the rhythm of the ventricles from that of the auricles; the ventricular rate is usually about 32 per minute and remains remarkably constant from hour to hour and from day to day. The duration of ventricular systole usually

becomes lengthened, lasting about 0·49 second instead of the normal 0·32 second. Ventricular diastole becomes much more prolonged, its duration usually amounts to approximately 1·3 or 1·4 second. One direct result of the lengthening of ventricular diastole is a pronounced difference between the systolic and diastolic blood pressures, a phenomenon first observed by Gibson.[15] Another direct consequence of auricular-ventricular dissociation is that the ventricles can no longer be influenced by any of the factors which in health, playing upon the sinus node, lead to variations in the general circulation rate according to the needs of the tissues for oxygen. The ventricular rate remaining constant, the supply of blood and therefore of oxygen to the tissues is the same whether they are at rest or in activity.

A remarkable series of events develops when a high grade of partial block becomes complete. The ventricles then stand still until the latent, dormant, rhythm of the bundle below the point of its severance is developed, or until the block is relieved and further stimuli from the sinus node reach the ventricles. The events collectively constitute the syndrome which bears the names of Adams and Stokes. The syndrome had, however, been described in 1762 by Morgagni, and in 1793 by a President of our College, Andrew Duncan, on the basis of a communication made to him by Nathaniel Spens, a Fellow of the College and a member of the Royal Bodyguard for Scotland. The ventricular stand-still results in cerebral anæmia. The cells of the central nervous system cannot long tolerate deprivation of oxygen, and the severity of the symptoms depends on the length of ventricular stand-still. Unconsciousness and convulsions usually ensue if the ventricular stand-still persists for ten or more seconds. The syndrome was graphically described by Sir William Gairdner who, in the "evening of life," was himself a sufferer.

If the stem of the bundle be intact and the block be in one or other of its main branches, stimuli of sinus origin can still reach both ventricles, but only through the branch which remains intact. The sole essential abnormality of response is that which is revealed in electrocardiograms. Each ventricular complex is diphasic, consisting of an initial deflexion in one direction and persisting for at least one-third of the whole period of the complex, and of a terminal deflexion in the reverse direction. If the initial deflexion is upward by deriva-

tion I and downward by derivation III, the block is in the right branch. If the initial and terminal deflexions are reversed, the former being downward by derivation I and upward by derivation III, the block is in the left branch. In the right branch of the bundle block is not uncommon, but it is rare in the left branch. The reason for this difference is not far to seek. The right branch is a long slender strand, which may be severed at any point in its course by a small focal lesion. A lesion which is to sever the left branch must do so before it has spread out, or if the lesion is at a lower level of the ventricular septum it must be a relatively extensive one.

Extrasystoles.—A cardiac response of wholly abnormal character is seen in an extrasystole. Extrasystoles originating in supraventricular portions of the heart are rare; the vast majority of all extrasystoles originate in the ventricles. A ventricular extrasystole yields an electrographic deflexion which differs in every essential respect from that of the normal beats which precede and follow it. The extrasystolic deflexion is diphasic, the summit being directed first upwards and then downwards, or alternatively first downwards and then upwards, according to the derivation employed in obtaining the record and to the site in the ventricles at which the extrasystole originated. The wholly abnormal form of the deflexion indicates that the stimulus did not reach the ventricles by the normal path but originated in the ventricular wall, probably in the terminal filaments of the bundle, and spread through the ventricular fibres in abnormal sequence.

A ventricular extrasystole interrupts the normal rhythm momentarily, is usually followed by a compensatory pause and usually recurs at inconstant intervals. An extrasystole may recur at regular intervals, for example, after each physiological beat, or after every second, third, or fourth physiological beat.

A form of abnormal response still less frequent is that in which there is a series of ventricular extrasystoles, two, three, four, or more, all of identical nature, occurring in rapid rhythmic succession, and only the last of the series being followed by a compensatory pause before the normal rhythm is regained. A long series of ventricular extrasystoles, starting abruptly, raising the ventricular rate to 150, 200, or 250 per minute, and ending abruptly, amply justifies the title of paroxysmal ventricular tachycardia. For one characteristic electrocardiogram of this disorder, I am indebted to Professor J. C. Meakins,

for another my thanks are due to Dr G. D. Mathewson. In paroxysmal ventricular tachycardia the rate of the auricles is usually the same as that of the ventricles, each stimulus being transmitted backward to the auricles while the property of stimulus production remains dormant in the sinus node. If the ventricular rate rises above 200 per minute, however, the auricular rate may be only one-half that of the ventricles because of inability on the part of the auriculo-ventricular node or bundle to transmit backward more than every alternate stimulus. The ventricular variety is the rarest form of paroxysmal tachycardia.

Nodal Rhythm.—Another form of abnormal cardiac response is that in which the heart is responding to a stimulus from the auriculo-ventricular node. A single response to a stimulus from this site constitutes a nodal extrasystole. This is represented electrographically by a premature contraction with an inverted auricular deflexion, a short *P-R* interval and a ventricular complex of normal form. When each cardiac contraction is initiated at the auriculo-ventricular node, the condition is termed nodal rhythm or auriculo-ventricular nodal rhythm. Paroxysmal tachycardia is sometimes nodal in nature. Our earliest knowledge of paroxysmal nodal tachycardia dates from the publication of Rihl's paper in 1907, but our conception of the disorder clinically and of the associated structural changes in the auriculo-ventricular node is mainly founded on the investigations of Cowan in the Royal Infirmary of Glasgow. He has demonstrated that the disorder is most likely to arise during the terminal stage of acute endocarditis when an acute inflammatory process is spreading inwards from the base of the mitral valve, and is implicating and irritating the auriculo-ventricular node.

The speed of the heart in a paroxysm of nodal tachycardia is usually about 160 to 180. It may rise to 220 or 230, and the maximal recorded rate is about 300. Whenever a stimulus arising in the auriculo-ventricular node is effective, the normal auricle-ventricle sequence of contraction is replaced by simultaneous contraction of all four cardiac chambers. In paroxysmal nodal tachycardia this synchronous contraction is occurring with each beat of the heart and is causing certain notable effects. The auricular contraction cannot drive the blood onwards into the ventricles; the intraventricular tension is not raised as it should be during the last phase of ventricular diastole; blood

during each auricular systole regurgitates from the auricles into the great veins.

Turning to the auricles, we find that their response often becomes abnormal. Apart from auricular extrasystoles, which are less frequent than ventricular extrasystoles, there are two abnormal forms of auricular response which are of much interest, namely, flutter and fibrillation.

Flutter.—In the Jubilee year of Queen Victoria's reign the term "flutter" was used by Professor MacWilliam to designate the very rapid rhythm of the auricles produced by mild faradic stimulation. Eighteen years later, on 23rd June 1905, it was my good fortune to obtain graphic records of human auricles beating rhythmically 274 times a minute. Dr Gibson's interest in this cardiac disorder was keenly aroused, and the following year (1906) he published records of a fatal case that had been under his care in the Royal Infirmary.[16] Three years later Professor Jolly and I, working in Sir Edward Sharpey Schafer's department, obtained electrocardiographic records of the fluttering auricles in my original case, and thus dissipated any doubt regarding the verity of flutter as a distinct disorder. Fluttering auricles are contracting rhythmically at a very frequent rate, one usually between 250 and 300 per minute. The ventricles may beat at the same pace. More commonly each alternate stimulus fails to pass through the auriculo-ventricular node and the ventricular rate is therefore one-half that of the auricles.

In flutter a mild degree of vagal stimulation leaves the auricles unaffected but blocks the transmission of stimuli to the ventricles, the rate of which is therefore retarded. Vagal stimulation of greater intensity does not retard or arrest flutter, but changes it into fibrillation.

In contrast to the tachycardia which accompanies increase of metabolic activity, a high speed of the ventricles in flutter and other forms of paroxysmal tachycardia does not represent a salutary process, but is harmful. In a case of paroxysmal tachycardia investigated by Barcroft and others,[17] the output per beat fell from 75 c.c. to 12·9 c.c., and the minute volume fell from 6 to 2·5 litres. In two of my cases of flutter, Professor Meakins very kindly estimated the cardiac output. In one, with a ventricular rate of 150, the output per beat was only 23 c.c., and the minute volume was only 3·46 litres. In the second case, the ventricular rate was 84, the output per beat 63 c.c., and the minute volume 5·26 litres. A comparison

of these figures indicates that in flutter the ventricles work more efficiently if their rate is not accelerated.

In explanation of flutter two hypotheses suggest themselves. There may be an irritative lesion in the sinus node or in some other part of the auricular wall, at which stimuli are generated approximately four times as frequently as in the healthy sinus node. As all the available evidence indicates that the sinus node is not at fault, it was thought that the very rapid auricular contractions were initiated at an irritable focus elsewhere in the auricular wall. A second hypothesis, which has much to commend it, is based on the phenomenon of circus movement, as recorded by Mines[18] a year before the outbreak of the war. In health the heart muscle responds to a single stimulus by a single contraction; a stimulus which is being transmitted around a ring of cardiac muscle does not circulate repeatedly around the ring because of the refractory phase of the muscle. If the refractory phase is very much shortened, the stimulus may circulate repeatedly around the ring. This is, in brief, the conception of circus movement. To the original researches of Lewis[19] we owe the application of this theory to flutter.

Auricular Fibrillation.—In each of the abnormalities of cardiac response which we have considered hitherto, all the auricular muscle fibres contract in a co-ordinate manner. When the contraction of individual muscle bundles throughout the auricles becomes inco-ordinate, these chambers, dilated and with quivering walls, are in fibrillation. When this event occurs, the ventricular muscle still contracts in a co-ordinate manner, but the ventricular rhythm becomes wholly irregular, as was first suggested by Cushny and Edmunds in 1906.

Auricular fibrillation is a common disorder. One-third of the cases occur in patients who are affected with chronic mitral endocarditis of rheumatic origin. In the majority of male cases, auricular fibrillation is the result of chronic degenerative changes in the coronary arteries and in the myocardium. Thus the maximal age incidence is later in the male than in the female sex (Fig. 3). The heart often becomes characteristically globular in form, with prominence of the right auricle and the conus arteriosus radiographically. Electrographically the disorder is revealed by the irregular spacing of the ventricular complexes, by the absence of the normal auricular deflexion, *P*, and by the small, rapid, irregular, auricular deflexions throughout. These are often most clearly represented when the action

currents are led off from the patient's left hand and left foot, or directly from the chest.

Auricular fibrillation may be paroxysmal (Fig. 4) and may then be due to temporary nervous influences, or to toxæmia, either endogenous or exogenous. Remediable auricular fibrillation of thyrotoxic origin furnishes an example. More often the fibrillation is persistent, lasting until the end. It is always a serious and not infrequently a grave disorder, because not only is the ventricular rate usually much accelerated and the

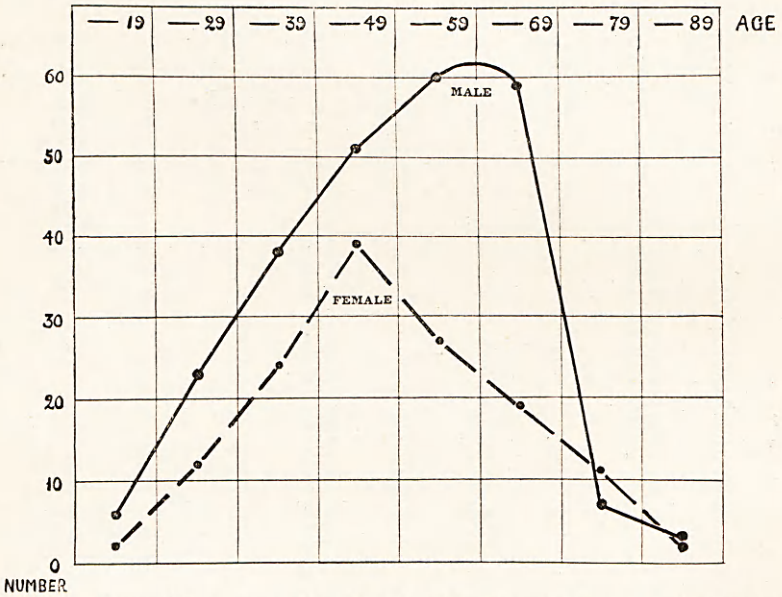

FIG. 3.—Curves showing age and sex incidence in 383 cases of auricular fibrillation. In females the maximal age incidence between 40 and 49 suggests the close association of auricular fibrillation with rheumatic heart disease. The later maximal age incidence in males is probably due to myocardial degeneration.

ventricular output per beat very inconstant, but the ventricular muscle is often implicated by subacute or chronic inflammatory and degenerative processes. Thus, auricular fibrillation is often accompanied by all the classic signs of cardiac failure.

Microscopic examination of the walls of auricles which had been in fibrillation may reveal similar subacute or chronic inflammatory and degenerative processes, but these are not constant. What is the functional defect which results in fibrillation? Gaskell's researches pointed to ventricular fibrillation being due to defective conduction of stimuli through

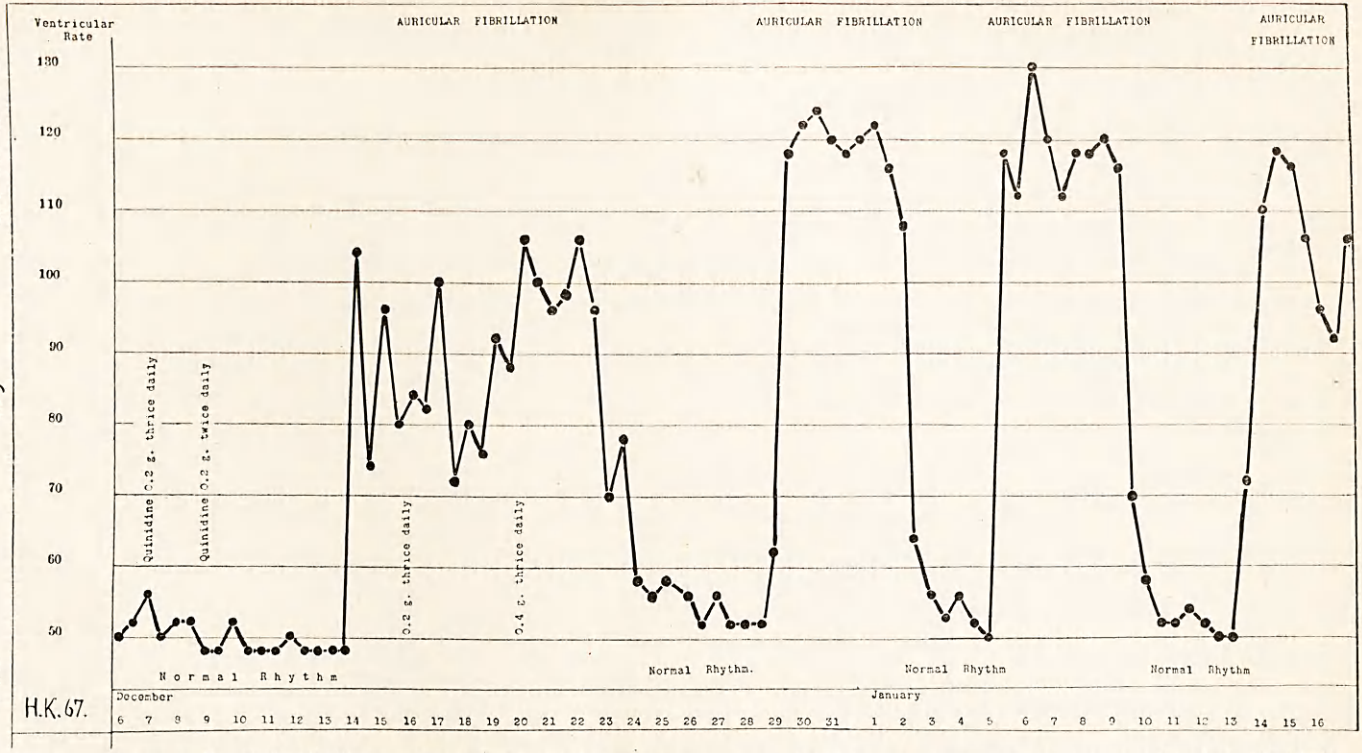

FIG. 4.—Paroxysmal auricular fibrillation. Chart of the ventricular rate, in a man aged 67, showing four periods of paroxysmal auricular fibrillation with rapid ventricular rate, alternating with periods of normal cardiac rhythm with a relatively slow ventricular rate.

the ventricular walls. By a series of elaborate investigations Lewis[20] has recently indicated that there is another important factor causing auricular fibrillation, namely shortening of the refractory phase of the auricular muscle. I shall refer to this later when considering the action of quinidine.

Turning to the **therapeutic aspects of disorders of the cardiac response**, we have certain general principles to guide us. The primary cause of the disorder must, if possible, be ascertained, and appropriate measures instituted in order to combat the cause, whether it be a bacterial, spirochætal or protozoal infection, an exogenous poisoning, such as that of tobacco, an endogenous toxæmia of faulty metabolism, or a psychical disturbance. To take but one example, the disordered action of the heart, so prevalent during the war and not infrequent in times of piping peace. Here, treatment directed to the heart alone is futile, for this disorder is essentially a manifestation of infection, emotional strain, or fatigue. Cardiac infrequency is relatively uncommon, and there is seldom any need to accelerate the heart's rate. Sinus bradycardia with a cardiac rate of 40 or 45 entails neither discomfort nor distress. In partial auriculo-ventricular block a fall of ventricular rate below 40 is often due to temporary vagal inhibition, and is an indication that this should be lessened. To this end *atropine*, which paralyses the vagal nerve-endings, may be employed with benefit. The subcutaneous injection of this substance causes an initial retardation of moderate degree and lasting for two to ten minutes; the normal vagal inhibition is then partially withdrawn and the cardiac rate is accelerated. The effect is usually maximal in twenty-five to thirty minutes; subsequently the normal vagal inhibition is gradually restored.

I had under my care recently a man who was suffering from acute rheumatism, chronic mitral endocarditis and auricular fibrillation. During the early phase of convalescence from acute rheumatism, partial auriculo-ventricular block was observed, the ventricular rate falling below 40 per minute. On two occasions the Adams-Stokes syndrome supervened. Subsequently, the block being relieved, the ventricular rate gradually became normal. While the block was still at its height and the danger of vagal inhibition had to be faced, atropine in doses of gr. $\frac{1}{25}$ was given intravenously; cardiac acceleration began within a minute, the maximal rate of 86 was attained in two minutes and a half, thereafter the rate gradually subsided. The intra-

venous administration of atropine is the most prompt and effective measure in warding off the risks which attend a severe grade of partial heart-block. Although all the chambers of the normal heart are accelerated by atropine, the drug has no direct action on the ventricles. This fact is well demonstrated by a study of the effects of atropine in complete auriculo-ventricular block. Here atropine does not increase the ventricular rate although the auricles are accelerated.

Adrenaline given subcutaneously produces its well-known vaso-constrictor effects, but exerts little or no action on the heart. Nevertheless, in virtue of its stimulant action on the sympathetic nerve-endings, adrenaline may be used with benefit instead of atropine in partial block. By stimulating the sympathetic supply to the ventricles, adrenaline may accelerate the ventricles in complete block and lessen the grave danger of ventricular stand-still. Adrenaline must be given subcutaneously; its intravenous administration is not permissible because this may cause ventricular fibrillation, a danger which was first brought to my notice by Professor W. E. Hume.

Digitalis and Strophanthus.—In tachycardia of sinus origin little, if any, benefit will accrue from direct attempts to lessen the cardiac rate by drugs which stimulate the vagus, such as morphine, pilocarpine, and the substances of the digitalis group. Here the action of digitalis is exerted mainly through the sinus node, but is not so constant or so pronounced as in auricular fibrillation. The difference of action is, I believe, a quantitative rather than a qualitative one.

If the cardiac action be enfeebled, measures should be adopted to stimulate the heart to more vigorous contraction and, by means of complete recumbence, to lessen the work of the heart. By the use of vaso-dilators, too, we can temporarily lessen the arterial pressure and thus lessen the work of the heart. The tachycardia following the administration of nitrites is secondary to vaso-dilatation. In flutter the transmission of stimuli to the ventricles is first impeded by digitalis and strophanthus. The ventricular speed falls to one-half of its previous rate; the auricles meanwhile continue to contract with unabated frequency. If the administration of either drug is continued, the flutter may be replaced by fibrillation.

Digitalis and strophanthus are most beneficial in patients who are suffering from chronic mitral endocarditis complicated by cardiac dilatation, dropsy, and persistent auricular fibrillation

(Fig. 5). In view of the great benefit obtained by these substances in auricular fibrillation, it is sometimes erroneously supposed that they arrest the fibrillation and restore the normal rhythm of the heart. All the benefit obtainable by the drugs can be explained by their stimulating the vagi and thus depressing the conductivity of the neuro-muscular conducting system. A partial block of vagal origin being produced, fewer stimuli are transmitted to the ventricles, the ventricular rate becomes less frequent, ventricular diastole becomes longer, the

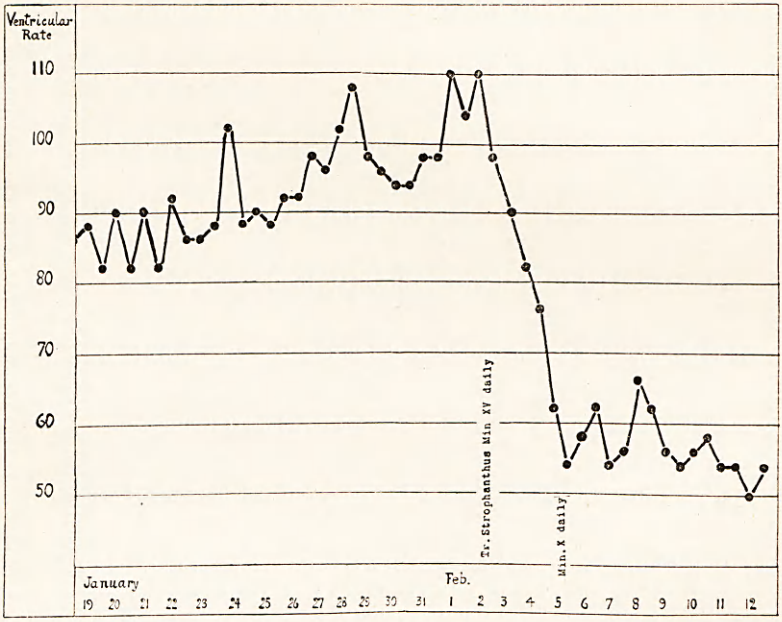

FIG. 5.—Chart showing the cardiac response to strophanthus: auricular fibrillation in a man aged 67.

ventricles are therefore given more time in which to rest, and their contractions are consequently more efficient. Thus the cardiac output is increased, diuresis is promoted, venous congestion, dropsy, and breathlessness vanish. I do not deny that digitalis and strophanthus may exert other effects—on the tone of the cardiac muscle, on the arterioles, on the kidneys—nevertheless clinical experience teaches us that all the good effects of digitalis and strophanthus are observed when the drugs produce the desired degree of partial auriculo-ventricular block, and that benefit is not obtained in the absence of that

block. A consideration of the preparation of the drug which should be employed need not detain us. In a case of average severity, the usual daily dose of digitalis tincture should be 60 minims; the beneficial effects will be becoming evident by the third day. In an urgent case, 60 minims should be given forthwith, and 30 minims every six hours thereafter. By thus giving 3 drachms of the tincture within twenty-four hours, the ventricular rate may be lowered from 200 per minute to 80 per minute within twenty-four hours. Benefit even more speedy is obtainable by an intravenous injection of 1 mg. of strophanthin. A patient who was sitting up in bed, panting for breath and as blue as a blaeberry, is, in a few hours, able to lie down and breathe easily, all his urgent symptoms having been relieved. After the initial days of treatment have elapsed, a fibrillator needs to take a small daily dose of the drug indefinitely. Failure to do so usually entails undue ventricular acceleration, and a recurrence of cardiac failure.

When the administration of digitalis or strophanthus is pursued beyond a therapeutic limit, a remarkable form of cardiac response is observed. It consists in a coupling of the ventricular beats, the second beat of each couple being a ventricular extrasystole, while the auricles continue to fibrillate. The cause of this form of coupled rhythm is not fully understood, but it is intimately related to a slow ventricular rate and is an invariable indication to reduce, or temporarily to discontinue, the administration of the drug, lest fatal ventricular fibrillation ensue.

Quinidine.—The last modification of the cardiac response to which I shall refer is that by quinidine. This substance, introduced in 1918, is a cardiac depressant and, as Lewis has demonstrated, has a direct action on the heart muscle, prolonging the refractory phase and lowering conductivity, and an indirect action through the vagus which becomes partially paralysed. When administered in therapeutic doses, quinidine has no appreciable action on the healthy heart. It is in flutter and fibrillation that the beneficial action of quinidine may be observed. In flutter, the drug may lower the auricular rate, as in the case of the man aged 45 from whom Fig. 6 was obtained. In the course of a week the auricular rate was lowered from 248 to 165 per minute. A similar fall of rate in auricular flutter, from 230 to 150, has been recorded by Korns.[21] Quinidine stands alone in its capacity to lower the rate of

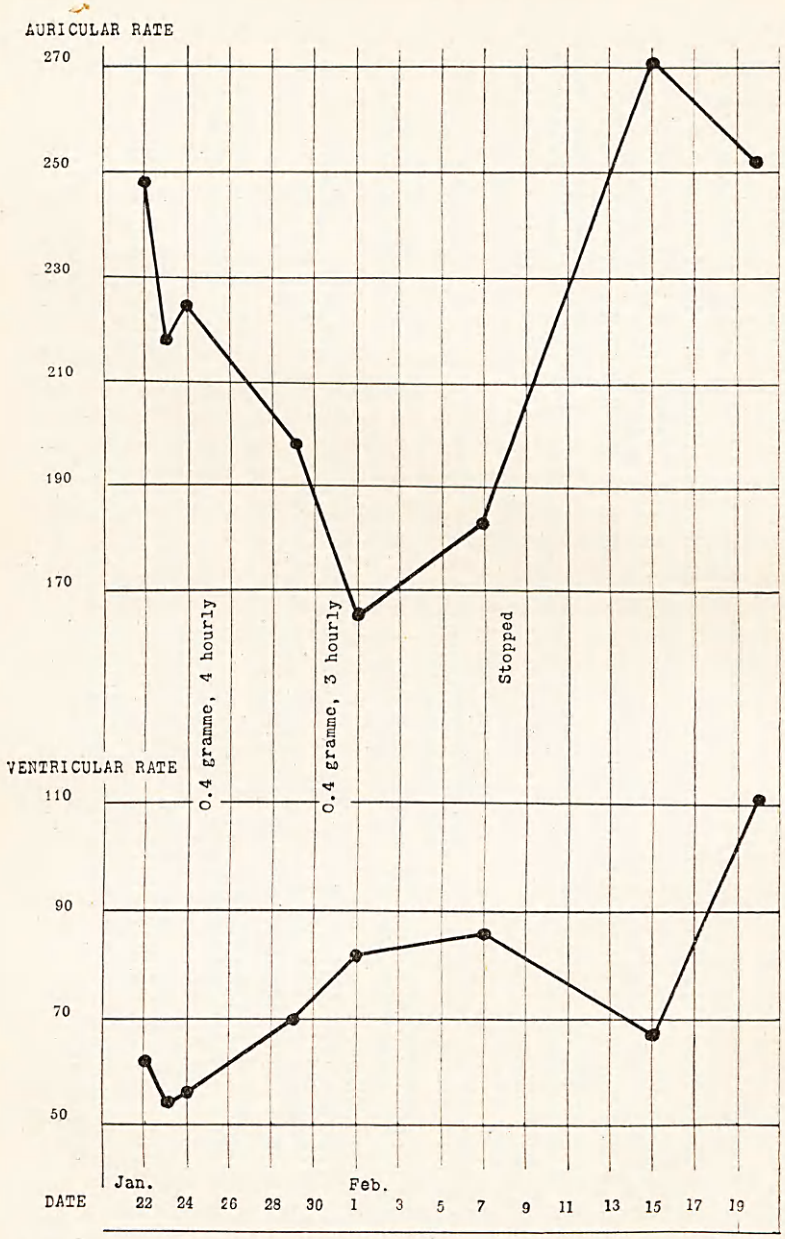

FIG. 6.—Curves showing how quinidine may modify the auricular and ventricular rates in auricular flutter.

fluttering auricles. No other alkaloid of cinchona has an equal power. The fall of auricular rate, interesting and remarkable as it is, is not necessarily advantageous, because when the auricular rate falls the ventricular rate may rise, an auricle-ventricle ratio of 4 : 1 becoming 3 : 1 or 2 : 1. Parkinson and Nicholl,[22] recording five cases of flutter treated by quinidine, obtained restoration of normal rhythm in two.

In auricular fibrillation quinidine lowers the frequency of the auricular deflexions. In favourable instances the next effect of quinidine is the conversion of fibrillation into flutter and, subsequently, the restoration of the normal rhythm. It is claimed that the normal rhythm can be restored in 57 per cent. of cases, but this satisfactory result was obtained in only eight of my twenty-eight cases. The restoration of normal rhythm may be accompanied by relief from distressing palpitation, tachycardia and other signs of cardiac failure. By the continued administration of quinidine in appropriate doses, the normal rhythm may be maintained for weeks. I have observed its maintenance for six weeks by means of 0·4 gram given twice daily.

Quinidine is more efficacious in restoring the normal rhythm if the fibrillation is of recent origin than if it be of long-standing. If the normal rhythm is not restored by means of small doses, for example 0·4 gram every eight or six hours, larger doses are not likely to restore it or to maintain it if once restored. Quinidine usually fails to restore the normal rhythm if auricular fibrillation is accompanied by evidence of long-continued ventricular failure, namely, dilatation and undue frequency of the ventricles, cyanosis, and dropsy. In such cases we gain nothing by restoring the normal rhythm; in such cases quinidine is valueless, whereas digitalis and strophanthus are most beneficial. After either of the latter drugs has relieved the patient of all urgent signs of ventricular failure, a trial may then be made of quinidine.

The administration of quinidine is not devoid of ill effects and even of dangers. I have had to discontinue its administration because it caused severe palpitation and nausea in one patient, diarrhœa in a second, persistent ventricular tachycardia in a third, the Adams-Stokes syndrome in a fourth. The risk of embolism has been recognised and commented on by several writers. In one of my fibrillators, a woman aged 30 who was suffering from mitral stenosis, a fatal issue by paralysis of the

respiratory centre ensued after the administration of quinidine although only two doses of 0·2 gram had been given.

In this Memorial Lecture it has been my aim to present some of the salient features of the heart's response in which Gibson was deeply interested, and of which the secrets were in some measure disclosed by his work. During the last ten years the limits of our knowledge have been extended. The war, while bringing old, unsolved, problems to the forefront revealed others of which we had been ignorant, but which are even now being explored. Yet there is no limit to the development of knowledge. We make a step forward and immediately a new vista into the unknown is revealed. Nevertheless each forward step does bring us nearer to the ultimate truth, and as we strive towards that goal it is fitting that now and again in the bustle of our worktime we pause to commemorate those to whom we owe much and who have gone before us. It is in this spirit of pride and thankfulness that we remember George Alexander Gibson.

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