THE THESIS.

STUDIES in COMPLETE HEART-BLOCK in MAN, with special reference to the ACTION of DRUGS on the RATE of the VENTRICLES.

BY


SUBMITTED FOR

THE DEGREE OF M.D., (Edin).

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TABLE of CONTENTS.

PREFACE. 

HISTORICAL ASPECTS of PULSE counting in RELATION to BRADYCARDIA. 1

CLINICAL ASPECTS of COMPLETE HEART-BLOCK.

I. ETIOLOGICAL FACTORS. 13

II. THE SYMPTOMATOLOGY. 44

The PULSE RATE in COMPLETE HEART-BLOCK. 71

The RELATIONSHIP between VENTRICULAR and AUERICULAR RATES in COMPLETE HEART-BLOCK. 87

The RELATION of VENTRICULAR RATE to certain BODILY MEASUREMENTS. 90

The NATURAL MAXIMUM RATE in the IDIO-VENTRICULAR RATE. 112

The RESPONSE to ATROPINE. 137

The INFLUENCE of VAGO-CAROTID PRESSURE. 167

The RESPONSE to AMYL-NITRITE. 183

The RESPONSE to ADRENALINE. 203

The REACTIONS to ADRENALINE and ATROPINE CONTRASTED. 245

The RESPONSE to EPHEDRINE. 253

The RESPONSE to DIGITALIS. 275

The RESPONSE to BARIUM-CHLORIDE. 298

RESPONSE to EXERCISE. 307
REMARKS on (1) The EFFECT of TEMPERATURE on the IDIO-VENTRICULAR RATE on (2) FUNCTIONAL AURICULO-VENTRICULAR DISSOCIATION and on (3) The NATURE of the STOKES-ADAMS SEIZURE.

(1) The Effect of Pyrexia on the Idio-Ventricular Rate. 332
(2) Functional Auriculo-Ventricular Dissociation. 336
(3) The Stokes-Adams Syndrome. 341

REFERENCES. I - XXVI.

CASE RECORDS. 350 - 469.
In the following pages an attempt is made to discuss certain aspects of complete heart-block as it occurs in man. While the nervous control of the auricles is well understood, much remains to be discovered regarding the influence of the extrinsic nerve supply to the ventricles. In approaching this problem, the heart, in which the auricles and ventricles are dissociated in their rhythms lends an admirable opportunity for the investigation of its nervous regulation. By the use of certain drugs and other procedures in a series of fourteen cases of complete heart-block, the facts accumulated suggests that the ventricles, despite the presence of complete block, are directly under the control of the parasympathetic and sympathetic systems. The evidence leading to this conclusion is summarised at the conclusion of each section of this report.

It is with special pleasure that I acknowledge a debt I cannot pay to Professor Murray Lyon for all the facilities granted me in the Clinical Laboratory of the Royal Infirmary. Without the opportunity to study patients, in his wards, often over/
over long periods of time, the work would not have been possible and I gladly express my very best thanks to him and the staff of the wards. Professor Ritchie has also invited me to see certain patients and given me facilities for their investigation. I likewise record my appreciation of the kindness of Professor Bramwell, Dr. Edwin Matthew, Dr. Alex. Goodall, and Dr. John D. Comrie all of whom have given me access to their patients. To Mr. T.H. Graham, of the Royal College of Physicians, I am indebted for his successful search for the portraits of Robert Adams and William Stokes which are reproduced in the text.
HISTORICAL ASPECTS of PULSE COUNTING in RELATION to BRADYCARDIA.
HISTORICAL ASPECTS OF PULSE COUNTING

in RELATION to BRADYCARDIA.

It is at first sight somewhat surprising that, though a diminution in the frequency of the pulse was well known to GALEN (77) in the second century, yet only in the last hundred years or more has much attention been devoted to this relatively common manifestation of Cardiac action. Even by 1628 HARVEY (98) had no clear notion of the significance of the rate of the heart and he makes but scanty reference to it beyond remarking that "in the course of half an hour the heart will have made more than one thousand beats, in some as many as two, three and even four thousand". A range in rate extending from 33 to 133 per minute thus receives but little attention.

It is however of interest to recall that the time recording apparatus available to the physicians of HARVEY'S generation was of inconvenient pattern, often inaccurate and generally unreliable. As a consequence of this, the significance of variations in the pulse rate was not appreciated.

The water clock, or clepsydra of the ancient Egyptians and the pendulum or pulsilogon of GALILEO/
GALILEO (78) both now of much historic interest, added but little to our knowledge of the heart rate either in health or disease. Although time recording instruments of a convenient portable nature were invented towards the end of the fifteenth century and by a gradual process evolved as that highly perfected instrument, the watch, with minutes and seconds hands as we now know it, yet even as late as 1825, the accurate numeration of the pulse rate was decried as a fallacious and useless procedure.

RUCCO (191) wrote at that time "The having recourse, as several physicians are accustomed to do, to an artificial standard, such as a watch, pulsilegium, or pendulum, as a substitute for the natural one afforded by the exact knowledge of the physiological state of the pulse, is an irregular and fallacious practice".

It is literally true that in the precise study of the pulse, medicine lagged behind the clock. FLOOR (70) published in 1707, the first serious study on the rate of the pulse in health and diseases a work remarkable in its breadth of outlook and rich in its shrewd observations. In many ways he anticipated present procedures and with a watch, which/
which was specially constructed to his direction, he made many notable additions to our knowledge. It was he who established the fact that it is a characteristic of the normal pulse to vary greatly in rate. He observed that passion, eating, exercise and fever accelerated the pulse by 20 beats or more per minute, and that rest, quiet and sleep had an opposite effect. On account of these influences he came to the conclusion that the natural healthy pulse was best observed by counting "the morning pulses before eating, exercise, or other external influences disturbed it".

As was true of WITHERING'S original account of the uses of digitalis, so also were many years to elapse before FLOYER'S work on the pulse rate received the more accurate and detailed investigation which it well merited. CUSHNY (46) has recorded that the indiscriminate use of digitalis continued for a hundred years after its introduction to therapeutics, without any endeavour to analyse its efficiency in different diseases of the heart. To a large extent the same fate befell FLOYER'S attempt to focus attention on the variations in the rate of the pulse. ROBINSON (184) apparently one of the first to apply mathematical methods/
methods to the study of physiology, published his original observations in 1738. In pointing out the influence of the mind and the effects of exercise on the pulse, he wrote, "The pulses in a minute of a man lying, sitting, standing, walking at the rate of two miles in an hour, at the rate of four miles in an hour, and running as fast as he could, were 64, 68, 78, 100, 140, and 150 or more. When a body stands up, the pulse begins to grow quicker the very instant the body begins to rise, or the soul begins to exercise the power which raises it, ........ A fit of laughter has quickened the pulse 25 beats in a minute; and breathing voluntarily three or four times faster than usual, has quickened it 13 or 14 beats: The pulse is quickened by coughing, swallowing, reading loud, or by any motion that is performed by the soul. From hence it appears, that the motion of the heart is changed mediately or immediately, by every change made in the affections, activity or power of the soul." HALLER (93)

HEBERDEN (101) and FALCONER (66) likewise discussed the influences which affected the rate of the pulse in health and the changes observed to occur in various diseased states.

One/
ROBERT ADAMS.

1791 - 1875.

Yours very truly,

Robt. Adams.
Due credit must be given to MORGAGNI (161) who was apparently one of the earliest writers to draw attention to infrequent action of the heart. In 1761 he described several clinical examples and referred to a pulse rate of 22 in one-sixtieth of an hour. Incidentally his was the first description of the Stokes-Adams syndrome. In his remarkable treatise SENAC (198) mentioned pulse rates of 27, 35, 39, 40 and 47 per minute, and PALCONEER (66) in 1796 states that "the slowest pulses I ever knew, that were well authenticated were of women; one of them being 24 in a minute and the other 36."

Meantime SPENS (203) in 1793 had recorded the remarkable case of an elderly man in whom the pulse rate was 23 per minute. He suffered from repeated fits preceded by a further retardation of the rate, the pulse falling to 10, and then to 9 per minute.

Only in the early years of the nineteenth century did pulse counting become a routine measure in the investigation of disease. As a direct consequence of more precise methods of recording the rate of the heart, clinical interest was at once aroused in those instances in which a gross departure from the usual range of rate was detected.
WILLIAM STOKES.
1804 - 1878.
(2) in 1827 described a pulse rate of 30 to the minute and in the same year Burnett (23) noted a similar case. In 1830 Graves (91), who by his teaching and example had done much to foster methods of precision in medicine, in the course of observations on the effect of posture on the pulse rate, briefly refers to a lady known to him, whose pulse since childhood, never exceeded 38 in a minute. The remarkable symptoms which might accompany slow pulse, as they affected a man 64 years of age, were recounted by Holberton (113). Thrown from a horse two years previously, this patient had a fainting fit and the pulse thereafter was found to be 20. Many fits were observed, the pulse ranging from 15 to 20 per minute. "It fell to 12, 10, 9, 8 and several times when the patient was sensible and not in a fit, I counted his pulse as low as 7½ a minute." Stokes (208 (209) in his important and well known contributions to the literature aroused fresh interest in the condition. By his shrewd observation regarding the independent jugular pulsations, this great clinician was the first to provide a clue as to the peculiar nature of that form of bradycardia, which so often is accompanied by fainting fits. He writes "...... a new symptom appeared, namely a remarkable pulsation in the right jugular vein." The phenomenon was/
was most evident with the patient lying down and the venous waves were more than double the ventricular rate. "The appearance of this patient's neck was very singular and the pulsations of the veins such as we never before witnessed".

The early years of the eighteenth century witnessed a remarkable enthusiasm in the study of the heart and circulation. ROBERT KNOX in his Edinburgh thesis (1814) entitled "De viribus stimulantium et narcoticorum in corpore sano" wrote of the effects of exercise on the pulse and came to the conclusion that "the most powerful stimulant which can be applied in order to increase the action of the heart is exercise" (129). ROBERT GRAVES of Dublin published a paper (91) in which he confirmed and extended the work of KNOX and at the same time LOUIS in Paris (143) urged the value of routine estimation of the pulse rate in various diseases. Largely under the influence of these three men it came to be realised that counting the pulse was a simple and valuable procedure which the physician could ill afford to neglect. Perhaps particular credit is due to GRAVES who by the example of his systematic methods had paved the way for the important contributions on slow pulse made by his colleagues, ADAMS and STOKES, of the Dublin school of medicine.
medicine.

By 1888 GROB (92) suggested the name, bradycardia, to describe the condition of slow heart action for which he assumed there were a number of causes, some of which were of extrinsic origin. Later HUCHARD (117) in his classical work on diseases of the heart made important contributions to the study of slow heart action recognising that bradycardia was no more than a symptom requiring investigation. "... pour faciliter le diagnostic", he writes "j'établis le tableau et la classification des diverses bradycardies". His breadth of view and wide range of clinical experience enabled him to offer a classification consisting of at least six different varieties, the physiological, the convalescent, the toxic (including digitalis, lead and bile) the reflex, the nervous (including meningitis, melancholia, and arterio-sclerosis) and finally bradycardia of cardiac origin (degenerative and vascular changes in particular).

It is unnecessary to review the extensive literature which has gradually accumulated since HUCHARD'S time. Reference should be made to the comprehensive papers of OSLER (164 & 165) & GIBSON (83). The modern conception of the nature of bradycardia of/
of purely intrinsic causation may be considered to have its origin in the experimental work of STANIIUS (204) who showed, by his second ligature, that the ventricle is possessed of the faculty of initiating its own beat when dissociated from the auricle. KENT (124) & HIS (111) in 1893 showed that the impulse to ventricular contraction was passed on from the auricle by means of a slender neuro-muscular bundle situated in the region of the septum. GASEKEL amplified and confirmed the work of HIS and shortly afterwards clinical confirmation of the experimental observations was produced by HANFORD (94) who in 1904 described a case of bradycardia in which gummata in the region of the bundle caused death by heart-block.

Methods of precision so long delayed in the study of cardio-vascular disease, therefore yielded, when once applied, remarkable results in a comparatively short period of time. It is worth recalling that though the putable time piece was not introduced until about the 1500 (7) nearly two centuries elapsed before FLOYER (70) applied it to the study of the pulse. The advent of the balance spring in 1575 had the effect of so improving the time keeping qualities of the watch, that with succeeding/
succeeding years it gradually ceased to be regarded either as a curious instrument or as a piece of decorated jewellery. Even after Floyer's memorable work a further century passed before the watch took its rightful place in the hands of the practising physician. Perhaps the explanation for the long delay in the general application of the watch of the study of the phenomena of disease is to be found in the fact that in the early days of its use there was but little recognition of the smaller units of time. Minutes mattered less then than now. The eighteenth century was well advanced before the minute hand came into general use, and even today watches continue to be made without the valuable dial and hand for recording seconds. To appreciate the difficulties, which the older physicians must have encountered in estimating the pulse rate, it is instructive to find that Baille in his interesting work on the history of watches (7) states that the seconds hand was but seldom incorporated on the face of the watch until the end of the eighteenth century. Though it was introduced by Fitter of Battersea about 1665 there was apparently little demand for this additional refinement. The inability to measure accurately and conveniently the smaller units of time is the undoubted explanation of/
of the scanty recognition accorded to bradycardia in the older treatise on diseases of the heart and circulation.

With the abundance of clocks and watches now available, the present day physician may well fail to realise the debt he owes to the genius of the early watch makers. The development of time recording apparatus of present day accuracy and precision has been the natural outcome of the patient labours of a large number of careful workers. The advances even in recent years have been enormous. While FLOYER complained that his watch was often inaccurate by as much as six pulse beats in the minute, and while STOKES and ADAMS may have considered themselves fortunate enough to find a watch equipped with a seconds hand, the physician today by the aid of the electrical time-maker can accurately measure the heart's action to the thousandth part of a second. Man's ability to record the beat of the heart in association with the modern development of the electrical timing device has opened up wide fields of investigation, hitherto unexplored.

Recent years have witnessed a renewed interest in the rate of the pulse and by the elaboration of such instruments as the polygraph and electrocardiograph/
electrocardiograph more detailed knowledge has become available. By means of an ingenious device, designed for the purpose and known as the cardio-tachometer BOAS and GOLDSCHMIDT (14) have studied the rate of the human heart over long continued periods of time and under greatly varying conditions. This apparatus, depends upon sufficient amplification of the action current of the heart to actuate a sensitive relay which in turn activates an electromagnetic counter and graphic recorder. By automatic means it has thus been possible to obtain accurate records of the pulse rate for indefinite periods of time in over one hundred healthy individuals during their waking and sleeping hours, and while they followed their usual mode of life.
CLINICAL ASPECTS OF COMPLETE HEART-BLOCK.

I. ETIOLOGICAL FACTORS.
CLINICAL ASPECTS OF COMPLETE HEART-BLOCK.

I. ETIOLOGICAL FACTORS.

Complete heart-block is the term applied to that condition in which the ventricles are functionally isolated from the controlling influence of the sino-auricular pacemaker, as a result of the inability of the conducting tract to transmit the impulse to contraction. Under such circumstances, two independent centres of stimulus production govern the chambers of the heart, the one in the S-A node regulating the auricles and the other, a new and separate centre, controlling the ventricles. The auricular and ventricular rhythms are therefore dissociated. Whether as a result of the involvement of the conducting tract in an organic lesion, or by the production of a state of functional depression due to toxic or perhaps nervous influences, or by the local action of some complex physico-chemical mechanism, if the link provided by the bundle of His become temporarily or permanently severed, then the ventricles are left to initiate their own rhythm and allowed to pursue their own course. Isolated in this way and dispossessed in large measure of the power of rapid and adequate readjustments to changing/
changing circumstances, the ventricles are of necessity deprived of the experienced leadership provided by the sino-auricular node. Without the resourcefulness of the skilled pilot, the ventricles may well pursue a dangerous and treacherous course. Nevertheless, as will be demonstrated in the following pages, despite the disadvantages imposed by dissociation whether functional or organic, the ventricles, at least in the human heart, are capable of remarkable adaptations. Mere slowness of action in itself imposes but a slight handicap to the efficiency of the circulatory system as a whole.

In medical practice, few conditions reproduce so perfectly the experimental findings of the physiologist as does complete heart-block. Probably for this reason, auriculo-ventricular dissociation is wellknown and its diagnosis seldom mistaken. No other condition produces such a slow pulse as may complete heart-block, and if independent auricular activity be demonstrated by graphic records, thus excluding the other forms of bradycardia, the diagnosis can be precisely established. Nevertheless complete block is an uncommon manifestation of heart disease and in the medical practice of/
of an individual it is a very rare disease. A rough idea of its frequency amongst a hospital population may be derived from the fact that in a consecutive series of 5000 patients submitted to electrocardiographic examination in the Royal Infirmary Edinburgh, complete heart-block was demonstrated in only 31 individuals. WHITE (225) has reported that of 10,000 patients electrocardiographed at the Massachusetts General Hospital, 79 suffered from this disorder of rhythm, in contrast to 1422 cases of auricular fibrillation. Similarly DOWNIE (54) collected 27 examples of complete block from a consecutive series of 9000 patients electrocardiographed at the National Heart Hospital in London. Considering a total of 24,000 patients known or suspected to have heart disease the incidence of complete heart-block is therefore only 0.57 per cent.

Despite the rarity of complete heart-block it has been my good fortune to have under my personal observation fourteen cases of complete heart-block during the past five years. While larger series have been reported in the literature from time to time, yet in but few instances were all the cases studied by a single observer employing uniform methods of examination and investigation. It is therefore/
therefore hoped that the unavoidable restrictions in the amount of clinical material available for these studies is in some measure made good by the systematic methods employed. The detailed investigation of a few patients is perhaps in many ways more profitable and more instructive than a general survey of a larger group over a longer period of time, were that available.

The studies reported at the present time are the result of the investigation of fourteen patients suffering from complete heart-block. In each instance the diagnosis was established by repeated electrocardiograms. Of the fourteen individuals, all but one (Case 14) had complete dissociation when they first came under observation. In two (Cases 7 and 9) the block was of the intermittent variety, being at times complete and at other times absent, full conduction of all auricular impulses alternating with complete dissociation. Case 14 was under observation as an example of partial block for two years. Only recently has the defect in conduction become complete. Clinically it has been possible to follow the development of the lesion in this patient and to accumulate observations on the effect of various procedures on the heart at different degrees/
degrees of block. Case 12 represents a rare form of block, recently described by MOBITZ (159 & 160) as "dissociation with interference". Otherwise the remaining patients (Cases 1, 2, 3, 4, 5, 6, 8, 10, 11, and 13) suffered from permanent complete heart-block.

THE SEX INCIDENCE.

Of the fourteen examples of complete dissociation, nine were males (Cases 2, 3, 4, 5, 6, 7, 8, 9, and 12) and five females (Cases 1, 10, 11, 13, and 14). The preponderance of males in this series finds support from the published findings of other observers. Of COWAN & RITCHIE'S (41) 23 cases of complete heart-block all were males with but one exception. The sex incidence of 112 cases collected from the literature, together with the 14 examples forming the basis of the present study is shown in TABLE I. By this means it is fair to conclude that the sex incidence is weighted against the male in the proportion of approximately 7 to 3.

The striking difference between the sexes has not in the past received the attention which/
TABLE I. To show the sex incidence of 168 cases of complete heart-block. Apparently 70 per cent of the cases occur in the male sex.
which it merits. No doubt the explanation is to be found in a study of the nature of the underlying pathological lesion. Evidence is gradually accumulating to substantiate the view that, of all the organic causes for dissociated activity of auricles and ventricles, fibrotic and degenerative lesions in the specialised conduction tissues are the most common. The importance of syphilis as an etiological factor in complete heart-block has probably been over-emphasised, as subsequent studies will demonstrate, and it would appear that the other etiological entities which may destroy or damage the bundle of His are as likely to affect one sex as the other. In his more strenous mode of life and greater economic urge, the male may well throw a greater burden on the heart muscle, and on the arterial system of the body, so that with advancing years degenerative changes of one kind or another are more likely to become manifest.

There seems to be no doubt that the male sex is led to seek advice on account of coronary artery sclerosis more often than the female. Fully 60 per cent of over 800 cases studied clinically by WHITE & JONES (226) were males. In a smaller group of cases of coronary artery thrombosis, which/
### TABLE II.

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>CASES REPORTED BY DOWNIE ( ) ELLIS ( ) AND WILLIUS ( )</th>
<th>THIS SERIES</th>
<th>TOTAL</th>
<th>PER CENT OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 20 years</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>21 - 30 years</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>7.6</td>
</tr>
<tr>
<td>31 - 40 years</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td>13.5</td>
</tr>
<tr>
<td>41 - 50 years</td>
<td>14</td>
<td>3</td>
<td>17</td>
<td>14.3</td>
</tr>
<tr>
<td>51 - 60 years</td>
<td>21</td>
<td>3</td>
<td>24</td>
<td>20.2</td>
</tr>
<tr>
<td>61 - 70 years</td>
<td>33</td>
<td>3</td>
<td>36</td>
<td>30.2</td>
</tr>
<tr>
<td>71 - 80 years</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>10.9</td>
</tr>
<tr>
<td>81 - 90 years</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>106</strong></td>
<td><strong>13</strong></td>
<td><strong>119</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

TABLE II To show the distribution in age groups of 119 cases of complete heart block. The maximum incidence (30 per cent) is found in the age period 61-70 years.
which is essentially a manifestation of vascular disease, PARKINSON & BEDFORD (167) on post mortem evidence found 72 examples amongst the male sex and only 11 amongst females. It therefore seems reasonable to suggest that the explanation of the greater incidence of complete heart-block amongst males is in large measure dependent upon their greater tendency to develop coronary artery disease.

The Age Incidence. In this group of fourteen cases the youngest subject was a male of 47 and the eldest a female of 84. There are but few series of collected cases in the literature, but taking the figures of WILLIUS (228), DOWNIE (54) and ELLIS (59) together with those of this series, the largest age incidence is found in the seventh decade. Of the 106 cases collected from the literature together with the 14 forming the basis of this report 75 first came under observation after the age of 50 years. The age distribution of 120 cases is presented in TABLE II and shown diagramatically in the accompanying CHART (No. 1). The greatest incidence falls in the age group 61-70 years.

The fact that the disease is discovered most frequently in the seventh decade is of interest, for this is the age period at which arteriosclerotic/
sclerotic changes are most prone to manifest themselves. According to WARTHIN (220) age 60 marks the period when "sclerosis of the arteries becomes the chief collaborative factor in hastening or exaggerating the parenchymatous involution of senescence" with its important effects on the heart, kidneys and brain. Vascular disease is apparently the most frequent etiological factor in the production of complete heart-block and at those ages when sclerotic changes are common the greatest incidence of this disorder is to be expected. WHITE & JONES (226) in an analysis by age groups of a series of 864 cases of coronary artery disease diagnosed clinically in New England found that it occurred most frequently (44 per cent) in the sixties. While complete heart-block may occur at any age, and while it is not necessarily a manifestation of arterial disease, it is perhaps significant that the greatest incidence of the disorder falls at that time of life when coronary artery disease becomes increasingly common.

From a pathological point of view it is only necessary to state here that a great variety of lesions have been found in the bundle of His in cases/
cases of complete heart-block. YATER & WILLIUS (234) have recently reviewed the pathological aspects of the condition. Amongst the lesions found have been gummata, areas of calcification, obliteratorive disease of the branches of the coronary arteries, fibrosis of the conducting tract, neoplasms and various other conditions. Similarly it is important to refer to the fact that in a few cases in which complete heart-block undoubtedly existed during life, yet no demonstrable lesion of the conducting tract has been detected by competent pathologists (234).

In seeking a cause for dissociated activity of the auricles and ventricles the clinician is often left without a clue as to the precise nature of the lesion. Present day histological methods may or may not reveal gross changes. It is known that the coronary arteries or their branches may be affected by sclerotic changes without peripheral evidence of vascular disease. Fibrotic changes may be strictly limited in their distribution. If the septum and neighbourhood of the specialised tissues be involved in an isolated and solitary lesion, the clinician may have little to guide him to the formation of such a precise diagnosis. It is true to say that in the presence/
presence of many possibilities, striking evidence during life as to the exact nature of the damage suffered by the conducting tract may be conspicuous by its absence. For this reason the clinician can often do no more than hazard an opinion as to the probable causation in a given case of permanent complete heart-block.

A CLINICAL CLASSIFICATION FOR PERMANENT COMPLETE HEART-BLOCK.

The difficulty encountered in assigning a cause for certain of the cases included in the present series has suggested that they might be considered in their clinical aspects under three main groups according to the evidence available. This method has certain unavoidable limitations, but if it reveals a weakness in our knowledge this in itself may serve to correct our notions and prove a refreshing stimulant for further endeavour.

To have a classification based on precise pathological data would be desirable, but as the clinical evidence may be of the scantiest and when present often conflicting, it may be regarded as/
as sufficient to subdivide the cases into three groups. These may be broadly considered as,

1. those in which degenerative processes of vascular origin are believed to be present. This subdivision has its counterpoint in pathological studies for local fibrotic change is probably the commonest cause of permanent complete heart-block.

2. those of syphilitic origin. Many cases of complete heart-block have been proved to be due to the involvement of the conducting tract by gummatous lesions.

3. those in which clinical evidence of the presence of arterio-sclerosis or syphilis is lacking. This forms a heterogeneous group, which, from analogy with experimental evidence and also indeed from a study of the cases themselves, suggests, that it might be called the "toxic" or unknown group.

The Degenerative Group. On the basis of classification according to probable causation, the first or degenerative group is taken to represent chronic vascular disease with associated fibrosis and local myocardial degeneration. The necessary criteria to establish such a diagnosis are often slender enough. They may be taken to be, the permanence of the block over a period of months or years,
the absence of any sign of syphilis either in the blood or viscera, the presence of arterio-sclerosis in the vessels of the periphery or retina and of necessity the absence of any other recognisable form of heart disease. It must of course be admitted on clinical and post-mortem evidence that arterio-sclerotic heart disease may exist without precise signs during life, and hence a number of cases may be inadvertently excluded from this group on account of the absence of recognisable vascular disease elsewhere e.g. in the peripheral vessels.

Of the fourteen cases under consideration there are five which may be placed in the first group. (One other patient (Case 14) might be justifiably included in the degenerative group, on account of the gradual failure of the conducting tract over a number of years. At the time of writing, however a sufficiently long period has not elapsed to justify the conclusion that the block is of a permanent nature. This patient is therefore omitted in the present discussion.) In two of these five patients gross fibrotic change was confirmed by subsequent post-mortem examination. The cases are noted in detail in TABLE III.
The fact that all these five cases had distinct evidence of arterio-sclerosis, and that the block was permanent makes good grounds for the belief that the failure of the conduction system was due to generative changes of vascular origin. The average age of the five patients was 70 years.

The Syphilitic Group. Syphilis is well recognised to be a cause of complete heart-block. Amongst the early cases reported in the literature and subsequently examined histologically, many instances are found in which a gumma had invaded the conduction system. Such a distinct lesion is relatively easy of detection by pathological methods and this may in part account for the fact that the literature is rich in examples of this type of destructive lesion.

Of the fourteen individuals in this series two had suffered from syphilis in youth though at the time at which they came under observation the Wassermann reaction was negative in each case. Both were males, one being the subject of tabes dorsalis. The other had also suffered for many years from acute and sub-acute rheumatism. In the latter subject, the double infection - rheumatic and specific - makes a/
<table>
<thead>
<tr>
<th>Case No., Initials, and estimated age at onset of complete block</th>
<th>Total duration of symptoms to death or to October 1932</th>
<th>Probable duration of cardiac symptoms before onset of block</th>
<th>Stokes-Adams Seizures Usual type</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. W.W. age 70</td>
<td>1 year 6 months</td>
<td>4 months</td>
<td>Transient giddiness. Consciousness lost for only an instant.</td>
</tr>
<tr>
<td>4. W.T. age 62</td>
<td>3 years 2 months</td>
<td>Seizures antedated onset of other cardiac symptoms by about 2 yrs.</td>
<td>Giddiness, weakness, and faintness without actual loss of consciousness.</td>
</tr>
<tr>
<td>5. A.H. age 64</td>
<td>4 years 9 months</td>
<td>2 years 11 months</td>
<td>Loss of consciousness.</td>
</tr>
<tr>
<td>10. Mrs C. age 82</td>
<td>4 years 2 months</td>
<td>2 years 3 months</td>
<td>Typical severe seizures. Electrocardiograms of attack.</td>
</tr>
<tr>
<td>11. Mrs D. age 71</td>
<td>2 years 6 months</td>
<td>1 year</td>
<td>Loss of consciousness.</td>
</tr>
</tbody>
</table>

**TABLE III.** To show the duration of cardiac symptoms and the probable duration of complete heart damage of degenerative vascular origin.
### Number and frequency of Stokes-Adams seizures.

<table>
<thead>
<tr>
<th>Description</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>One attack at intervals of 3 to 6 weeks. About 30 to 35 in all.</td>
<td>Alive. Able to go about in comparative ease.</td>
</tr>
<tr>
<td>One severe faint unconscious for 2 minutes or more.</td>
<td>Alive. Suffers from chronic bronchitis and emphysema. Able to go about in comfort and capable of performing light duties.</td>
</tr>
</tbody>
</table>

block in five individuals in whom the lesion of the conduction tract was believed to be of
a precise etiological diagnosis difficult. In this man (Case 3) it may be that sclerotic changes with scarring and fibrosis have resulted from a syphilitic lesion involving the specialised tissues, but the evidence is inconclusive. This man was aged 64, when he first came under observation. The second syphilitic subject (Case 7) suffered from intermittent complete heart-block over a period of 9 weeks. This is a distinct type of block which persists only for relatively short periods of time and results from a temporary complete failure of the conduction system. The bundle recovers its powers at intervals for a greater or longer period and normal rhythm then alternates with complete heart-block. While syphilis may have played some part in the production of the attacks of complete heart-block in this man, the fact that the dissociation was intermittent in type does not justify us in assuming that in this case syphilis was necessarily the causative factor of importance. Indeed subsequent histological examination of the conducting tract failed to reveal any evidence of damage to the bundle of His in this man's heart. For this reason we are justified in relegating this instance of heart-block to the/
the third or toxic group. Case 3, being also of
doubtful etiology is also perhaps best considered
in the following group.

The fact that of these fourteen patients
only 2 presented evidence of syphilis is worthy of
some attention, because in the past emphasis has been
made on this etiological factor in the causation of
dissociation. Further in the one syphilitic subject
in whom histological examination of the conducting
tract was made, no structural defect was found. It
would seem justifiably to conclude that even in the
presence of a history of syphilis or even in the
presence of syphilis of the central nervous system,
block in such a subject is not necessarily of luetic
origin. Neither of these two cases can be placed
with assurity in the syphilitic group and on review-
ing the cases reported in the literature it is found
that but few examples of complete heart-block occur
in syphilitic subjects. Of DOWNIE'S (54) 27
patients, who suffered from this disorder, only 4
had been infected with syphilis. Similar results
are found in collecting a series of clinical cases
as the accompanying TABLE IV shows. ELLIS states
(59) that even in his two subjects who each had a
positive/
positive Wassermann reaction, another etiological factor in the shape of arterio-sclerosis was also present. For many reasons it is difficult on clinical grounds to establish that a given example of complete block is of luetic origin.

**TABLE IV.**

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>No. of SYPHILITIC CASES.</th>
<th>TOTAL No. of CASES.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOWNIE (54)</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>ELLIS (59)</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>GOODALL (87a)</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>WILLIUS (228)</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>This Series.</td>
<td>? 2</td>
<td>14</td>
</tr>
<tr>
<td>TOTAL</td>
<td>9</td>
<td>126</td>
</tr>
<tr>
<td>Percent of Total</td>
<td>7·1</td>
<td>100</td>
</tr>
</tbody>
</table>

Of the total of 126 cases syphilis can at the most only be considered of clinical significance in 9 or approximately 7 percent. A similar view has recently been expressed by BICKEL (13). Clinical studies (as distinct from post-mortem evidence) reveal that the importance of syphilis as an etiological/
etiological agent in the production of complete heart-block has in the past been over emphasised.

The Toxic or Unknown Group. Of the fourteen cases under review it has only been possible to classify five. This implies that for more than half the cases, the nature of the precise etiological factor in their causation remains obscure. From a consideration of experimental evidence, and indeed from a study of the clinical features of the cases themselves, there would appear to be some justification for including these more obscure examples of dissociation in a single heterogeneous group, which for want of a more exact title the term, "toxic", has been selected, using it in its widest sense. Such a definition has been purposely chosen, recognising that actually in the human subject there are in all probability causes for complete heart-block which remain unknown to us at the present time. In clinical work no clue may be forthcoming as to the exact nature of their causation, just as the pathologist may on occasions find no lesion of the conducting tract. Certain cases must therefore remain a mystery. Heart-block of congenital origin, while a well recognised though rare condition, can hardly be/
be included as an etiological factor of importance in the adult. While a number of cases may reach adult life, yet it is unlikely that such a striking condition would then be recognised for the first time.

Experimental findings teach that besides gross mechanical damage, various chemical substances of one kind or another are capable of exerting a profound influence on the facility with which the bundle conducts impulses. It is only necessary to recall that by the introduction to the blood stream of such bodies as digitalis and its derivatives (217) aconitine (44) muscarine (186) veratrine (17) potassium salts (155) and quinidine (138) and many others, all grades of heart-block up to complete may be readily induced. Whether this results reflexly through vagal influences or by direct action on the bundle tissues is not within our province to discuss at the moment. Similarly asphyxia (136) or the administration of fatal doses of diphtheria toxin may be followed by the development of auriculo-ventricular block. It may also be induced in animals dying from anaphylaxis (5). In clinical experience digitalis is a potent agent in the/
the production of heart-block. This drug is an outstanding example of a specific toxic agent affecting the conduction tract. Minor degrees of block from this cause are common enough but complete dissociation due to the administration of the drug is but seldom seen. Toxic block also occurs in many of the acute fevers, notably in diphtheria in which its presence is taken to indicate a profound infection and indeed often heralds a fatal termination. Electrocardiographic proof of the presence of dissociation in the course of the disease has been presented by various authors (199) and more recently MARVIN & BUCKLEY (151) have described two cases in detail. In one, subsequent histological examination demonstrated oedema and infiltration around the bundle of His, and its branches, as well as in the sino-auricular and auriculo-ventricular nodes.

It may well be that in a small proportion of cases of complete heart-block seen in adult life, diphtheria or perhaps some other infection contracted in youth, has been the determining cause. Such an infection as diphtheria may be a cause of heart-block during the acute phase of the illness, but survival after diphtheria with persisting complete heart-block/
heart-block must be rare (24). Presumably in such an instance the local intoxication of the specialised cells in the conducting tract, and the surrounding oedema and infiltration, are ultimately replaced by atrophic and fibrotic changes.

On the other hand it is possible that the heart may apparently escape damage during the acute stages of the illness, betray no evidence of a lesion for some years afterwards, and yet in later life a defect in conduction may appear for the first time, as a result of insidious and unsuspected fibrotic changes in the specialised tissues. Strong support for this view is obtained by a consideration of the findings of BUTLER & LEVINE (24) who collected twenty cases of heart-block of unknown or doubtful etiology. Ten of these admitted a severe diphtheritic infection in youth, from which apparently they made a good recovery only to suffer from block on the average 39 years later. These authors conclude that diphtheria in some way, after a variable latent period, either brings about impairment on the conduction apparatus as the sole cause of the heart-block, or predisposes the heart to the insidious process of sclerosis which, in the absence/
absence of diphtheria, would have matured at a later age.

Such a conception of the etiology of certain cases of complete heart-block observed in middle or later life is of some importance. It suggests that a similar relationship may possibly exist for other acute infections besides diphtheria. It is known that acute rheumatism, influenza, pneumonia and typhoid fever may be accompanied by defects in conduction during the acute stages of the illness. If it be correct that block may develop after a long latent period in the case of diphtheria - and the evidence in support of this conclusion is highly suggestive - it would seem equally rational to suppose that such infections as those mentioned above may also in some way predispose to the ultimate onset of block. In this suggestion the clinician may find an explanation for those cases of permanent complete heart-block in which the causation is otherwise obscure.

The studies of COHN & SWIFT (39), which other workers have repeatedly confirmed (189) show that minor conduction defects are almost the rule in/
in the acute and subacute stages of rheumatic infection. Even complete heart-block has been recorded during the course of acute rheumatism (41). In lobar pneumonia according to DE GRAFF and his colleagues (89) defects in conduction are not uncommon and may appear for the first time during convalescence. Typhoid infection is another cause for the occasional appearance of this arrhythmia. But specific fevers are not the only intoxications with which block may be associated. LEWIS (137) mentions the case of a boy admitted to hospital on account of a subacute B. Coli cystitis in which electrocardiograms revealed the presence of partial heart-block with dropped beats. As the cystitis subsided the block disappeared. Heart-block may also be associated with an acute tonsillitis. A girl suffering from simple goitre developed, while under observation in the ward, an acute tonsillitis, two days later the pulse became irregular and on further investigation, electrocardiograms demonstrated the presence of high grade partial block. The throat condition gradually subsided and in the course of a few days the block disappeared. CAMERON & HILL (25) in reporting two similar cases, empha-

/
emphasise the association of the block with a recent throat infection.

It would seem reasonable to suppose that if block may appear as an acute and perhaps temporary event in the course of such infections as those mentioned above, so also may it occasionally occur in later life as the first indication of damage sustained years previously. In other words the suggestion of BUTLER & LEVINE (24) that diphtheria may influence the onset of heart-block many years after the occurrence of the original infection, may perhaps be applicable to those other acute infections during which conduction defects are liable to occur.

With these considerations in mind, it is of interest to study our eight examples of complete heart-block (excluding Case 14) for which obvious cause in the form of vascular disease or syphilis was lacking. The eight cases are included in the accompanying table. Amongst these eight cases are two examples of intermittent complete heart-block. In both of these, periods of complete dissociation alternated with normal rhythm (Cases 7 and 9) TABLE V.
### TABLE V. (contd.)

<table>
<thead>
<tr>
<th>CASE NO., INITIALS, AND AGE</th>
<th>TOTAL DURATION OF SYMPTOMS TO DATE OR TO OCTOBER 1932</th>
<th>PROBABLE DURATION OF CARDIAC SYMPTOMS BEFORE ONSET OF BLOCK</th>
<th>STOKES-ADAMS SEIZURES USUAL TYPE</th>
<th>NUMBER AND FREQUENCY OF SEIZURES</th>
<th>PREVIOUS ILLNESSES</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. B.H. age 67</td>
<td>10 weeks</td>
<td>Same period</td>
<td>Typical Stokes-Adams seizures. Electrocardiograms of attacks</td>
<td>About 250 seizures in 10 weeks of which 10 or more occurred in the last 24 hours of life</td>
<td>Syphilis in youth. Tabes dorsalis.</td>
<td>Died in a Stokes-Adams seizure. No lesion of the bundle found on histological examination.</td>
</tr>
</tbody>
</table>

### TABLE 5.

To show the duration of cardiac symptoms and the probable duration of complete block in whom the nature of the defect in conduction was of doubtful origin. The relation between the above and other conditions is considered.

<table>
<thead>
<tr>
<th>CASE NO., INITIALS, AND AGE</th>
<th>TOTAL DURATION OF SYMPTOMS TO DATE OR TO OCTOBER 1932</th>
<th>PROBABLE DURATION OF CARDIAC SYMPTOMS BEFORE ONSET OF BLOCK</th>
<th>STOKES-ADAMS SEIZURES USUAL TYPE</th>
<th>PREVIOUS ILLNESSES</th>
<th>REMARKS</th>
</tr>
</thead>
</table>

**NOTE:** In two intermitted cases, from date of first seizure in eight individuals to past or present infection is shown in the column "Previous Illnesses."
As the defect was not of a permanent nature, these two cases are best considered as a subgroup which will be referred to later. Taking the six individuals (Cases 1, 3, 6, 8, 12, 13) in whom no obvious cause could be discovered for the presence of the block, enquiry revealed certain features worthy of attention.

The fact is elicited that five of the six gave a history of infection, antedating the block. Case 1 had a severe attack of tonsillitis at the age of 49 a few months before the probable onset of the block as judged by the first Stokes-Adams attacks. Case 3, although believed to have been infected with syphilis, had also suffered from many attacks of sub-acute rheumatism. He had a definite regurgitant leak at the aortic orifice. Case 6 gave a history of a severe attack of diphtheria in childhood which confined him to bed for 3 months and caused a paralysis of both legs from which he ultimately recovered. Case 8 suffered from rheumatic heart disease (mitral and aortic endocarditis) when he came under observation at the age of 47. He had had a severe attack of scarlet fever at the age of five which probably marks the time of the first cardiac invasion. In Case/
Case 12, the most careful enquiry failed to elicit any previous illness of significance. As will be shown later the block in this case despite its persistence was probably not of organic origin. Experimental methods demonstrated that adrenalin was capable of relieving the dissociation. This case is quite exceptional and may be classified as a functional dissociation rather than a permanent complete heart-block. Case 13 suffered a severe attack of rheumatic fever at age 18, and 2 months before the probably onset of block had an attack of tonsillitis, so called "influenzal throat". With the exception of Case 12, all the others gave a history of infection, either immediate or remote.

By way of contrast it is instructive to turn a moment to the records of those individuals classified as Group 1. Strangely enough only one - (Case 10) - of the five individuals classified as primarily arterio-sclerotic gave a history of an antecedent infection, even on careful questioning. This woman (Case 10) had suffered from a mild attack of influenza. The post-mortem examination revealed advanced degenerative changes throughout the heart muscle and a marked degree of coronary artery sclerosis. Though these of five cases cannot be regarded as/
as an adequate control group yet nevertheless it would seem justifiable to conclude that the more severe of certain acute infections, either recent or remote, may possibly play a part in determining the onset of complete heart-block in certain individuals. It is probably of significance that in three of these five cases, there was a definite history of rheumatic infection. Two individuals suffered from sore throats about two months before the onset of symptoms. Diphtheria seemed a likely etiological cause for the later development of complete block in one subject.

The two cases of intermittent heart-block, which have been included in this, the "toxic" group, may now be briefly considered in that they represent a type of dissociation presenting distinct features. The exact nature of the disturbance which produces transient periods of complete heart-block is not fully understood, but these two cases have certain features which justify their inclusion in this group. The fact that the bundle might lose all its power of conduction for even days or weeks at a time, and as readily regain its function (so that full conduction was re-established) for similar periods/
periods, is sufficient to indicate that the disturbance in rhythm was not due to a complete transection of the conducting tract by a gross organic lesion. From analogy with other organs it is probably right to suppose that the bundle of His had a considerable reserve of function and that even a few strands may serve as an efficient link between the upper and lower chambers of the heart, at least for a time. Fatigue, toxic or nervous influences may be sufficient to turn the scale with the result that the stimulus in its downward path enters an area of refractory tissue and fails to bridge the gap. It is justifiable to assume that some temporary and extraneous influence acting on the conducting tissues, perhaps in a state of increased susceptibility owing to the presence of an associated organic lesion of one kind or another - must be the determining factor in the production of the attacks of complete heart-block in these instances.

The two cases under consideration shed but little light on the nature of the provoking cause for the attacks. Both were males, one 57 years of age, a syphilitic subject, with peripheral evidence of arterio-sclerosis (Case 7), while the other was aged/
aged 77 and had but slight evidence of vascular disease (Case 9). In Case 7 no provoking cause for the onset of complete heart-block was discovered. Examination revealed no active infection. The aural rate was much the same during the periods of conduction and during block. In Case 9 however a bladder infection was present. This may have played some part. The auricular rate did not vary significantly during the periods of conduction or block. CARTER & DIEUAIDE (26) in reporting a case of intermittent complete block have collected eight similar examples from the literature and conclude that the condition is usually indicative of a progressive anatomical lesion of the bundle, being essentially dependent upon vascular sclerosis and inadequate blood supply. It may be that the higher rate of the ventricles when beating in normal rhythm throws too great a burden on the conducting pathway and complete block ultimately results from a relatively inadequate blood supply to the A-V node and bundle of His. Some subtle local circulatory disturbance would seem probable. In this connection the work of GÉRAUDEL (81) is worthy of attention. He has shown that in certain cases/
cases of complete heart-block in which the bundle apparently escaped recognisable damage, there were accompanying changes in the neighbouring vessels. Partial thrombosis of the artery to the A-V node and sclerotic lesions in the vessel wall were apparently sufficient to account for the dissociation in his cases.

**SUMMARY.**

Complete heart-block is a rare manifestation of heart disease, its incidence amongst 24,000 patients known or suspected to be suffering from cardiac disease being 0.57 per cent.

Fourteen examples of this disorder form the basis of the present studies. Including these with cases collected from the literature it is found that the sex incidence is weighted against the male in the proportion of approximate 7 males to 3 females.

Similarly analysis by age groups reveals that of 120 cases, 75 first came under observation after the age of 50 years. The greatest incidence falls in the seventh decade. This marks the period when vascular disease becomes increasingly common.
It has been possible to classify these cases of complete heart-block into three broad groups.

(a) In the first or degenerative group there were five cases. In all these individuals the lesion was believed to be primarily the result of sclerotic vascular changes, perhaps associated with partial local thrombosis, and resulting in fibrotic replacement. The average age of these individuals was 70 years.

(b) In the second, or syphilitic group, there were no cases in which this etiological factor could be regarded as the sole cause of the block. One patient suffered from tabes dorsalis. The block was of the intermittent type and there was peripheral evidence of slight arteriosclerosis. One other man, in whom syphilis was suspected also gave a history of repeated attacks of subacute rheumatism. In the past the importance of syphilis as an etiological factor in the production of complete heart-block has probably been over emphasised.

(c) In the toxic or unknown group there were in all eight individuals. Two were cases of intermittent complete heart-block, in one of whom an acute cystitis may have played some part in determining the onset of dissociation. One was an example of a functional dissociation of unknown etiology. The remaining five cases each gave a history of a severe infection - tonsillitis, diphtheria, scarlet fever or rheumatism.

It is suggested that in those instances of permanent complete heart-block occurring in adult life/
life in which an obvious cause is lacking, careful enquiry into the previous health may reveal a history of certain significant acute infections. Though the heart may have apparently escaped damage during the acute phase of the infection, yet as a result of some subtle vascular or fibrotic lesion, evidence of permanent damage may not appear until after a variable latent period of months or years. Excluding Case 8, (age at onset, indefinite) the remaining seven subjects in this group were on the average affected with this disorder of rhythm at 55 years of age. This is in contrast to the degenerative group whose average age at onset was 70 years.

Intermittent complete heart-block may be classified as a sub-group, in which perhaps more than one factor is operative. Local vascular or sclerotic changes of greater or lesser degree may be the primary lesion but some other factor, - be it auricular rate, toxins, nervous influences, or fluctuations in the local blood supply, doubtless determines the onset of the dissociation in these peculiar cases.
CLINICAL ASPECTS OF COMPLETE HEART-BLOCK.

II. THE SYMPTOMATOLOGY AND COURSE.
CLINICAL ASPECTS OF COMPLETE HEART-BLOCK.

II. THE SYMPTOMATOLOGY AND COURSE.

In the preceding section an attempt has been made to justify on clinical grounds the classification of our cases into two broad groups. Admittedly this has been done with the intention of emphasising the frequency with which frank evidence of causation is lacking, but on the other hand it is possible that by a detailed clinical study of the various cases other distinctive features, common to the respective groups might be elicited. It would be of interest to discover whether in their symptomatology, physical signs, or clinical course, any further distinctions could be drawn between these two main types, the degenerative and the unknown or "toxic". For instance, as regards the age distribution it has already been shown that for those individuals in whom we have every reason to believe that the lesion was essentially of a vascular nature, the average age at onset was 70 years. On the other hand in the toxic or unknown group, composed of individuals in whom peripheral evidence of vascular disease was lacking, the average age was 55.
A wide variation in the age incidence is not surprising. It is at least sufficient to suggest that, if it be significant, there may likewise be some other distinctions in regard to symptomatology. Physiologically it is of common experience that the response to a given stimulus varies somewhat with the age of the tissue tested. In clinical medicine however clear cut experiments are the exception rather than the rule. Accurate deduction is handicapped by a multiplicity of factors and complicated interactions obscure the individual's response. Complete heart-block must of necessity be of relatively sudden onset. Such an event is a cause for abrupt and far reaching circulatory readjustments in blood flow in circulation rate, in blood pressure to mention but a few of the more obvious adaptations. It is all the more surprising that the inception of a slow idio-ventricular rhythm is in itself so often unaccompanied by characteristic symptoms of circulatory inefficiency.

In considering the reaction of the individual to the sudden onset of an independent ventricular rhythm, it is natural to suppose that the pre-existing state of the heart must determine in large measure the nature and course of the symptoms experienced.
experienced. The facility with which the tissues of the body adapt themselves to the altered cardiac mechanism may perhaps bear some relation to the age of the patient, but the major influence would appear to be the actual functional efficiency of the circulatory mechanism as a whole, particularly in regard to the capability of the heart and vessels for an immediate and continued adaptation.

In actual practice the occasions on which complete heart-block occurs in the presence of an otherwise healthy heart muscle must be very rare, if in fact such an event can occur. Consequently it is not always easy to differentiate between those symptoms due to pre-existing heart disease and any directly attributable to the mere disorder of rhythm. Occurring as a manifestation of generalised vascular disease, complete heart-block is to be regarded as part and parcel of a diffuse coronary artery sclerosis, accompanied by scattered fibrotic changes throughout the myocardium. Hence in these instances symptoms directly attributable to a failing cardiac efficiency may antedate the onset of the total failure of conduction. Even before the onset of complete dissociation the limitation in the response to effort varies widely in different individuals.
individuals, and in certain cases the occurrence of complete heart-block apparently makes but little difference either to the degree of cardiac distress or to the natural course of the degenerative process as a whole.

In the thirteen patients at present under consideration electrocardiograms established the presence of complete heart-block. They were led to seek advice for various reasons chief amongst which were a sense of fatigue and breathlessness induced with an unusual ease. In only one respect do the clinical histories of these individuals differ from those obtained from other cardiac patients of a similar age. A history of single or repeated fainting attacks is unusual in the subject of organic heart disease (18), and is only prone to occur in the presence of a marked aortic reflux or as an accompaniment of heart-block. Of the thirteen patients all but one (Case 8) admitted having suffered from fainting attacks of greater or less severity.

It is often difficult, even on closely questioning the patient or his friends to decide whether a so-called "faint" or "weak-turn" warrants the title of a Stokes-Adams attack. This is easily understood for the reason that the typical attack, which/
which begins suddenly with a sense of weakness and helplessness, and passes rapidly on through a stage of convulsions to profound coma to be followed by almost as an abrupt recovery of all the faculties, depends upon a relatively long period of ventricular asystole. When the pause in the ventricular rhythm is short the symptoms are necessarily milder, and may only amount to a sense of transient weakness or a passing giddiness. The mere frequency of repeated fainting attacks of greater or less severity amongst these subjects of heart-block is too great to suggest that they are not of considerable significance. In fact it has been possible in more than one instance to demonstrate by means of the electrocardiograph, that a "weak feeling" on the part of the patient was in fact a mild Stokes-Adams attack in which ventricular arrest only persisted for 10 seconds or less. All grades of severity, ranging from transient weakness, a "sinking-feeling", or giddiness to profound coma of several hours duration may be observed at different times in the same patient. So far as these clinical studies go this is the one symptom which distinguishes the clinical histories of sufferers from complete heart-block from individuals afflicted with similar types of heart/
heart disease without block.

Though fainting attacks are commonly recorded during the course of complete heart-block, yet this disorder of rhythm may exist for years without their occurrence. Nevertheless, on both theoretical grounds and in clinical experience, there is some justification for the belief that seizures of the Stokes-Adams type are very prone to occur at that instant when the block first becomes complete. An adequate circulation then depends upon the immediate development of an independent idio-ventricular rhythm. Delay in the initiation of stimulus formation at a new focus, below the lesion in the conducting tract, probably accounts for the seizure which marks the onset of complete heart-block. On the other hand certain sufferers from permanent heart-block are fortunate enough never to experience a Stokes-Adams attack even of the mildest degree. In these people there is as a rule no means of knowing accurately how long the block has existed. A history of slow pulse may have been noted years previously but this in itself does not mean that the block then was necessarily complete. High grade partial block (e.g. 2 to 1, or 3 to 1) may yield a pulse rate less/
less than 30 per minute for months, if not years, before the defect in conduction becomes complete. In such instances, the change to a totally independent ventricular rhythm may occur with ease and pass quite unnoticed by the patient. In complete heart-block of the intermittent type, Stokes-Adams seizures are particularly common and can be sometimes induced by various procedures. Though all evidence of heart-block may disappear for a time, yet in such individuals the tendency is for it ultimately to become of the permanent type. In such instances the first seizure is probably quite a reliable guide to the time of onset of the failure in conduction. The mechanism responsible for repeated Stokes-Adams attacks in sufferers from permanent complete heart-block probably varies not merely in different cases but perhaps also in the same individual at different times. In estimating the duration of complete heart-block in a given instance, often the only available clinical guide is the date of the first seizure, whether this be a mild syncopal affair, or the fully developed Stokes-Adams attack. At the best such a method can be but a rough assessment of the duration of the block on account of the fallacies referred to above. If we assume that the first recorded faint
or seizure marks the onset of complete heart-block - though it may actually have existed for a longer period - then it is possible to form an estimate of its probable minimum duration in a given instance. On the other hand, certain individuals may have suffered from a period of intermittent block, with one or two seizures to mark its times of onset, before the block became permanently complete. Broadly speaking it is fair to conclude that the date of the first seizure gives a rough approximation of the duration of the block in a given instance.

There are twelve individuals in this series of thirteen cases, in whom it is possible to estimate the probable minimum duration of the condition if we admit that a fainting attack is of sufficient significance to mark the onset. In the single individual in whom nothing to suggest even the mildest of Stokes-Adams attack has ever been experienced a slow pulse rate had been present to his certain knowledge over a period of 16 years, (Case 8). In spite of this, he had no symptoms to suggest an impairment of cardiac function until fifteen years after the slow pulse was first noted. It is therefore not possible to form an exact conclusion/
conclusion regarding the duration of the total heart-block in this man.

In those in whom fainting attacks were recorded a study of the case histories reveals that the seizures varied in type and in frequency in different individuals. A reasonable accuracy in gauging the duration of the complete dissociation is to be had in those instances where attacks of a similar nature continued to occur at shorter or longer intervals during the period of observation. For example in Case 1, three or four seizures a year have occurred over a period of 9 years, for the last four of which the patient is known to have suffered from permanent dissociation. Similarly in Case 10, a total of 352 fully developed seizures occurred in the space of 1 year 11 months. On the other hand a single attack is admittedly less conclusive, particularly if unaccompanied by loss of consciousness.

Cases 2 and 6 each admitted having experienced a solitary unexpected giddy turn accompanied by a feeling of weakness without coma or convulsions. In each instance complete heart-block was either demonstrated by the electrocardiograph or suspected by the private medical attendant a few weeks later.

Attacks of greater severity, either single or perhaps/
perhaps repeated once or twice in the course of a day or two are of much greater significance, particularly if they occurred in the absence of any recognisable cause and with the patient reclining in a position of ease and comfort. It must be a rare event for a patient, even one suffering from heart disease, to be overcome by a single syncopal attack when resting quietly in bed. Such a history as was indeed obtained from more than one of the patients, in whom complete heart-block was subsequently demonstrated is strong presumptive evidence of a Stokes-Adams attack and may well serve to mark the onset of the dissociation of rhythms.

Assuming then that the first faint, giddy turn, or actual Stokes-Adams seizure marks the onset of complete heart-block it is possible to form a rough estimate of the probable duration of the disorder of rhythm. Of the twelve individuals who admitted or frankly complained of this symptom it is found that seven suffered from general cardiac symptoms before the probable onset of block. These cases are No. 1, 2, 3, 5, 10, 11 and 12. In four cases (CASES 6, 7, 9 and 13) cardiac symptoms coincided with the advent of the first Stokes-Adams seizure. In one case (CASE 4) there were no cardiac symptoms/
symptoms (with the exception of seizures of minor severity) until a period of just over 2 years had elapsed from the date of the presumable onset of complete block. This patient did not make a very reliable witness but even on cross questioning him he did not admit to any distinctive cardiac symptoms during the two years when his seizures were most common. In one individual (CASE 8), though it was known to him that he had had an unusually slow pulse for 16 years, yet the non-occurrence of any symptoms suggestive of even a mild Stokes-Adams attack, makes it impossible to form any estimate of the duration of complete heart-block in this man. He had only had symptoms referable of his heart for 14 months.

When the cases are examined on a basis of probable causation some interesting facts are elicited by a study of the two tables (No. 3 and 5) referred to above. In the degenerative group (TABLE 3), all but one individual complained of general cardiac symptoms for sometime before the first seizure was experienced and therefore probably before the onset of complete block. Analysing the symptoms of the four individuals CASES 2, 5, 10 and 11) it is found that in each instance a sense of undue fatigue and breathlessness produced by exertion antedated/
antedated the first seizure by 4 months, 2 years 11 months, 2 years 3 months and 1 year respectively. Flatulence was a troublesome symptom in CASE 10 and appeared to bear a relationship to the production of numerous Stokes-Adams attacks in this individual. In only one individual in this group did the illness commence with a seizure (CASE 4). This man had previously suffered from epilepsy, and was a poor witness, but apparently no general symptoms of a cardiac nature were experienced until approximately two years had elapsed from the date of inception of complete heart-block. 

Contrary to what might be anticipated none of these individuals suffered from a great aggravation of general cardiac symptoms after the block became complete. Even in those who ultimately died the illness ran a slowly downward course all the symptoms becoming progressively worse as death approached. The failure of conduction, it is true, was ultimately followed by a gradual aggravation of such symptoms as dyspnoea and undue fatigue, but these symptoms were themselves increasing before the probable time of onset of complete block. In other words the block was apparently but one feature in a progressive deterioration and not the dominating factor.
factor. In this connection it may be recalled that in the elderly arterio-sclerotic subject dying from congestive heart failure a relatively slowly acting heart is common. It is not uncommon to find heart rates in the neighbourhood of sixty per minute or less (even in the presence of congestive failure and apart from digitalis therapy) when degenerative vascular disease is the etiological agent. Complete heart-block may be regarded as a special manifestation of a similar tendency. The natural downward course of the disease does not appear to be appreciably hastened by the mere presence of a slow and more or less independent ventricular rhythm. Even in the single instance (CASE 4) in which minor seizures, repeated at intervals of a few weeks preceded the onset of general cardiac symptoms, two years or more elapsed before dyspnoea led the man to seek advice. Since then he has sufficiently recovered from a mild attack of congestive heart failure to enable him to go about in reasonable ease. It would therefore appear that, the block itself plays a minor part in the production of general symptoms, the incapacity resulting from a progressive myocardial deterioration.

Of the five individuals in the degenera-
degenerative group three died having suffered from complete heart-block for 14 months, 22 months and 18 months respectively. Two are still alive, one in poor health but the other able to perform light physical duties without great distress, - the duration of the block to date being respectively 38 months (CASE 4) and 22 months (CASE 5). The average age of the five at the time of onset of the block was 70 years. Incidentally death has come to the three individuals eldest at the onset of the block.

In the "toxic" or unknown group a variety of different types of complete heart-block have been brought together. Clinically, a brief analysis of the symptoms and course of the disorder would suggest that this group is composed of a number of apparently disconnected and unrelated examples of heart-block. Closer investigation reveals however that they have not only certain features in common, but that they contrast sharply in certain respects with the degenerative group referred to above.

This group is composed of eight individuals. In three, (CASES 1, 3 and 12) symptoms of general cardiac distress preceded the onset of block by 2 months, 9 years and probably 2 years respectively.
respectively, while in four other individuals (CASES 6, 7, 9 and 13) seizures of varying severity were the first indication of illness. In one case (CASE 8) no fit or seizure has ever been experienced.

Considering first the three individuals mentioned above (CASES 1, 3 and 12) it is found that, just as in the degenerative group, the symptoms, which were experienced before the apparent onset of complete block, were an easily induced fatigue and breathlessness on slight exertion. In Case 1, these symptoms commenced after a severe attack of tonsillitis and had continued for about two months before the first seizure was experienced. Heart-block has apparently been permanently established in this woman for the past 9 years. She is alive at present, having been under observation at intervals for over four years, and is able to perform all her household duties with little or no discomfort. Case 3, is of rather a different type from the others placed in the "toxic" group in that this man gave a history of both syphilitic and rheumatic infection. He suffered from valvular disease, which no doubt accounted for the fatigue, dyspnoea/
dyspnoea, and praecordial pain which antedated the first and only fainting attack by 9 years. Alive and in fair health at the present time, the block has presumably been complete for 9 years. He has been under observation at intervals for the past six years and all the electrocardiograms taken at intervals over this period demonstrate the presence of complete dissociation. It is remarkable that a man, beginning to have symptoms of gross valvular disease at the age of 52, developing complete heart-block at 61, and yet at 70, though not able for work should be capable of a fair amount of activity, going out and about daily without much distress. It is difficult to believe, in such an instance as this that the independent ventricular rhythm can be of itself much of an handicap. Whether the nature of the cardiac disease be primarily syphilitic or rheumatic, the man has already survived more years than many an individual whose cardiac affection dates from a similar age and whose conducting tract has escaped damage. This man and one other (CASE 8), also suffering from aortic regurgitation, were the only two of the whole series who complained of praecordial pain on exertion. The third individual (CASE 12)
(CASE 12) of this group who had probably symptoms before the apparent onset of block, is quite an exceptional example of complete heart-block. Experimental evidence indicated that in this man the bundle of His was capable of conducting the sino-auricular impulse only when the heart was under the influence of a dose of adrenalin. He suffered from a slight degree of fatigue and dyspnoea for about two years before the first of a small series of minor seizures commenced. The conduction disturbance has now apparently persisted for five and a half years without any further appreciable deterioration in cardiac efficiency. The man is handicapped to some extent it is true, but his symptoms today are no worse than they were over five years ago.

In contra-distinction to the degenerative cases described above, there are four individuals in this group who confessed to no general symptoms of cardiac origin before the first seizure. CASES 6, 7, 9 and 13 exemplify this type of symptomatology. In each of these patients the first indication of heart-block - as manifested by a Stokes-Adams attack coincided with the appearance of definite symptoms of cardiac distress. Two (CASES 7 and 9) are examples of intermittent complete heart-block occurring at/
at age 57 and 77 respectively. Both enjoyed good health until the first sudden and unexpected seizure. Death occurred after an illness lasting 10 weeks in CASE 7 and was no doubt accelerated by a violent series of Stokes-Adams attacks numbering approximately 250, at least 168 of which occurred during the last 24 hours of life. In the other individual (CASE 9) an elderly man aged 77, the block at first intermittent in type, has become permanently established for the past three months. He was in good health, active, and able to attend to his affairs before the first sudden and unexpected seizure. During the four months which have elapsed since that time his general strength has deteriorated. Bodily weakness and some dyspnoea on exertion have to date been his main symptoms. In the third man (CASE 6) in whom a single mild seizure coincided with the onset of cardiac symptoms, the block has remained permanent for the past 18 months. His symptoms have likewise consisted of dyspnoea and fatigue and culminated in an attack of congestive heart failure eight months after the onset of the heart-block. The fact that this man developed auricular fibrillation of the permanent type while under observation in/
in the hospital would serve to indicate that the pathological changes were not confined to the conducting tract. His symptoms of cardiac distress are therefore attributable as much, if not more, to a generalised myocardial damage as to the mere disorder of ventricular rhythm. CASE 13, a female patient, suffered from repeated minor seizures for over 6 years. Her cardiac disability is of the slightest degree, and though afflicted with complete block, she is able to undertake all her usual duties with but the slightest handicap. The remaining individual (CASE 8) who had suffered from brady-cardia for at least sixteen years, a sense of fatigue, dyspnoea and praecordial pain had only been a burden to him for the last fourteen months. How long the block had been complete it was not possible to estimate, but as he also suffered from rheumatic heart disease, an aortic regurgitant lesion predominanting with auricular fibrillation, it would appear probable that the mere presence of complete heart-block played but a small part in the production of symptoms.

Of the eight individuals whom we have thought it fitting to include in the "toxic" group of cases, only one has died. An example of intermittent/
intermittent complete heart-block, this man lived for ten weeks after the first of a large number of severe Stokes-Adams attacks. On the basis of the clinical histories, there is some justification for the belief that to this date six of the other subjects (CASES 1, 3, 6, 9, 12 and 13) have been afflicted with complete heart-block for 8 years 10 months, 9 years, 3 years 10 months, and 5 years 6 months, and 6 years 3 months respectively. The average age at onset for these six cases was 55 years. To judge from the relatively slight degree of functional impairment, (as estimated by their ability to undertake exertion) several of these individuals may have a life expectancy of perhaps more years than might be anticipated at first sight. Two of them, for instance, in whom all electrocardiograms (repeated at intervals over periods of 4 and 6 years respectively) have confirmed the presence of permanent dissociation, have suffered little or no appreciable deterioration in cardiac efficiency with the passage of time. In these two individuals, as in others observed, it is true, for a shorter time, there is nothing to suggest that a fatal issue is appreciably nearer today than when the presence of complete/
### TABLE VI.

To show the relation of the probable duration of complete heart block to the age at onset.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>CASES ALIVE AT THIS DATE (OCTOBER 1932)</th>
<th>CASES NOW DEAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CASE NO.</td>
<td>AGE AT ONSET</td>
</tr>
<tr>
<td>Degenerative Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average of Degenerative Group</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>&quot;Toxic&quot; or Unknown Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>61</td>
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<tr>
<td>6</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>731</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>Average of &quot;Toxic&quot; group (omitting case 8)</td>
<td>51</td>
<td>6 yrs. 4 months</td>
</tr>
<tr>
<td>Intermittent</td>
<td></td>
<td>77</td>
</tr>
</tbody>
</table>

None are dead (Oct. 1932)
complete heart-block was first diagnosed with certainty. Had it been possible to continue observations on all thirteen cases until the fatal termination more reliable information on the exact course and symptomatology of the condition might be presented, and more crucial distinctions drawn between the two main groups. Nevertheless it would appear that in those individuals in whom permanent complete heart-block appears at a late age and as a manifestation of a diffuse cardio-sclerosis, the natural tendency to a fatal issue is not thereby appreciably hastened. As the block occurs in the later years of life in such individuals, its total duration is likely to be shorter in them than amongst those in whom it becomes established in middle life. It has already been shown that a considerable difference in age separated the two groups of cases, and it is therefore reasonable to suppose that other factors being equal, the duration of the heart-block in the two groups will also differ considerably.

The accompanying TABLE (NO. 6) has been arranged to show the relationship of age at onset to the duration of the heart-block. In the degenerative group 3 cases have died after block had been present/
present on the average for 19 months. These three were the oldest individuals in the group, the average at onset being 74 years. Two others are still alive at this date, their ages at the inception of block being 62 and 64 respectively. In the toxic group on the other hand, to this date only one of the patients have died (CASE 7 - intermittent block) yet the average duration amounts to 6 years 7 months. Excluding other factors the duration of complete heart-block is apparently regulated in large part by the age at onset. Block, the result of degenerative vascular lesions runs a relatively short course for the reason that the independent rhythm is developed in the last years of life. On the other hand, complete block of "toxic" or unknown etiology developing in middle life, is on the average likely to be of longer duration. This must mean that the damage done to the heart is more confined in its distribution than in the degenerative group and that the functional efficiency of the myocardium is not so grossly impaired. It would therefore appear that complete block, though it impose an added burden on the ventricular muscle, is less crippling to the younger person than might be anticipated, and is/
is not of itself a cause for early death.

Indeed it may be that in certain cases of, say, rheumatic heart disease with valvular defects, the presence of heart-block is perhaps of some small advantage in that it may serve to shield the ventricle from exercise stimulation. It is well known that in the presence of auricular fibrillation of rheumatic origin, congestive heart failure is prone to develop as a consequence of an excessive ventricular rate. This results from the abundance of effective stimuli showered upon the ventricles by the fibrillating auricles. Digitalis is of pre-eminent value in such a condition largely as a result of its remarkable powers of inducing some degree of block. The frequency of ventricular systole is thereby reduced, the effectiveness of systole increased, and by the prolongation of diastole adequate filling ensured. Coronary blood flow is augmented and myocardial nutrition improved. For these reasons there is perhaps some justification for the suggestion that, at least in those people, whose underlying cardiac lesion is one which predisposes to a high rate of beating, complete heart-block may help to conserve myocardial/
myocardial efficiency by its protective influence on the ventricular rate. Such an assumption is difficult of proof, but in so far as heart failure is due to the excessive formation and propagation of the impulse for ventricular contraction, so will complete heart-block be a means of conserving the powers of the ventricle. On the other hand, it is difficult to believe that those easy and spontaneous fluctuations in heart rate, which result from a labile sino-auricular pacemaker are not of advantage to the circulation as a whole. These spontaneous fluctuations, the ventricles in complete heart-block are in some measure denied, and the ventricular rate is dependent upon a relatively stable and dissociated centre of impulse formation. Myocardial efficiency then depends upon the degree of compensatory hypertrophy, the adequacy of the associated coronary blood flow, and the adaptability with which demands for an increased circulation rate are made good by alterations in the volume output per beat, if not by an actual increase in the rate of the independently beating ventricles.

The duration of life after the assumption of/
of complete heart-block will depend on many factors. The age of the patient, the nature of the lesion, the frequency of the Stokes-Adams attacks, the presence of valvular disease and the state of the myocardium are all of importance. As each and all may vary considerably in different individuals it is not possible to draw definite conclusions from the small number of cases under consideration. It is however noteworthy that complete heart-block is less crippling than commonly supposed, and is not in itself a cause for early death. HARRIS (97) in reporting a case of 28 years duration, lays emphasis on the fact that complete block is compatible with an normal active life and that the prognosis depends upon the degree of myocardial involvement.

It has no symptoms which differentiate it from those forms of heart disease with which it may be associated, unless fainting attacks of greater or less severity are included under this heading. The Stokes-Adams seizure is actually a symptom of cerebral anaemia a consequence of either ventricular arrest or excessive retardation in ventricular rate. All the patients, with one exception/
exception, gave a history of seizures of greater or less severity.

SUMMARY.

In its clinical aspects, complete heart-block occurs in at least two broad etiological groups. In the degenerative group, composed chiefly of elderly individuals, the duration from the time of inception of the dissociation until death is shorter than in those individuals in whom the condition first becomes established in middle life. The latter individuals suffer from heart-block at an age when the arterio-sclerotic process is less developed and block occurs often for no precise reason which clinical methods are capable of revealing. Such forms of block have been designated "toxic" or unknown. In these individuals the total duration of dissociation may be considerably longer than in the degenerative group. It would appear that complete heart-block is not in itself a cause for early death. After its development the subsequent course of the illness depends more upon the functional integrity of the myocardium as a whole than upon the mere dissociation of auricular and ventricular/
ventricular activity. As a disorder of rhythm it is much less crippling than might be supposed. The probability is that as block serves to shield the ventricle from excessive stimulation, so may it help to prevent the onset of congestive heart failure, in so far as that is associated with an unduly high auricular rate.

The symptoms of heart-block are not in themselves distinctive. Seizures of the Stokes-Adams type vary greatly in severity, even in the same individual at different times, and may or may not occur at the onset of dissociation or after the idio-ventricular rhythm has become established. No characteristic symptoms antedate the onset of complete heart-block. Its occurrence cannot be anticipated from a study of the earliest symptoms of cardiac distress.
THE PULSE RATE IN COMPLETE HEART-BLOCK.
THE PULSE RATE IN COMPLETE HEART BLOCK.

Of all the physical signs associated with complete heart block, without doubt the most striking and most easily elicited is the extremely slow rate of the pulse. While the symptoms associated with this condition vary greatly in their severity - and may indeed be so trifling as to be disregarded by the patient - yet even the most casual observer can hardly fail to have his interest aroused by a pulse rate of 40 to 30 or even less per minute.

It was this fact, amongst others, which particularly impressed the clinicians who first placed on record their observations on bradycardia. In 1761 Morgagni (161) wrote his classical account of his patient "Anastasio Poggi, a grave and worthy priest" whose pulse rate was 22 per minute. Adams (2) 1827, describing his case of bradycardia, wrote "An officer of the revenue, aged 68 years, of full habit of body, had for a long time been incapable of any exertion as he was subject to oppression of his breathing and continued cough. In May 1819, in conjunction with his ordinary medical attendant Mr. Duggan, I saw this gentleman, he was just then recovering from an apoplectic attack, which/
which had suddenly seized him three days before. He was well enough to be about his house, and even to go out. But he was oppressed by stupor, having a constant disposition to sleep, and still a very troublesome cough. What most attracted my attention was the irregularity of his breathing, and remarkable slowness of the pulse, which generally ranged at the rate of 30 in a minute". (The italics are mine). Likewise Stokes, writing nineteen years after Adams, describes in greater detail similar cases with and without apoplectic attacks.

**The Rate and Range of the Pulse in Health.**

Before considering the pulse rate in complete heart block, it is well to review briefly the rate and range of the heart rate in the healthy individual. It is not too much to say that if there be one characteristic of the pulse in health it is its variability in rate. The pulse rate like the tides, ebbing and flowing, now rising now falling, has for its very nature an incessant vacillation. A minute's record of the pulse rate is but an instant on a waxing or waning curve. This aspect of the heart's activity is often not sufficiently/
sufficiently appreciated, but is beautifully illustrated by the charts published in the monograph of BOAS and GOLDSCHMIDT. With the onset of sleep, these authors have shown, that the rate diminishes progressively for about six hours, to be followed by an oscillation about a low level. A gradual rise in rate begins about an hour or so before awakening. Even apart from this general trend, the curves of heart rate show minor fluctuations, now higher now lower not unlike the succession of water-marks left by the waves on the seashore as the tide ebbs or flows. These minor variations in rate may perhaps be an expression of fluctuating vagal and accelerator tone, and serve to indicate the ceaseless activity of the autonomic nervous system. Realising that it is natural for the healthy heart to vary in rate, it can be said with BENEDICT and CARPENTER (12) that "there is no normal pulse rate which can be accurately referred to all cases even with the same individual". BOAS and GOLDSCHMIDT (14) sum up the position in the following words - "The heart rate fluctuates from moment to moment in response to manifold intrinsic and extrinsic stimuli, indeed the frequency may be considered a most sensitive gauge of the physiological processes of the body. Exercise and rest, alterations in environmental temperature and in altitude, various bodily functions, such as/
as digestion and muscular activity, the emotions, and even thought, are accompanied by changes in rate. Recognising the variability of the rate, these authors found that, during a day of ordinary activity, the average maximum rate was, for the male subjects 111.8 per minute and for the females 120.6, whereas the minimum sleeping rate averaged 52.7 and 57.7 respectively. In other words, the heart rate ranged in rate by approximately 60 beats per minute for either sex.

So sensitive is the controlling mechanism of the heart in the healthy, that from day to day in the same individual some variation occurs in the rate even under similar conditions of rest and activity. Nevertheless, for each individual, there is broadly speaking, an average range of rate under standard conditions. BOAS and GOLDSCHMIDT found that those people who, when awake had a relatively high heart rate, likewise tended to have high maximum sleeping rates, and vice versa. In other words, there appears to be some justification for the belief that in a given person, there is a more or less average pulse rate within a certain range peculiar to the individual.
THE IDIO-VENTRICULAR RATE UNDER CONDITIONS OF BODILY REST.

In virtue of the absence of a functional link between the upper and lower chambers of the heart, complete heart block yields an admirable opportunity to study in man the independent response of auricles and ventricles to a uniform set of conditions. For the moment, attention is directed to the effect of a state of prolonged bodily rest on the rate of the dissociated chambers of the heart. This yields results which are not only of some interest and importance in themselves, but which must be appreciated in order to gauge the influence of artificial stimulation, whether induced by drugs, muscular exertion, or other means.

The facts to be presented indicate that, in contrast to the opinion of many writers on complete heart-block, the idio-ventricular rate does vary, sometimes considerably, even under uniform conditions of bodily rest. It has been shown above that this is also true of the heart rate in health. VACQUEZ (214) writing in 1924 makes the following statement, "Another peculiarity of complete heart-block which we were the first to describe in 1889, and the importance of which we have emphasised --- consists/
consists in the invariability of the bradycardia and the impossibility of altering it by the influences which ordinarily accelerate or retard the pulse. The invariability has been recognised by all writers. In this country other authorities have been less dogmatic. MACKENZIE'S (150) experience led him to conclude that "circumstances that usually excite the heart to rapid action have little effect upon the independent ventricular rhythm. COWAN and RITCHIE (41) conclude that "the rate may vary slightly from time to time, but is little influenced by emotion, exercise, fever, etc. which produce notable effects upon a normal heart".

The fact that the ventricular rate does vary even under uniform conditions is based on a careful study of the behaviour of the slowly beating ventricles in eleven individuals. (Cases 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13). The influence of rest, sleep, and activity form an interesting contrast with the results already described for healthy people.
METHODS EMPLOYED IN ESTIMATING THE AURICULAR AND VENTRICULAR RATES DURING BODILY REST.

In estimating the resting rates of auricles and ventricles, electrocardiograms were recorded two or three hours after a light breakfast. The subject was brought from his bed in a wheeled-chair to the electrocardiograph and allowed to rest comfortably on a couch in a position of maximum ease, for an hour or more, at the end of which time, tracings of the heart's action were secured. Frequent visits had previously rendered him familiar with the somewhat strange surroundings of the laboratory and during his stay, quiet was maintained and strangers excluded. A fall in blood-pressure to uniform readings was taken to indicate that an approximately steady level of nervous and metabolic activity had been reached. Three electrocardiograms at intervals of a few minutes, were then recorded unknown to the patient. This procedure was repeated with each individual on several occasions, about the same hour, on different days. The auricular and ventricular rates were then calculated from the electrocardiograms, and averaged for each attendance of the individual. The resulting figures obtained from repeated/
<table>
<thead>
<tr>
<th>CASE NO. &amp; INITS.</th>
<th>AUR. VENT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURICULAR VENTRICULAR</td>
<td>AURICULAR VENTRICULAR</td>
</tr>
<tr>
<td>Max. aur. Rate</td>
<td>Min. aur. Rate</td>
</tr>
<tr>
<td>81.8</td>
<td>69.0</td>
</tr>
<tr>
<td>78.8</td>
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<tr>
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</tr>
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</tr>
<tr>
<td>24.9</td>
<td>27.6</td>
</tr>
</tbody>
</table>

**Table VII (contd.)**

To show the general trend and particular rates of different cases of auricular fibrillation, Table VII is arranged to show the percentage of resting auricular rate and the percentage of resting ventricular rate, showing the auricular rate as a percentage of the ventricular rate. The average rate is reported as the percentage of the resting auricular rate as a percentage of the resting ventricular rate. The average rate is calculated as the percentage of the resting auricular rate as a percentage of the resting ventricular rate.
repeated determinates are shown in the column headed "Average resting rate" in TABLE VII. Under resting conditions, the average auricular rate for the series was 72.2 and the ventricular 34.3 per minute.

THE VENTRICULAR AND AURICULAR RANGES UNDER UNIFORM CONDITIONS OF REST.

A brief study of the rates on different days, but under similar conditions is sufficient to show that the ventricular rate is not constant even in the same individual. For example, in Case 1, the average of separate determination on ten different days was 24.9, with a maximum of 29.2 and a minimum of 21.0, yielding an available ventricular range under resting conditions of 8.2 beats per minute. Under similar conditions, the auricular range is 12.8 with an average reading of 74.9 contractions per minute. Of the whole series of eleven cases, studied as far as possible under similar conditions, the maximum ventricular rate recorded was 55.2 (Case 12) and the minimum 21.0 (Case 1). The maximum ventricular range at rest was 10.7 (Case 11 - 6 determination) and the minimum 0.3 (Case 10 - 3 determinations). The ventricular rate under approximately/
approximately uniform conditions of bodily rest is not a fixed quantity. It varies from day to day, and also, even more considerably in different individuals.

By considering the maximum and minimum rates recorded for each individual, it is possible to form an estimate of the extent of the spontaneous fluctuations. This value which is entitled the "Ventricular range" is entered for both the auricles and the ventricles in Table VII. It is, of course, only an approximate quantity and forms at best, only a rough estimate of the natural fluctuation in rate, for the number of determinations varied in the different subjects, none of whom was, strictly speaking, in the basal state of metabolism. It is however justifiable to refer to the observation of Boas and Goldschmidt (14) that, the heart rate at absolute rest two or three hours after a light meal, is frequently considerably less than the basal rate recorded for the same individual. By consulting the table it is evident, as pointed out above, that while the auricular range varied from 18.2 to 6.0 beats per minute, the ventricular range varied from 10.7 to 0.3.

By plotting the resting auricular range against the corresponding ventricular, it becomes evident/
evident that a relation exists between the two. The available figures are at best only approximate values but in general, it would appear that under fairly uniform conditions of bodily rest, a high ventricular range exists in association with a high auricular and vice versa. The fact that even after a prolonged bodily rest the ventricles do exhibit a fluctuation in rate is sufficient to suggest that with appropriate stimulation, it might be possible to estimate the maximum ventricular range. Thus after as great physical exertion as the individual feels capable of undertaking, the ventricular (and auricular) rates may be greatly increased. By determining the maximum ventricular range, and comparing it with the auricular, more reliable figures for the respective ranges are obtained. This aspect of the relationship between auricular and ventricular ranges is discussed more fully on page 112.

It is sufficient for our purpose at the moment to consider the variations in rate observed during bodily rest. There is every reason to believe that all the usual influences tending to augment the heart rate, become gradually reduced in intensity during a period of subdued nervous tension associated with a prolonged rest and quietness. It is true that some/
some of these, such as the individual's emotional tone and train of thought at the moment, are out with experimental control. Other influences, for instance the important metabolic activities, though somewhat reduced, must have varied slightly from case to case and even in the same individual on the different occasions on which records of the heart's rate were made. That the actual auricular range was uniformly greater than the corresponding ventricular, may be interpreted in a number of ways.

It may be, for instance, that the usual stimulants to the heart rate, were delivered with unequal intensity to the upper and lower chambers of the heart. Under resting conditions it is well known that the rate of stimulus production is largely controlled by the balance struck between vagal inhibitory influences on the one hand, and sympathetic accelerator on the other. The auricle receives a rich vagal supply and it may be that release from inhibition acts more powerfully on the sino-auricular node, than elsewhere. Nevertheless, the fact that the auricular fluctuations in rate are accompanied by a similar but smaller ventricular variation, indicates that the idio-ventricular rate is capable of responding to the common stimulus. In the case of blood-borne hormones,
hormones, there is every reason to suppose that the specialised tissues received at least a sufficient blood supply to meet their requirements in a resting state. Impulse production is an inherent property of the specialised tissues. It seems reasonable to suppose that in complete heart-block during states of subdued bodily activity, both rhythmic centres, the one is the S-A node, and the other situated somewhere in the bundle or its branches below the level of the lesion producing the dissociation, will receive an equal concentration of the stimulus to contraction, assuming the rate of blood flow through the centres to be equally distributed. As the response varies in the two situations, (the auricular range being greater than the ventricular), the explanation must then lie in an inherent difference in rhythmicity. Perhaps this is only one aspect of the truth.

Suppose for instance, that little or no difference in rate separated auricles and ventricles and that complete heart-block was present. This implies a spontaneous rhythmicity of about equal degree in the two controlling centres. It would be natural to expect that under such conditions the range in rate of auricles and ventricles would be similar. As shown in the table, the average resting auricular rate/
rate was 72.2 with a resting range of 10.9 and the average ventricular rate was 34.3 with a resting range of 4.7. Assuming a complete dissociation with an A/V ratio of 100/100 then, on the basis of the averages quoted, the available ranges would be 15.1 per cent and 13.7 per cent for auricles and ventricles respectively. In other words it would appear that the observed range in the rate of the ventricles is on the average proportionate to that observed in auricles. Under resting conditions, the variations in rate in auricles and ventricles are on the average apparently of the same order of magnitude. Individual exceptions occur, for in certain of the cases studied, the percentage range of ventricular rate actually exceeded that of the auricular, but on the average the auricular and ventricular ranges are of a similar order of magnitude under conditions of bodily rest. It will be shown later, as indicated by a study of the maximum ranges (in contrast to these resting ranges) that this relationship is more fictitious than real.

SUMMARY/
SUMMARY

We therefore conclude that the ventricular rate in complete heart-block is not a fixed quantity, even under uniform conditions of bodily rest.

Further, the fluctuations in ventricular rate during uniform conditions of bodily rest, are on the average of the same order of magnitude as those occurring in the auricle under similar circumstances.

Individual differences occur. In certain subjects the ventricles are actually more mobile and may exhibit a greater percentage range of activity than do the auricles under similar conditions of rest.
THE RELATIONSHIP between VENTRICULAR and AURICULAR RATES in COMPLETE HEART-BLOCK.
All cases - degenerative and "toxic".

\[
y = 0.51x + 3.08
\]

\[
\frac{\sum xy}{n} = +.642
\]
THE RELATIONSHIP between VENTRICULAR and AURICULAR RATES in COMPLETE HEART-BLOCK.

The fact, demonstrated in previous pages that in general the percentage range of auricular and ventricular rates is similar under conditions of bodily rest, is suggestive that other relationships may exist. If their fluctuations in rate be on the average of the same order of magnitude, it is conceivable that likewise the actual resting auricular and ventricular rates may bear some definite proportion the one to the other. The accompanying GRAPH, No. 2 in which corresponding auricular and ventricular rates, have been plotted against each other, demonstrates that some relationship does in fact exist.

Excluding the two cases in which auricular fibrillation accompanied complete heart-block, 48 observations of the corresponding auricular and ventricular rates in nine individuals are recorded in TABLE 7.

Applying the law of least squares, where:

\[ y = \text{the ventricular rate} \]
\[ x = \text{the auricular rate} \]

and \[ a = \frac{\sum(x) \times \sum(xy) - \sum(x^2) \times \sum(y)}{[\sum(x)]^2 - n \sum(x^2)} \]

and \[ b = \frac{\sum(x) \times \sum(y) - n \sum(xy)}{[\sum(x)]^2 - n \sum(x^2)} \]

then/
then from the straight line formula, \( y = bx + a \), there is obtained the regression line \( v = v \) as entered on the chart from which a theoretical value for the ventricular rate at a given auricular, may be read off. The actual values for \( a \) and \( b \) are found to be respectively 3.03 and 0.51. Substituting we have \( y = 0.51x + 3.03 \).

Inspection of the chart reveals a considerable "scatter" over a range of auricular rate extending from 48 to 98 per minute. Applying the test of correlation where \( \sigma = \) the standard deviation,

\[
\sigma_x = \sqrt{\frac{(x^2) - (\bar{x})^2}{n}}
\]

\[
\sigma_y = \sqrt{\frac{(y^2) - (\bar{y})^2}{n}}
\]

and where \( \rho = \) coefficient of correlation then

\[
\rho_{xy} = \frac{\bar{xy} - (\bar{x} \cdot \bar{y})}{\sigma_x \cdot \sigma_y}
\]

It is found that the correlation between the resting auricular and ventricular rates is of fairly high degree. The calculated value is +.642. Perfect positive agreement is 1.000 and absence of correlation is zero. It is therefore established that, not only are the fluctuations in rate of auricles and ventricles of a similar order, but that under resting conditions the actual rates are closely related.

Reference/
Degenerative cases.

\[ y = 0.53x + 3.63 \]

\[ \text{Sxy} = +0.9012 \]
Reference has already been made to a suggested clinical classification of cases of complete heart block. It was found possible to divide the cases into two broad groups a degenerative, and a "toxic" or unknown variety. The degenerative were on the average older individuals and the block occurred apparently as a manifestation of a more or less generalised cardiac fibrosis. Each group had certain features in common, the "toxic" being composed of a variety of cases of a mixed type, as heterogeneous in their etiology as in their functional capacity. The amount of "scatter" depicted in the chart of the whole series, suggested that probably by replotting the two groups of cases separately a more perfect correlation between auricular and ventricular rates might be demonstrated for one or other.

In GRAPH 3 the observed auricular and corresponding ventricular rates of the four degenerative cases (Cases No. 2, 4, 5, and 11) have been plotted. A very high degree of correlation is found to exist for this group of individuals, the coefficient being +.9012. The regression line V-V from which the ventricular rate (y) may be calculated for a given auricular rate (x) is drawn to the calculated value $y = 5.3x + 3.63$. 

GRAPH/
GRAPH 3b is composed of the readings obtained from the individuals included on a basis of clinical classification in the "toxic" or unknown group. A glance at the plottings is sufficient to demonstrate a sharp contrast when this chart is compared with that of the previous group. The "scatter" is over a greater range and the regression line V-V, drawn to the calculated values $y = 0.48x + 3.02$, is of necessity somewhat isolated from the surrounding readings. In GRAPH 3a on the other hand the "scatter" is less, and the readings are more compact and closely associated with the regression line.

In other words the degree of dispersion is greater in the toxic than in the degenerative group. Furthermore, the coefficient of correlation, +.497, is less perfect in the "toxic" than in the degenerative group.

The mathematical relationships may be compared in the following Table:

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF CASES.</th>
<th>CHART</th>
<th>COEFFICIENT OF CORRELATION</th>
<th>CALCULATED VALUE of y. (y = bx + a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole series.</td>
<td>9</td>
<td>2</td>
<td>+.6420</td>
<td>0.51x + 3.08</td>
</tr>
<tr>
<td>Degenerative Group.</td>
<td>4</td>
<td>3a</td>
<td>+.9012</td>
<td>0.53x + 3.63</td>
</tr>
<tr>
<td>&quot;Toxic&quot; Group.</td>
<td>5</td>
<td>3b</td>
<td>+.4970</td>
<td>0.48x + 3.02</td>
</tr>
</tbody>
</table>

SUMMARY/
The mathematical analysis of the available data demonstrates that a fair degree of positive correlation exists between the auricular and ventricular rates under resting conditions for all the cases. Moreover, this treatment indicates a further justification for the proposed clinical subdivision of the cases. It is found that a very high degree of correlation exists between the auricular and ventricular rates of the homogeneous degenerative group. As might be expected, the agreement found to exist in the "toxic" group - composed of a variety of dissimilar cases - is less perfect. The relatively wide degree of dispersion in this group indicates a more labile regulation of rhythms.

Despite the clinical subdivision a close agreement exists for calculated values for $y$ in the two groups, and indeed also for the whole series. It is evident from the lie of the regression line (drawn to $y = .51x + 3.08$) that, under conditions of bodily rest, the optimum ventricular rate in complete heart-block is rather less than half a given auricular rate.
THE RELATION OF VENTRICULAR RATE TO CERTAIN BODILY MEASUREMENTS.
<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>NAME</th>
<th>AGE</th>
<th>WEIGHT</th>
<th>HEIGHT</th>
<th>VENTRICULAR RATE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mrs. T.</td>
<td>21.0</td>
<td>8.2</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>W.W.</td>
<td>33.8</td>
<td>3.0</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>D.C.</td>
<td>42.8</td>
<td>4.3</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>W.T.</td>
<td>23.6</td>
<td>1.5</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>A.H.</td>
<td>28.5</td>
<td>5.4</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>J.W.</td>
<td>29.0</td>
<td>3.5</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>J.B.</td>
<td>33.3</td>
<td>3.3</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Mrs. D.</td>
<td>40.3</td>
<td>10.7</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>J.D.</td>
<td>46.6</td>
<td>8.6</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Mrs. H.</td>
<td>39.8</td>
<td>2.8</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SURFACE AREA SQ. M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.640</td>
</tr>
<tr>
<td>1.725</td>
</tr>
<tr>
<td>1.361</td>
</tr>
<tr>
<td>1.831</td>
</tr>
<tr>
<td>2.000</td>
</tr>
<tr>
<td>1.572</td>
</tr>
<tr>
<td>1.805</td>
</tr>
<tr>
<td>1.670</td>
</tr>
<tr>
<td>1.729</td>
</tr>
<tr>
<td>1.521</td>
</tr>
<tr>
<td>1.860</td>
</tr>
</tbody>
</table>
THE RELATION OF VENTRICULAR RATE TO CERTAIN BODILY MEASUREMENTS.

It has been shown above that, under conditions of bodily rest, the auricles and ventricles, though dissociated functionally, pursue a fairly steady rate in relation one to the other, and that such fluctuations as do occur are on the average of the same order of magnitude for each chamber of the heart. While this is true, yet each sufferer from complete heart-block presents an average ventricular rate more or less peculiar to the individual himself. To demonstrate this phenomenon the essential features have been incorporated in the accompanying Table IX.

For our present purposes, attention is particularly directed to the first two columns of figures in which are set out the minimum and maximum ventricular rates recorded under conditions of bodily rest approximately three hours after a light breakfast. The peculiar feature is that for each individual the rate of the ventricles is confined to a relatively small range. For instance in Case 1, the ventricular rate varied from 21.0 to 29.2 per minute in Case 5 from 30.6 to 36.0 and in Case/
Case 11. from 40.3 to 51.0.

This fact suggests that the idio-ventricular centre which governs the rate of the beating ventricles is set within relatively narrow limits at an optimum pace peculiar to the individual. What explanation can be offered for the fact that under these conditions of prolonged bodily rest the rate of the independently beating ventricles in Case 13 never fell below 39.8, whereas in Case 1 they did not exceed 29.2? As regards their functional efficiency both of these women (Cases 1 and 13) were remarkably fit. They were able to do all their housework, and walk long distances with little or no discomfort. Neither had ever presented evidence of congestive heart failure, and yet the actual ranges in ventricular rate differed in striking degree.

It was thought that, as the available figures for the whole series extend over a fairly wide range (from 21.0 to 46.6 for minimum rates) it might be possible to correlate the idio-ventricular rate with some structural peculiarity of the individual - e.g. height, weight or surface area. In this connection it is instructive to turn for a moment to the relationship of the healthy pulse rate to anatomical build.
THE RELATION of the HEART RATE in the HEALTHY to BODILY MEASUREMENT.

In the past many attempts have been made to correlate pulse rate with bodily structure. Due credit should be given to BRYAN ROBINSON for his endeavour in 1732 to solve a problem which still remains unsolved. Robinson was a man before his time and in his remarkable book "A Treatise on the Animal Economy" he writes (184). "I took the pulses in a minute and measured the lengths of a great number of bodies: I took the pulses when the bodies were sitting, that they all might be situated alike with respect to the Horizon: and in the morning before breakfast, that their hearts might be as free as possible from the influences of all disturbing causes: And when I had a very large stock of observations, I took the mean of the pulses, each mean from a considerable number of bodies of the same length, and found those means to be nearly as the biquadrate roots of the cubes of the lengths of the bodies inversely."

Robinson apparently took as his standards a height of 72 inches with a pulse rate of 65 under approximately basal conditions. To calculate the/
the theoretical rate in a man of say, 5 feet (60 inches) simple proportion is used inversely:—

\[ \frac{\sqrt{72.5}}{65} : x = \frac{\sqrt{60.5}}{21.558} : x \]

\[ \therefore \quad \frac{24.717}{65} : 21.558 : x \]

\[ \therefore \quad x = \frac{24.717 \times 65}{21.558} = 74.52 \]

According to this method, a height of 5 feet will be accompanied by a more or less basal pulse rate of 74.5. FALCONER (66) compared the theoretical and observed rates over a wide range of heights, and found "some foundation for this opinion of Dr. Robinson" particularly as the agreement was reasonably good in the middle of the series but less satisfactory at either extreme. Actually the theoretical values calculated by Robinson's method are at a rate six or eight beats in excess of the observed.

For our present purposes it is not necessary to examine the method further. While Robinson's attempt to correlate the rate of the pulse with the height of the individual has escaped the recognition it deserves, modern studies have shown that the pulse rate is not merely a simple function of height. Where individual variations are known to be great, and where a biological problem, such as this, is complicated/
complicated by a multiplicity of interacting factors, a clear cut agreement between theoretical and observed rates over a wide range can hardly be expected. Even as late as 1900, LEONARD HILL (109) only goes so far as to admit that "tall men have as a rule slower rates than short men". More recently, HARRIS and BENEDICT (96) employing the data derived from a large series of basal metabolic duties could find no relationship between stature and heart rate in adult men and women, nor indeed between body weight and heart rate. They were, however, able to demonstrate a slight but significant correlation between the basal rate of the pulse and the metabolism at the moment. As basal metabolism bears a close relationship to the surface area of the body it is therefore possible to anticipate a slight degree of correlation between the surface area of the individual and the heart rate under resting conditions.

Incidentally surface area (and hence metabolism) is related to the body weight, but as pointed out above, Harris and Benedict were unable to demonstrate a correlation between pulse rate and weight, at least within the range of weight studied./*
studied. CLARK (29) has shown that for animals ranging in size from a mouse to an ox the pulse rate does not run parallel to the metabolic rate and that this is due to differences in the proportions between the heart weights and body weights. It therefore follows that, if it were possible to measure accurately the heart-ratio (i.e. the heart weight as a percentage of body weight) and knowing the basal metabolic rate of the individual, it ought to be possible to calculate a theoretical pulse rate with a greater degree of assurance for the normal individual at least under basal conditions. BUCHANAN (22) has shown that, in mammals and birds, the

\[ \text{Pulse rate} = K \frac{\text{metabolic rate}}{\text{heart ratio}} \]

where \( K = 1400 \). This formula yields satisfactory results over a very wide range in the animal kingdom.

In man the heart-ratio probably varies considerably in different individuals, as is suggested by even a superficial acquaintance with the post-mortem room. Figures, quoted by HESSE (107) give a range of heart-ratio varying from 0.613 to 0.535/
0.535 for men of 47 and 68 kilos respectively.

There is, unfortunately no reliable method of assessing the heart-ratio during life, although some approximation to the truth might be derived from x-ray studies of the cardiac area. Radiological observations on the precise size of the heart, even by modern methods, are liable to be fallacious. With a technique designed to minimise the distortion produced by the divergent rays, the error in assessing the heart size in the transverse diameter may vary from 0.5 to 1.5 centimetres (4 to 12 per cent) even with a distance of 2 metres between the chest and the x-ray tube (224). Obviously the error is greatly enhanced when measurements are applied to the area of the cardiac shadow. Practical experience has taught that it is often difficult to outline and measure the heart shadow with much accuracy. Furthermore, the changes in heart-area, which are associated with respiration, are sometimes very great and there is no doubt that the antero-posterior area of the heart, as recorded on an x-ray plate, varies very greatly in shape and position in different healthy individuals of similar build. For these reasons it may be doubted if the x-ray determination of the cardiac area, reflects/
reflects with much accuracy the heart-ratio for man. It is therefore not possible to foretell with accuracy the basal rate of the pulse in man. The surface area of the individual is but one factor. Individual variations will not permit of detailed analysis and the heart-ratio is at best an approximation. This conclusion is supported by the work of BOAS and GOLDSCHMIDT (14) who were unable to demonstrate any constant relationship between the basal rate of the pulse with age, height, sitting height, weight, chest circumference, or surface area of the body in a group of healthy individuals.

It is probably true that the degree of vagal and sympathetic tone, which varies from individual to individual even in health, is an important factor in regulating the heart rate. This factor cannot be measured with any degree of accuracy. On the other hand, if an organ, such as the heart be isolated from its nerve supply, it exhibits a spontaneous rhythmic activity. CLARK (29) has shown from the records of 84 experiments on the heart-lung preparation by Starling and his co-workers, that there is a well marked correlation between/
between the body weight and the frequency of the isolated heart in dogs of varying size.

We have seen that the actual range in ventricular rate in complete heart-block is relatively small and that the spontaneous rhythm of the ventricles is less liable than that of the auricles. VAQUEZ (214) believes that the vagus and the sympathetic, are as a general rule incapable of influencing the autonomic ventricular rhythm in complete heart-block. This implies that in the presence of complete heart-block, while the auricles are capable of responding to vagal and sympathetic influences, the ventricles are functionally isolated from nervous control. "A study of isolated tissues, which show rhythmic activity, proves that the frequency of these tissues, which are deprived of all nervous control, varies in a manner very similar to the variations observed in the metabolic rate" (29).

It is therefore of some interest to compare the ventricular rate in complete heart-block with bodily measurements, particularly in relation to the metabolic rate or surface area of the individual. We have seen that there is in health a slight/
slight but significant correlation between metabolism and heart rate. It it be true that the ventricular rate in complete heart-block does not reflect nervous tone in the sympathetic and parasympathetic systems then, other factors being equal, it ought to be possible to demonstrate a more perfect degree of correlation between the ventricular rate and the metabolism, than between the auricular rate and metabolism.

**VENTRICULAR RATE in RELATION to SURFACE AREA.**

It has been shown that in man, the metabolic exchange is directly related to the surface area of the body under basal conditions. In this series of cases the actual metabolic rate was not estimated but on purely clinical grounds there was no reason to suspect any departure from the normal, except in one individual (Case 11) who presented some slight evidence of a mild degree of myxoedema. The cases are comparable in a general way in that each was studied after a prolonged rest in the recumbent position about two to three hours after a light meal. Auricular and ventricular rates were recorded synchronously.
\[ y(\text{auricles}) = 5.88 - 0.286x \]
\[ r_{xy} = -0.38. \]

\[ y(\text{ventricles}) = 5.19 - 0.18x \]
\[ r_{xy} = -0.236. \]

Heart Rate per minute

Ventricular

Surface Area (x) in sq. cm.

1500 1600 1700 1800 1900 2000 2100 2200
On subjecting the data presented in TABLE IX to mathematical analysis, it is found that only a slight inverse correlation exists between the ventricular rate and the surface area of the body. The coefficient of correlation is -0.236. The regression line V-V drawn to the equation $y = 5.19 - 0.18x$ represents the value for the ventricular rate ($y$) where the $x$ is a given surface area. This is shown in Chart 4. Such a poor agreement over the range studied becomes of more significance when it is compared with that found to exist between the auricular rates and the surface areas of the same individuals. It is found that the coefficient of correlation for this group (auricular rate and surface area) is -0.387, rather better than that existing between the ventricular rate and the surface area. The line a-a, representing the calculated auricular rate ($y$) from the equation $y = 5.88 - 0.286x$, is also entered in Chart 4. Comparing the two regression lines it can be seen that though they are not parallel, yet higher auricular and ventricular rates tend to accompany the lower surfaces areas and vice versa.

It is therefore permissible to conclude that,
that, in this group of cases, the presence of complete heart-block does not enhance the slight but significant correlation known to exist under uniform conditions between ventricular rate and surface area. It has been shown that the correlation between auricular rate and surface area is a shade the better of the two. We are therefore unable to substantiate the view, which has been suggested above, that a more perfect correlation might exist between the idio-ventricular rate and the surface area. This does not disprove the supposition of Vaquez, that the ventricles are isolated from nervous control. It merely fails to confirm such a proposition.

VENTRICULAR RATE in RELATION to BODY WEIGHT.

In this series of observations the body weight recorded was that registered when the patient was first admitted to the ward a few days before regular electrocardiographic examinations of the heart were commenced. A few patients lost a little weight during the days which elapsed while they were under detailed observation. Others gained a few pounds. The initial weight has been selected as a uniform one throughout this series of individuals.
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individuals. By the same methods of mathematical analysis it is found that an insignificant degree of correlation exists between body weight and the ventricular frequency. The coefficient is +0.1003, so low as to be negligible. As regards auricular rate and body weight, the coefficient is a trifle higher and inverse, being -0.1170. It may therefore be concluded that the ventricular and auricular rates in complete heart-block are to all intents and purposes unrelated to the body weight in this series of individuals.

VENTRICULAR RATE in RELATION to BODILY STATURE.

As a further test, the heart rates recorded under the same resting conditions have been compared with the corresponding heights. The individuals studied were all adults, the extremes of height being 61 and 71 inches. On plotting the data presented in TABLE IX, a distinct relationship to height both for auricular and ventricular rates, becomes at once evident. Mathematical analysis demonstrates that a substantial degree of correlation exists between the ventricular rate and the height of the individual, and that even better correlation/
\[ y(\text{auricles}) = 6.13 - 2.58x \]
\[ r_{xy} = -0.7890. \]
\[ y(\text{ventricles}) = 5.56 - 1.73x \]
\[ r_{xy} = -0.5840. \]
correlation exists in relation to auricular rate. The coefficients of correlation are, \(-0.584\) for the ventricles and \(-0.789\) for the auricles. The corresponding regression lines, V-V and a-a, drawn to the equations \(y\) (ventricles) = \(5.56 - 1.73x\) and \(y\) (auricles) = \(6.13 - 2.58x\), are presented in Chart 5.

This result is anomalous. To find such a substantial degree of correlation between height and heart rates in complete heart-block must occasion some surprise in view of the insignificant agreement known to exist in health. WHITING (227) found a coefficient of correlation of only \(-0.078\) for pulse rate and stature amongst a prison population. She concludes from her study that such a physiological variate as pulse rate is a peculiar property of the individual, modified only slightly by age and only moderately linked with other bodily functions. It may well be that such a state of affairs becomes altered by the presence of disease, it is difficult to understand why the rate of the diseased heart in the adult should vary inversely with stature. The figures shown above indicate that such a relationship does exist. The group of cases is however a small one and the data scanty to subject to mathematical/
mathematical analysis. It would appear desirable to test a larger group of individuals in whom the heart rate was influenced by the presence of structural cardiac disease. Nevertheless there is a closer correlation between the auricular rate and height than between the ventricular rate and height in these cases of complete heart-block.

For convenience the coefficients or correlation between heart rates and other bodily variates are grouped in the accompanying TABLE X.

<table>
<thead>
<tr>
<th>VARIATES</th>
<th>COEFFICIENT OF CORRELATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular Rate and Surface Area</td>
<td>-0.236</td>
</tr>
<tr>
<td>Auricular Rate and Surface Area</td>
<td>-0.387</td>
</tr>
<tr>
<td>Ventricular Rate and Body Weight</td>
<td>+0.100</td>
</tr>
<tr>
<td>Auricular Rate and Body Weight</td>
<td>-0.117</td>
</tr>
<tr>
<td>Ventricular Rate and Height</td>
<td>-0.584</td>
</tr>
<tr>
<td>Auricular Rate and Height</td>
<td>-0.789</td>
</tr>
</tbody>
</table>

**TABLE X** to show the relation between ventricular rate and certain bodily variates.
RELATION of VENTRICULAR RATE to OTHER FACTORS.

The total number of cases being relatively small it is not permissible to draw definite conclusions regarding the influence of sex on the idioventricular rate. Of the thirteen cases, forming the basis of the present study, four were females (Cases 1, 10, 11 and 13). In two of the male subjects (Cases 7 & 9) it was not possible to secure appropriate conditions of observation uniform with the others. They have not been included. Observations are therefore restricted to four females and seven males. If the average rates of these two small groups may be compared no significant distinction exists between the sexes. The average minimum resting rate for the males is 32.3 and for the females 31.8. The maximum and minimum rates (the difference representing the observed range) are shown in the accompanying TABLE XI.

FEMALES /
### FEMALES.

<table>
<thead>
<tr>
<th></th>
<th>MIN. RATES</th>
<th>MIN. of SERIES</th>
<th>MAX. of SERIES</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mrs. T</td>
<td>21.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mrs. C</td>
<td>26.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mrs. D</td>
<td>40.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mrs. H</td>
<td>39.8</td>
<td>21.0</td>
<td>40.0</td>
<td>19.0</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>31.8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MALES.

<table>
<thead>
<tr>
<th></th>
<th>MIN. RATES</th>
<th>MIN. of SERIES</th>
<th>MAX. of SERIES</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.W.</td>
<td>33.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.C.</td>
<td>38.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W.T.</td>
<td>22.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.H.</td>
<td>30.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. Whd.</td>
<td>25.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.B.</td>
<td>29.7</td>
<td>22.1</td>
<td>46.6</td>
<td>24.5</td>
</tr>
<tr>
<td>J.D.</td>
<td>46.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>32.3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The figures above are presented for what they are worth, realising that the groups are unequal in numbers and that the totals are small. There is no significant difference between the sexes in this group of cases of complete heart-block. On the other hand there has been a tradition that in health women tend to exhibit a faster heart rate than men under similar conditions of observation. VOLKMANN (216)
(216) however asserts that no difference can be detected when men and women of similar stature are compared. As has been pointed out above, however, height plays an insignificant role in determining the heart rate of the adult in health. If a difference in heart rate between the sexes does exist it is more probably related to a greater reflex excitability of the heart (14) and some variation in the degree of vagal and sympathetic tone. It has been shown above that, strangely enough in complete heart-block a definite correlation between both auricular and ventricular rates and height does appear to exist. The number of cases in this series is too small to allow of a study of the influence of sex on the relationship between rate and stature in complete block.

The figures at our disposal show no relationship to exist between the age of the individual and the minimum resting rate of the ventricles.

SUMMARY.
A review of the literature indicates that in health, individual variations are so great as to prevent the establishment of definite criteria on which to formulate a standard pulse rate for different individuals under uniform conditions. In this respect the individual is largely a law unto himself. WHITING (227) has tersely expressed this aspect of physiological activity when she says "the individual is such not only by his existence in space but by his manner of existing in time". In the healthy, numerous workers have shown that with the exception of metabolic rate and hence the surface area no significant correlation exists between heart rate and various anatomical measurements. Even in association with surface area the relationship is but slight.

In cases of complete heart-block the ventricle beats at a fairly constant rate peculiar to the individual. In some the rate is more or less in the neighbourhood of 23 per minute, in others about 27, and others again have rates from day to day as high as 35 or even 50. An attempt has been made/
made to solve the problem of individual variations in ventricular rate on a basis of peculiar bodily features.

By statistical analysis minimum ventricular and auricular rates under uniform conditions of bodily rest have been compared with certain anatomical measurements. It has been found that no significant degree of correlation exists, between body weight and the rate of either the auricles or the ventricles.

On the other hand amongst these cases a substantial agreement is found to exist between the heart rates - both auricular and ventricular - and the height of the individual, the coefficients of correlation being - .789 for the auricular rate and - .584 for the ventricular. So far as can be discovered there are no figures in the literature to show whether this correlation is peculiar to complete heart-block. By contrast it would be desirable to discover if, for instance, in the presence of some degree of myocardial exhaustion the rate of impulse production at the S-A node bore an inverse relationship to bodily stature. The analysis of these cases of complete heart-block indicates that/
that broadly speaking the higher ventricular rates (and auricular rates) occur in the smaller individuals and vice versa. In the absence of related data concerning the rate of the heart in other diseases, it is not possible to advance any reason why such a peculiar relationship should exist. The fact is here recorded that in this small group of individuals the ventricular rate varied inversely with height.

A minor degree of correlation was found to exist between the ventricular or auricular rate and the surface area of the body. When an organ, exhibiting rhythmic activity, is severed from its nerve supply and removed from the body, it has a frequency related to its metabolic rate and its variations in oxygen consumption are similar to those observed in the intact animal. These facts are of some interest in connection with the independent ventricular frequency observed in complete heart-block. VACQUEZ' belief that the ventricles are to all intents and purposes isolated from their nerve supply, would therefore predicate a fair degree of correlation between the metabolism of the individual and the rate of the independent ventricular/
ventricular rhythm. The low degree of correlation found to exist between ventricular rate and surface area in this group of cases fails to substantiate this author's view. In other words the rate of the ventricles is apparently modified to some extent by certain extraneous influences exerted upon their inherent rhythmicity.

The data presented show that sex and age bear no decisive influence on the rate of the ventricles in complete heart-block. The height of the individual appears to bear an inverse relation to the idio-ventricular rate, but the available figures are too small in numbers to allow of definite conclusions.
THE NATURAL MAXIMUM RANGE
IN THE IDIO-VENTRICULAR RATE.
THE NATURAL MAXIMUM RANGE IN THE IDIO-VENTRICULAR RATE.

It has already been shown that under uniform conditions of bodily rest, fluctuations in the rate of both the auricles and ventricles occur from day to day in the same subject. This is, of course not peculiar to complete heart-block for it it a common observation in the healthy that under like conditions of rest, activity and metabolism, the heart rate may vary considerably in a given individual (14). The data, which have been dealt with in previous pages, show that the ventricular frequency in complete heart block is not set at a fixed rate. When the observed auricular and ventricular ranges are compared it has been found that, on the average they are each of the same order of magnitude. In the following pages it is proposed to study a little more closely the variations in auricular and ventricular rate under similar conditions.

Under resting conditions it is evident that certain individuals have a smaller fluctuation in ventricular rate than others. This may depend on a number of causes. For instance it may be that those people with a smaller range may have initially a/
a high average ventricular rate, or vice versa. Again individuals differ in their emotional tone. A greater fluctuation in rate might be anticipated in those of an excitable nature, than in those of more impassive temperament. In order to obtain comparable figures for the range throughout the series, it is desirable to study the maximum range for each individual.

For our present purposes the maximum natural range in either ventricular or auricular frequency may be defined as the difference between the rate immediately after exercise and the minimum rate recorded under resting conditions. Actually, in certain cases, it is possible to produce a greater acceleration of the ventricles than that recorded after exercise. For instance, not uncommonly in the course of a febrile reaction to a foreign protein, the ventricular rate is greater than that observed after a standard exercise test. Similarly, the lower rates observed under uniform resting conditions do not necessarily represent the absolute minimum frequency of the ventricular rhythm. In certain individuals the minimum ventricular rate was observed to occur after the use of digitalis. These extremes, produced artificially either in the course/
course of the protein shock reaction or after digitalis administration do not concern us for the moment. It seems more justifiable to consider that range represented by the difference between the maximum rate after exercise and the minimum rate under more natural conditions of bodily rest.

The response to exercise is considered more fully elsewhere. It is sufficient to state here that a simple exercise test caused some acceleration of the auricular and ventricular frequency in each individual studied. By means of the electrocardiograph and a continuous film record it was possible to obtain information on the respective rates of auricles and ventricles for varying periods after the exercise had been completed. The maximum rate here considered is that recorded 15 to 30 seconds after climbing up and down a small flight of steps for 90 seconds as quickly as the individual's powers permitted.

The minimum rate, used in the estimation of ventricular range was that observed under prolonged conditions of bodily rest. This rate was selected for the reason that, in obtaining it uniform conditions were present throughout the whole series of cases and synchronous auricular rates could be readily/
readily calculated. Actually, as will be seen later, the frequency thus observed is probably not the minimum natural heart rate. In three individuals the ventricular rate declined by a further 2 or 3 beats per minute during sleep. For a number of reasons it was not possible to measure the sleeping ventricular rate throughout the whole series of cases. The effect of sleep on the ventricular rate is discussed elsewhere.

THE NATURAL MAXIMUM AURICULAR AND VENTRICULAR RANGES.

Under the conditions described above it is found that the maximum natural range of rate for auricles and ventricles varies a good deal in different individuals. The results obtained are presented in the accompanying table. (No. 12.)

The study of this table is instructive as it reveals certain unexpected features. It includes two cases (No. 8 and 10) in which complete heart-block was accompanied by auricular fibrillation. The range in auricular rate could neither be measured accurately in these instances, nor could it be compared with those other cases in which the rate of auricular/
<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>AVERAGE RESTING RATE</th>
<th>MINIMUM RESTING RATE</th>
<th>MAXIMUM RATE AFTER EXERCISE</th>
<th>MAXIMUM NATURAL RANGE IN RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUR.</td>
<td>VENT</td>
<td>AUR.</td>
<td>VENT</td>
</tr>
<tr>
<td>*1. Mrs T.</td>
<td>74.9</td>
<td>24.9</td>
<td>69.0</td>
<td>21.0</td>
</tr>
<tr>
<td>2. W.W.</td>
<td>73.7</td>
<td>35.4</td>
<td>69.9</td>
<td>33.8</td>
</tr>
<tr>
<td>*3. D.C.</td>
<td>74.3</td>
<td>40.6</td>
<td>72.0</td>
<td>38.5</td>
</tr>
<tr>
<td>*4. W.T.</td>
<td>58.8</td>
<td>23.0</td>
<td>55.2</td>
<td>22.1</td>
</tr>
<tr>
<td>*5. A.H.</td>
<td>64.4</td>
<td>32.3</td>
<td>58.0</td>
<td>30.6</td>
</tr>
<tr>
<td>*6. W.Whd.</td>
<td>53.1</td>
<td>27.0</td>
<td>51.5</td>
<td>25.0</td>
</tr>
<tr>
<td>8. J.B.</td>
<td></td>
<td></td>
<td>A.Fib.</td>
<td>33.7</td>
</tr>
<tr>
<td>10. Mrs C.</td>
<td></td>
<td></td>
<td>&quot;</td>
<td>25.7</td>
</tr>
<tr>
<td>11. Mrs D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*12. J.D.</td>
<td>82.4</td>
<td>49.5</td>
<td>73.1</td>
<td>46.6</td>
</tr>
<tr>
<td>*13. Mrs H.</td>
<td>74.8</td>
<td>41.4</td>
<td>71.3</td>
<td>39.8</td>
</tr>
<tr>
<td>Average in whole series.</td>
<td>71.9</td>
<td>34.5</td>
<td>67.2</td>
<td>32.2</td>
</tr>
<tr>
<td>Average for 7 marked with *</td>
<td>69.0</td>
<td>34.2</td>
<td>64.3</td>
<td>31.7</td>
</tr>
</tbody>
</table>
auricular activity was governed by the normal pacemaker. Two cases (No. 2 and 11) were unable to take part in the standard exercise test owing to their muscular weakness. They were too feeble to attempt to climb the flight of steps used in testing the other individuals. Of the eleven individuals, the exercise test was therefore of uniform nature in seven. They are marked with an* in the adjoining table. (No. 12.)

**THE RELATION BETWEEN THE AURICULAR AND VENTRICULAR RANGE.**

In each instance the rate of the ventricles was greater after exercise than immediately before and likewise even greater than the minimum rate recorded for the individual under average resting conditions. Exercise also accelerated the auricular rate. Averaging the figures for the whole series, we find that the minimum A-V ratio is 67.2 to 32.2 and the maximum 114.1 to 48.7, representing a natural maximum range of 38.0 for the auricles and 16.0 for the ventricles. If the respective ranges be expressed as percentages of the corresponding minimum rates, then it is found that while the auricles accelerated by 56.6 per cent the ventricles accelerated/
accelerated by 49.7 on the average for the whole series of cases. If the figures be restricted to the seven individuals mentioned above, then the respective average rates are, - 64.3 and 31.7 under resting conditions, and 119.5 and 53.7 after exercise yielding auricular and ventricular ranges, of 55.2 and 21.8. The two latter figures represent a percentage increase over minimum resting rate of 86.2 and 70.7 respectively. This suggests that the available range of rates is of much the same order of magnitude for both auricles and ventricles. Closer inspection of the TABLE XII however reveals how false such a conclusion would be. Too often do averages tend to masquerade as facts.

The truth is revealed by plotting auricular range against the corresponding ventricular range. It then becomes evident that in general those individuals who exhibit a great range of auricular rate have by contrast only a small range of ventricular rate. Similarly those whose ventricles exhibit a large range have relatively less auricular acceleration. The facts are best demonstrated by expressing the auricular and ventricular ranges as percentages of the minimum resting rate and plotting one against the other. This has been done in the/
\[ y = -0.92x - 5.66 \]

\[ r_{xy} = -0.765 \]
the accompanying GRAPH (No. 6). This demonstrates quite conclusively that the auricular and ventricular ranges are not of the same order of magnitude throughout this series of cases. Incidentally it points out how fallacious conclusions drawn from averages may be. Were the ranges of a uniformly similar order of magnitude then the points in the chart would fall along a line extending from the bottom left hand corner of the chart to the top right hand - almost exactly the opposite of that observed.

The regression line (v-v) entered on the chart and drawn to the equation \( y = -0.92x - 5.66 \) represents the percentage ventricular range (y) for a given auricular (x). From this it is evident that an increase of approximately 150 per cent in auricular rate is accompanied by only a 10 per cent rise in ventricular, whereas a 50 per cent gain in auricular rate coexists with a 100 per cent gain in ventricular. In other words under a standard test of the natural maximum range of the auricular and ventricular rates, it is found that when the ventricles accelerated but slightly the auricles exhibit their greatest gain in rate. In contrast to this it is also evident that the greater the percentage ventricular acceleration the less the auricular. That a close/
close relationship exists between the two sets of ranges is evident from the coefficient of correlation, which is \(-0.765\). The observations are, of course rather few to treat mathematically and it may be that a straight line formula is not the best expression of the relationship between the auricular and ventricular ranges. Nevertheless the available figures indicate the existence of an inverse correlation. The greater the auricular range the less is the ventricular and vice versa.

THE INVERSE RELATION BETWEEN AURICULAR AND VENTRICULAR ACCELERATION.

These findings demand explanation in the light of physiological knowledge. Exercise increases the frequency of the normal heart in virtue of a number of circulatory reactions amongst which are the psychic and reflex nervous influences initiating and accompanying bodily activity, and also the important physical factors associated with the accumulation and excretion of metabolites and the redistribution of blood in the periphery. According to WRIGHT (233) the principal factor concerned is the BAINBRIDGE reflex (8). As a result of increased venous pressure different impulses are transmitted along the vagus/
vagus from its nerve endings in the right auricle and great veins. These produce a reflex depression of the vagal centre in the medulla, and to a less extent a stimulation of the sympathetic acceleration fibres with the result that the frequency of the heart beat is augmented. The rapidity of the reaction suggests that the immediate cause of the cardiac acceleration is largely, if not entirely due to release from the vagal inhibition. It is of interest to note that the degree of cardiac acceleration is proportionate to the rise in venous pressure (233). The venous return is greatly increased by even a short bout of exercise. The increased respiratory movements, the contractions of the skeletal muscles and the associated rise of capillary pressure are the chief factors responsible for the augmented venous flow to the right auricle. By means of the Bainbridge reflex the rate of the heart is therefore adopted to the venous return.

In complete heart block the ventricles are dissociated from the normal pacemaker of the heart - the sino-auricular node. It is reasonable to suppose that, if the ventricles be incapable of an adequate readjustment to an increased venous return, then auricular distension with further augmentation of the Bainbridge reflex must occur. A slight/
slight increase in ventricular rate may be partly compensated by a greater volume output per beat, but should the venous supply exceed the demand, then excessive auricular acceleration is all the more likely. On the other hand, in those instances where the ventricles respond by a brisk increase in rate (and probably also in stroke volume) venous distension of the auricle must be of minor degree. Hence the range in auricular rate is likely to be less where the ventricle is better adapted to the demands of exercise. This suggestion finds support from the clinical observation that the individuals with the greatest percentage increase in auricular rate (and the least ventricular gain) were decidedly more dyspnoeic after the exercise test than those in whom the ventricular increase was maximum and the auricular least.

It would therefore appear that the less successful the ventricles are in adapting themselves to the demands of muscular exercise the more does the auricle accelerate in an endeavour to overcome the venous distension. This does not imply that the auricular beat has necessarily any decided influence on ventricular filling, although READ (176) quotes GESELL (82) in support of her contention that in man, in the presence of complete heart-block, the/
the auricular contractions do play a part in filling the ventricle. GESELL came to the conclusion that auricular systole increased the ventricular output by 50 per cent over that maintained by venous pressure. It is however not without interest to note that, probably as a result of the Bainbridge reflex, every endeavour is made to compensate for auricular engorgement.

**THE RELATION OF VENTRICULAR RANGE TO MINIMUM RATE.**

It has been already shown that under conditions of subdued bodily activity a relationship exists between the auricular and ventricular rates. Similarly an inverse correlation exists between the auricular and ventricular ranges. It is therefore of interest to enquire if the ventricular range bears a relationship to the minimum rate. In other words, is the degree of ventricular acceleration proportionate to the minimum rate throughout the series?

The ventricular range has been measured in nine individuals (including the two cases complicated by auricular fibrillation). By plotting ventricular range against the corresponding minimum ventricular rate for each of these individuals it becomes at once evident that no relationship exists between/
between the two. This may be surmised from the TABLE XII in which it is shown, for example that a minimum rate of 22.1 (Case 4) is accompanied by a range of 24.1 (109%) in this individual, and in another with a similar rate of 21.0 the range is 12 (57%). Taking the group as a whole, it is impossible to predict the range in rate for a given ventricular frequency. So far as this series of cases will allow of judgement it seems fair to conclude that the degree of ventricular acceleration is determined by factors other than the initial rate and that the response varies in a surprising way in different individuals.

This conclusion finds support from similar observations on the response of the heart in healthy people. The degree of acceleration produced by a given amount of work varies enormously throughout a series of healthy subjects. It even varies a little in repeated observations on the same individual. The range in rate of the heart of the normal healthy individual cannot be predicted from the initial rate before exercise.
THE RELATION OF VENTRICULAR RANGE TO AGE.

It is difficult to find any distinct relationship between ventricular range and other factors. Age may be of some importance. In general the older the individual the less the range but, such definite exceptions occur that this factor can hardly be regarded as of much importance in itself.

THE RELATION OF VENTRICULAR RANGE TO EMOTIONAL TONE.

The heart has long been recognised to be an organ easily disturbed in its action by emotional processes. While differences in temperament are easily recognised clinically they are well nigh impossible to measure accurately or record quantitatively. At the best it is only possible to offer a rough classification, ranging from the nervous, anxious, and highly-strung on the one hand, to the individual of more apathetic and indifferent outlook on the other. Selecting two extreme examples from each of these two groups it is found, that the range in ventricular rate does not bear any appreciable relation to the psychic make-up of the individual. The degree of ventricular acceleration varies as much or as little in the phlegmatic as in those of more impressionable and vivacious temperament.
VENTRICULAR RANGE AND MYOCARDIAL EFFICIENCY.

The available range in rates does however appear to bear some relationship to the functional capacity of the individual. Analysis of the available data reveals the fact that the range in ventricular rate is greatest in those symptoms are the least incapacitating. An attempt has been made to grade individuals according to their ability to undertake physical activity. The method of classification employed is that recommended by the American Heart Association (163). Practical experience of its use extending over a number of years has proved the worth of this method particularly in relation to the assessment of the fitness of cardiac patients for the strain of pregnancy and delivery (86) and there is no reason to believe that in its application to cases of heart-block, the conclusions are less valid. For purposes of grading patients according to their functional capacity three broad groups may be considered.

Group 1 consists of patients with organic heart disease who are able to carry out all their ordinary physical activities without discomfort. Of the present series Case 13 may be placed in this group/
<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>OBSERVED RANGE</th>
<th>FUNCTIONAL EFFICIENCY GROUP</th>
<th>AVERAGES RANGES FOR EACH GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUR.</td>
<td>VENT.</td>
<td>AUR. and VENT.</td>
</tr>
<tr>
<td>13. Mrs H.</td>
<td>38.0</td>
<td>50.2</td>
<td>38.0 and 50.2</td>
</tr>
<tr>
<td>1. Mrs T.</td>
<td>60.6</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>3. D.C.</td>
<td>56.7</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>4. W.T.</td>
<td>42.2</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>12. J.D.</td>
<td>50.7</td>
<td>36.3</td>
<td>52.6 and 22.8</td>
</tr>
<tr>
<td>5. A.H.</td>
<td>58.3</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>6. J.Wd.</td>
<td>79.5</td>
<td>5.6</td>
<td>68.9 and 6.8</td>
</tr>
<tr>
<td>8. J.B.</td>
<td>a.fib.</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>2. W.W.</td>
<td>18.5</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>10. Mrs C.</td>
<td>a.fib.</td>
<td>0.8</td>
<td>22.5 and 4.8</td>
</tr>
<tr>
<td>11. Mrs D.</td>
<td>26.3</td>
<td>10.7</td>
<td></td>
</tr>
</tbody>
</table>
group. This woman had only slight distress on severe exertion and the presence of complete heart-block was only detected by a routine examination.

Group 2 is composed of patients with organic heart disease unable to carry out their ordinary physical activities without discomfort. There are two subdivisions in this group, (a) consisting of those whose incapacity is slight, and (b) those having a definite limitation of physical activity. Of the present series, Cases 1, 3, 4, and 12 may be selected as suitable for inclusion in Group 2a, and cases 5, 6, and 8 in group 2b.

Group 3 consists of those patients with symptoms and signs of heart failure when at rest. Unable to carry on any physical activity without discomfort, their capacity for exertion is greatly limited. Three individuals belong to this group,—Cases 2, 10, and 11. Analysis of the available data is facilitated by the use of the subjoined TABLE XIII.

Comparing the groups it is evident that as functional efficiency declines so does the available ventricular range tend to decrease. It should be pointed out that, as might be expected, the cases included in Group 3 were not able to take part in the/
the formal exercise test adopted by the other individ-
duals. They were merely able to walk across the examination room, once or twice and, on account of their general weakness, had to receive a good deal of assistance even for such a trifling amount of exertion. With the exception of this group it is of interest to note that as the ventricular range tends to de-
crease from Group 1 to Group 3, the auricular likewise tends to increase.

In the circumstances it seems justifiable to conclude that in a general way the ventricular range varies with the individual's capacity to under-
take exertion. This is of some importance in form-
ing an estimate of the circulatory adaptations conse-
quent upon the inception of an idio-ventricular rhythm. It implies that in general those sufferers from complete heart-block who are capable of augment-
ing the ventricular rate, when muscular exercise is undertaken, suffer the least distress and have a correspondingly high grade of functional capacity. This subject is discussed more fully elsewhere.
THE VENTRICULAR RANGE IN RELATION TO PULSE PRESSURE.

It has just been shown that a fair agreement exists between the functional capacity of the heart and the extent of the ventricular range. Probably other circulatory phenomena are also related to the ability of the ventricles to increase in rate. For instance it is known that in health the height of the systolic blood pressure bears an intimate relation to the heart rate. Reflexes from the cardio-aortic area and from the carotid sinus (104) help in some measure to control the frequency of the heart, a rising pressure producing increased vagal inhibition. As will be shown later (Page 307) the diastolic pressure under resting conditions correlated with the minimum heart rate. Similarly the systolic pressure at rest is related to the maximum heart rate after exercise in a proportion of these cases of complete heart-block. It is therefore not unreasonable to suppose that the difference between the minimum and maximum rates (i.e. the range) is related to the difference between the diastolic and systolic pressures (i.e. the pulse pressure). Actually only seven cases show such relationship, the four exceptions being/
being, two complicated by aortic regurgitation and two in which the block may not have been of organic origin. Nevertheless from the facts just stated and from plotting of the available data in seven similar cases, it may be concluded that the pulse pressure at rest bears a rough relation to the ventricular range. This may be appreciated by study of the accompanying table in which the cases are arranged in descending order of pulse-pressure.

**TABLE XIV.**

<table>
<thead>
<tr>
<th>CASE No. and INITIALS.</th>
<th>PULSE PRESSURE</th>
<th>VENTRICULAR RANGE.</th>
<th>B.P. in mm. Hg. SYSTOLIC and DIASTOLIC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. W.T.</td>
<td>146</td>
<td>24·1</td>
<td>220/74</td>
</tr>
<tr>
<td>2. Mrs. T.</td>
<td>109</td>
<td>12·0</td>
<td>165/56</td>
</tr>
<tr>
<td>6. J.W.</td>
<td>94</td>
<td>5·6</td>
<td>158/64</td>
</tr>
<tr>
<td>10. Mrs. C.</td>
<td>90</td>
<td>0·8</td>
<td>170/80</td>
</tr>
<tr>
<td>11. Mrs. D.</td>
<td>85</td>
<td>10·7</td>
<td>200/115</td>
</tr>
<tr>
<td>2. W.W.</td>
<td>82</td>
<td>3·0</td>
<td>180/98</td>
</tr>
<tr>
<td>5. A.H.</td>
<td>78</td>
<td>5·4</td>
<td>162/84</td>
</tr>
</tbody>
</table>

It would therefore appear that the higher pulse pressures are accompanied by the higher ranges. The results are at best an approximation for blood pressure, particularly diastolic pressure, is difficult/
difficult to record with accuracy and is itself influenced by a number of factors. No great stress is laid upon this relationship and, in the analysis of the scanty data just presented, it does not seem justifiable or profitable to employ mathematical methods. Incidentally there does not appear to be any direct relationship between the ventricular range and the diastolic or systolic blood pressures.

THE VENTRICULAR RATE DURING SLEEP.

In discussing the estimation of the natural ventricular range, reference has been made to four instances in which the ventricular rate was counted in the early morning hours while the individual slept. In the preceding pages the minimum rate used in the calculation of the ventricular range was that found to occur under uniform resting conditions in the forenoon. This reading is probably not the absolute minimum for in the three individuals in whom it was possible to estimate the ventricular rate during sleep, a reading two or three beats less than their minimum resting rate was recorded.

This is not surprising in view of the influence of sleep on the heart rate in healthy people. The truth of GALEN'S dictum (76) "pulsus in somno parvi, languidi, rari" has been confirmed and elaborated many/
many times, particularly in recent years. The studies of GOLDSCHMIDT and BOAS (14) using the cardiotachimeter, are the most recent and complete. These authors have found that in women the minimum heart rate during sleep is 17.4 per cent and in men 13.8 per cent below the rate observed under basal conditions. Sleeping heart rates of from 40 to 45 per minute were commonly observed and occasionally rates as low as 38 or 39. From the tables published by these workers it is found that for 61 healthy adults the average minimum heart rate during sleep was 52.75 (±7.5), and that the corresponding minimum rate while awake was 61.15 (±7.51) yielding an average difference of 8.4 beats per minute. The sleeping rate is less than that recorded during basal conditions. Apparently even a greater range occurs in childhood. SUTHERLAND and McMICHAIL (212) found amongst thirty convalescent children varying in age from 2 to 12 years, that the average sleeping rate was 73, whereas the average rate awake was 107 - a difference of 34 beats per minute. In an interesting review of this subject BOAS and GOLDSCHMIDT (14) come to the conclusion that the slowing of the heart rate during sleep is produced by two main factors, the one passive and the other active. The first is the natural result of a diminuation/
diminuation in mental and muscular tone, of a reduction in temperature and metabolism, and of a decrease in reflex excitability. The other is due to positive increase in vagal tone probably associated with an increased activity of a sleep regulating centre in the hypothalamus.

In the three cases of complete heart-block in which attention was directed to the influence of sleep on the idio-ventricular rate the pulse was counted by the nurse in attendance during the early morning hours, while the patient slept. The electrocardiograph was not used but the nurse was instructed to count either the radial pulse by palpation or the visible carotid beat for two consecutive minutes. In this way some of the inevitable inaccuracies associated with routine pulse counting was avoided. A note was made of the time at which the sleeping rate was observed, and twelve hours later, a second count was made the patient having remained in bed and being awake. In this way it has been possible to contrast sleeping and waking rates employing a uniform method of observation. An attempt was made to record the sleeping rate on a series of consecutive days - but this was not always possible as the patient's hours of sleep sometimes varied considerably. The depth or duration of sleep at the time of counting was not measured/
<table>
<thead>
<tr>
<th>CASE No. and INITIALS</th>
<th>AVERAGE RATES COUNTED by HAND.</th>
<th>No. and HOUR of DETERMINATIONS</th>
<th>DIFFERENCE BETWEEN AWAKE and ASLEEP RATES.</th>
<th>MINIMUM RESTING RATES (from E.C.G's)</th>
<th>DIFFERENCE BETWEEN MIN. RESTING RATE and SLEEP RATE*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asleep</td>
<td>Awake.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Mrs. C.</td>
<td>22.4</td>
<td>23.1</td>
<td>10. (2 a.m. &amp; 2 p.m.)</td>
<td>0.7</td>
<td>26.5</td>
</tr>
<tr>
<td>12. J.D.</td>
<td>45.6</td>
<td>56.0</td>
<td>6. (11 p.m. &amp; 11 a.m.)</td>
<td>10.4</td>
<td>46.6</td>
</tr>
<tr>
<td>13. Mrs. H.</td>
<td>39.0</td>
<td>45.6</td>
<td>6. (4 a.m. &amp; 4 p.m.)</td>
<td>6.6</td>
<td>39.8</td>
</tr>
</tbody>
</table>

**TABLE XV:** To show that in three patients confined to bed, the heart rate was less during sleep than during waking hours.
measured.

From the table it is evident that for these three individuals the sleeping ventricular rate is 4.1, 1.0 and 0.8 beats per minute less than the minimum resting rate recorded during the forenoon by the electrocardiograph. The difference may well be greater than these figures indicate for it is known that the heart rate fluctuates during sleep and that the absolute minimum rate occurs at different times not only in different healthy subjects but even in the same individual. For this reason the rates recorded in these three patients during their natural sleep do not necessarily represent the absolute minimum sleeping rate. The figures merely express counts made at a given time during sleep. There is apparently a range of rate during sleep just as there is a range of rate during waking hours. It would be of interest to study (with the cardiotachometer) the details of the sleeping range in complete heart-block and contrast it with that observed during a day's activity. As a further consideration it would appear probable that those individuals who have a wide range of idio-ventricular rate during the day's activities have likewise a relatively wide range during sleep and vice versa. It has been shown above that there is apparently a fairly close association between the degree of ventricular acceleration and/
and the functional capacity of the heart muscle in complete block — the greater the range the better the response to exercise. It may therefore be that future studies will demonstrate a more labile rate during sleep in those individuals with a satisfactory cardiac reserve, and a more fixed rate if the ventricles in those whose capacity for exertion is minimal. Support for this view is found in the studies of KLEWITZ (128) and of BOAS and GOLDSCHMIDT (14), who have demonstrated that during sleep the customary fall in heart rate does not occur in the presence of myocardial insufficiency. The probability is that a similar conclusion holds good in cases of complete heart block — a reduced range of ventricular rate during sleep being associated with a much impaired response to effort.

Finally the difference observed between the rates of the ventricles during sleep and during the gentle activities of the day lend support to the view that the idio-ventricular rate is not absolutely constant for the individual.
SUMMARY.

It has been shown that the idio-ventricular rate in complete heart-block fluctuates through a range peculiar to the individual. In the estimation of the maximum natural auricular and ventricular ranges, the difference between the minimum rate observed under resting conditions and that recorded immediately after an exercise test, was calculated for each individual. In this way it was possible to compare the maximum auricular range with the ventricular in a series of cases of complete heart-block under uniform conditions.

It has been found that the ventricular range bears an inverse relation to the auricular. In general they are not of the same order of magnitude, as the greater the gain in auricular rate the less is the ventricular response, and vice versa. Mathematically the correlation between the auricular and ventricular ranges is of high degree, the coefficient of correlation for this series of cases being $-0.765$.

The significance of this peculiar relationship is discussed, the evidence presented leading to the conclusion that a low ventricular range is associated with a relatively poor functional capacity of the myocardium and vice versa.

The available data does not indicate that the extent of the range bears a definite relation to the/
the initial resting ventricular rate, nor to the age, or emotional tone of the individual.

There does however appear to be some correlation between the pulse pressure at rest and the range in the ventricular rate. The cases are too few in numbers to yield precise information on this aspect of the problem.

In three individuals the pulse rate was accurately counted during sleep over a consecutive series of nights. The sleeping ventricular rate was observed to be lower by one or more beats than that observed during waking hours. The probability is that during sleep the idio-ventricular rate exhibits a minor fluctuation comparable to that observed in normal sleeping individuals. In health the heart range during sleep reflects in some measure the range observed during waking hours. As the largest ranges in complete heart block occurred in the more physically fit individuals it is probable that they likewise have correspondingly greater ranges during sleep and that the smallest ventricular range in sleep will occur in those sufferers from complete heart-block whose myocardial efficiency is minimal.
THE RESPONSE TO ATROPINE.
THE RESPONSE TO ATROPINE.

Atropine is an alkaloid, which as a result of its power to paralyse the inhibitory action of the vagus has, as one of its leading pharmacological features, the remarkable property of accelerating the action of the normal heart. In complete heart-block, it has long been a tradition that the paralysing influence of the drug is confined to the auricles, which therefore accelerate in the usual manner, but the ventricles, isolated from vagal control, continue to beat at their accustomed rate. So well established is this belief, that it has formed the basis of a test for the differentiation of the different types of bradycardia.

As the results obtained in this series of cases are contrary to prevailing opinion, it would first seem desirable to describe in detail the technique of the experimental observations and the methods employed in their analysis.
EXPERIMENTAL METHODS.

The patients were brought from their beds in a wheeled chair to the electrocardiograph department and allowed to rest on the examination couch for upwards of an hour or more until the pulse rate and blood pressure reached a constant level. All the subjects were investigated in a similar manner and each was already well acquainted with the surroundings and workers in the laboratory. The room temperature was comfortable, the patients were shielded from draughts, and strangers were excluded. Each patient lay in a position of maximum ease with the hands and left foot immersed in the warm saline solution of the non-polarisable electrodes. All were under constant observation throughout the experiment.

Three electrocardiograms were recorded at intervals of five minutes or thereabout, before the dose of atropine was administered, the last one being taken immediately before the needle-point was inserted into a convenient vein at the bend of the elbow. The dose employed was the same for each patient, viz. 1/30 grain of atropine sulphate dissolved in 1.0 c.c. of sterile normal saline and administered intravenously. In order to avoid, as far as possible, any reflex acceleration/
acceleration of the heart which might result from the
pain of the needle prick, a particularly sharp needle
of fine bore was used. A minute was allowed to elapse
after the needle had entered the vein before the solu-
tion of atropine was injected. In this way the pos-
sibility of the registration of a transient acceler-ation due to pain or excitement, was in a large measure
avoided.

Given by the intravenous route, a dose of
atropine acts with great rapidity, and the maximum
acceleration of the heart beat is reached as a rule,
within two or three minutes from the time of the
drug's injection. A succession of slow running
plates was therefore exposed at short intervals.
The first of these was photographed immediately the
injection was completed. At intervals of half a min-
ute, or a minute, succeeding records were made and
after the first three exposures, further electrocardio-
grams were registered every two minutes until one
hour had elapsed from the time of injection. In a
number of cases simultaneous blood pressure readings
were made, using the auscultatory method and the
Baumanometer apparatus. Notes were made of the pa-
tient's reaction to the drug, e.g., dryness of the
mouth, paralysis of the iris, or general restlessness.
Incidentally/
Incidentally, a control injection of normal saline alone was made in one or two cases, using a similar technique throughout.

Thirty of more electrocardiograms were recorded during the experimental period. Each of these was subsequently analysed, often in duplicate, as regards auricular and ventricular rates. The time marker recorded accurately in fifths and twenty-fifths of a second, and it was therefore possible to measure the deflections to 0.01 second with the aid of a hand lens. A comparator was not found to be necessary.

Every patient in this series of cases of complete heart-block was tested with atropine, according to the technique described above, with the exception of two, in whom the dose of atropine was 1/50 grain instead of 1/30. One other patient (Case 2 W.W.) received 1/30 grain, but at the time of the investigation, was far advanced in congestive heart failure, from which he died shortly afterwards. The results obtained in 10 Cases of complete heart-block may therefore be compared, as they form a uniform series. In each instance a definite acceleration of ventricular rate was observed.

The effect of the dose of 1/30 grain of atropine/
<table>
<thead>
<tr>
<th>CASE NO. &amp; INITS.</th>
<th>AURICULAR RATE PER MINUTE</th>
<th>GAIN IN RATE AURICLES</th>
<th>PERCENTAGE GAIN IN RATE AURICLES</th>
<th>VENTRICULAR RATE PER MINUTE</th>
<th>GAIN IN RATE VENTRICLES</th>
<th>PERCENTAGE GAIN IN RATE VENTRICLES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEFORE</td>
<td>MAX. RATE</td>
<td></td>
<td>BEFORE</td>
<td>MAX. RATE</td>
<td></td>
</tr>
<tr>
<td>1. Mrs T.</td>
<td>75.3</td>
<td>101.6</td>
<td>26.3</td>
<td>34.7</td>
<td>22.2</td>
<td>1.2</td>
</tr>
<tr>
<td>3. D.C.</td>
<td>72.0</td>
<td>127.4</td>
<td>55.4</td>
<td>77.0</td>
<td>42.8</td>
<td>19.5</td>
</tr>
<tr>
<td>4. W.T.</td>
<td>63.1</td>
<td>80.1</td>
<td>27.0</td>
<td>42.3</td>
<td>23.6</td>
<td>2.5</td>
</tr>
<tr>
<td>5. A.H.</td>
<td>72.5</td>
<td>92.3</td>
<td>19.8</td>
<td>27.3</td>
<td>31.0</td>
<td>8.8</td>
</tr>
<tr>
<td>6. J.Whd.</td>
<td>57.7</td>
<td>77.0</td>
<td>19.3</td>
<td>33.5</td>
<td>28.5</td>
<td>1.8</td>
</tr>
<tr>
<td>8. J.B.</td>
<td></td>
<td></td>
<td></td>
<td>30.7</td>
<td>41.0</td>
<td>10.3</td>
</tr>
<tr>
<td>10. Mrs C.</td>
<td></td>
<td></td>
<td>Auricular fibrillation pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. J.D.</td>
<td>91.3</td>
<td>135.0</td>
<td>43.7</td>
<td>48.0</td>
<td>49.3</td>
<td>47.0</td>
</tr>
<tr>
<td>13. Mrs H.</td>
<td>77.3</td>
<td>100.5</td>
<td>23.2</td>
<td>30.0</td>
<td>42.6</td>
<td>33.8</td>
</tr>
<tr>
<td>14. Mrs D.</td>
<td>64.6</td>
<td>87.0</td>
<td>22.4</td>
<td>25.7</td>
<td>29.1</td>
<td>3.7</td>
</tr>
<tr>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td>V</td>
<td>VI</td>
<td>VII</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
atropine sulphate intravenously on the auricular and ventricular rates is shown in the following table No. 16. In spite of the very marked acceleration observed in certain cases, in not one instance was the degree of heart-block reduced. The dissociation in every instance remained complete.

An increase in ventricular rate after the dose of atropine occurred in each individual examined - the figures derived from those patients who each received a 1/30 grain intravenously being presented in the table. The maximum gain in ventricular rate occurred in Case 12. The patient's ventricular rate increased from 49.3 to 96.3, a range of 47.0, representing a gain of 95.9 per cent. The minimum range was that recorded in Case 1. Before injection the ventricular rate was 22.2, some minutes after the dose it was 23.4, a gain of 1.2 beats per minute, a 5.4 per cent increase over the resting value. The table shows that the gain in auricular rate was, on the whole, less variable than the ventricular, the maximum being 55.4 per cent in Case 3, and the minimum 19.3 per cent in Case 6. These figures, taken in conjunction with those derived from the three other patients referred to above (Cases/
(Cases 2, 7, 11), in whom the administration of atropine was also followed by ventricular acceleration, clearly cast a doubt upon the statement frequently made that atropine has no effect, or only a trifling one upon the rate of the ventricles in complete heart-block. It further emphasises how valueless the atropine test is as a means of distinguishing bradycardia due to complete heart-block from other causes. As the figures show, even in the presence of complete dissociation, the ventricles may accelerate by as much as 95 or 80 per cent.

It has already been shown in a previous section, that the ventricles in complete heart-block exhibit under resting conditions, a spontaneous variation in rate. To establish the view that atropine when injected intravenously, is responsible for the acceleration observed, it is therefore necessary to show that the rate recorded after its administration, not merely exceeded the frequency immediately before its use, but was, in fact, greater than the maximum spontaneous rate observed under similar resting conditions. In other words, it is necessary to establish the fact that the rate after atropine was greater than the upper limit of the resting range for a given individual. In TABLE 7 (on page 78a) are/
## TABLE XVII.

<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>MAXIMUM RATES AT REST</th>
<th>MAXIMUM RATES AFTER ATROPINE FROM TABLE</th>
<th>VENTRICULAR GAIN OVER MAXIMUM RESTING RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AURICLES</td>
<td>VENTRICLES</td>
<td>AURICLES</td>
</tr>
<tr>
<td>1. Mrs T.</td>
<td>81.8</td>
<td>29.2</td>
<td>101.6</td>
</tr>
<tr>
<td>3. D.C.</td>
<td>78.0</td>
<td>42.8</td>
<td>127.4</td>
</tr>
<tr>
<td>4. W.T.</td>
<td>63.1</td>
<td>23.6</td>
<td>80.1</td>
</tr>
<tr>
<td>5. A.H.</td>
<td>72.5</td>
<td>36.0</td>
<td>92.3</td>
</tr>
<tr>
<td>6. J.Whd.</td>
<td>57.7</td>
<td>28.5</td>
<td>77.0</td>
</tr>
<tr>
<td>8. J.B.</td>
<td>Aur. fib.</td>
<td>33.0</td>
<td>Aur. fib.</td>
</tr>
<tr>
<td>10. Mrs C.</td>
<td>Aur. fib.</td>
<td>26.8</td>
<td>Aur. fib.</td>
</tr>
<tr>
<td>12. J.D.</td>
<td>91.3</td>
<td>55.2</td>
<td>135.0</td>
</tr>
<tr>
<td>13. Mrs H.</td>
<td>77.3</td>
<td>42.6</td>
<td>100.5</td>
</tr>
<tr>
<td>14. Mrs Dev.</td>
<td>—</td>
<td>30.0</td>
<td>87.0</td>
</tr>
</tbody>
</table>
are shown the maximum rates for each individual under uniform conditions of bodily rest. In the following table, for the sake of contrast, the maximum resting rate of several determinations on different days and the maximum rate after atropine, are placed side by side for each individual. (TABLE 17).

This demonstrates that amongst ten individuals, the maximum rate after atropine, was greater than that observed to occur under similar conditions of bodily rest in eight individuals. In one subject (Case 1), the acceleration produced by atropine was less than that which occurred spontaneously. In another (Case 14) the upper limit of the spontaneous variations in rate could not be determined with sufficient accuracy to allow of strict comparison. In this case the heart-block was complicated by an irregularity in the idio-ventricular rhythm - with the result that distinct, but transient variations in rate made the upper limit of the ventricular range difficult to determine for more than very short periods of time. The average resting ventricular rate in this patient was in the neighbourhood of 30. Considering the group as a whole, it is justifiable to conclude that the intravenous injection of atropine sulphate increases the idio-ventricular rate, and applying the more/
○ = Case reported by Lewis (1967)
☒ = Cases reported by de Graaff and Weis (1969)
☒ = This series.

\[ y = 1.62x - 1.04 \]

\[ \sqrt{2xy} = 0.9722 \]
more stringent test associated with the spontaneous ventricular range, it may be said that the acceleration produced by atropine, definitely exceeded the maximum natural fluctuation in 8 out of 10 instances.

THE VENTRICULAR RANGE AFTER ATROPINISATION.

It has been shown above that in the presence of complete heart-block, atropine increases the idio-ventricular rate. The TABLE XVI shows that the gain in rate varies considerably in different individuals. The state of affairs is best demonstrated by plotting the range (i.e. the gain in ventricular rate) against the rate observed immediately before the injection. This has been done in the accompanying GRAPH (No. 7) in which $x =$ the initial ventricular rate and $y =$ the observed ventricular range after atropine. These values are plotted one against the other for each individual.

By this means it is possible to demonstrate effectively that there is a measure of agreement between the acceleration produced by atropine and the rate existing immediately before the injection. The greater the initial ventricular rate, the greater the acceleration produced, and vice versa. Mathematical analysis established a high and striking degree of correlation/
correlation for this series of cases - the coefficient being + .9722. The probability is, however, that the law expressing the relation between the initial rate and the degree of acceleration after atropine, is not best represented by a straight line formula. As the plottings are too scanty in number to determine the optimum expression, the regression line g-g has been entered on the chart. This line represents the theoretical gain in rate (y) for a given initial rate (x) and has been drawn to the equation

\[ y = 1.62x - 1.04. \]

It is evident from the graph, that the regression line g-g cuts the base line at a value approximately 24. Theoretically, this would imply that for the initial rates below 24 per minute, the response to atropine would be a minus quantity - in other words, slowing of the heart would follow the drug's administration. On the other hand, for initial rates above 24, acceleration might be anticipated as indicated by the lie of the line g-g. There is no particular reason to believe that such a peculiar state of affairs does exist in fact. In practice, a negative response was never encountered and the obvious explanation is that the relation between rate and range after atropine is probably best expressed by a curve - perhaps logarithmic - rather than by a straight/
straight line formula. The points however are too few in number to yield any indication of the exact law expressing the relation between the rate before and the rate after atropine. It is not without interest to refer at this point to the response of the ventricles to digitalis. The subject is discussed on page 275, where it is shown that at the critical rate of 24 (as in the case of atropine) a change takes place in the reaction to the drug. For rates above 24 per minute, digitalis induces slowing of the ventricles. Below 24 quickening results.Apparently atropine and digitalis, at least in complete block, act in a reverse manner on a similar mechanism.

As the majority of cases of complete heart-block have a ventricular rate in the neighbourhood of 30 per minute or less, it may be for this reason that the peculiar nature of the response to atropine has escaped the attention which it deserves. As pointed out above, the usual statement that atropine has little or no effect on the ventricular rate requires modification. The fact that at the slower idio-ventricular rates atropine yields a minima reaction is probably in large part responsible for the oft quoted statement that the drug is without effect on the rate. At low rates of beating the gain/
gain in rate after atropinisation is only rendered appreciable by exact and systematic methods of measurement. At higher rates the action of the drug has not been previously tested.

When FRANCOIS - FRANK in 1884 (71) and DEHIO (52) in 1892 put forward the suggestion, that atropine might be used to distinguish the slow pulse of vagal origin from other forms of bradycardia, whose nature was at that time not fully appreciated, theory was ahead of knowledge. By 1899 as a result of the application of pulse tracings to the study of the heart's action, WENCKEBACH (221) and HIS (110) both described block in man and were prepared to suggest that a lesion of the auriculo-ventricular bundle was responsible for the condition. Six years later HAY (99) in 1905 was able to offer postmortem evidence of a lesion situated in the bundle in a case in which he had made the diagnosis during life. In the same year RITCHIE (180) reported the remarkable case of a man aged 55 suffering from complete heart-block, in whom after the use of atropine the ventricular rate was 36.6 per minute. For fourteen months the rate had been almost constantly 32 to 34. Incidentally after atropine the auricular rate increased to 274.7 - which is almost certainly the earliest record of auricular flutter known, and without/
without doubt the first graphic record of what must be a very rare combination of arrhythmias. The dose and method of administration of the drug are not stated. VACQUEZ (214) concluded from the study of a group of cases of bradycardia that atropine had little or no effect on that form due to intra-cardiac lesions. Even before the nature of the heart block or the Stokes-Adams syndrome were fully appreciated atropine was used in the treatment of syncopal attacks associated with bradycardia. One of the earliest records is that reported by KINKEAD (126) in 1898, in which it is recounted that the heart rate in a man was 6 per minute for probably 6 or 7 hours. After atropine, given hypodermically the rate was 72. In the light of modern knowledge this was probably a case of intermittent complete heart-block with numerous Stokes-Adams seizures and it is questionable if the small dose of atropine used (1/100 gr.) was responsible either for the increase in rate or the return of full conduction. After 1905, many instances of undoubted cases of complete heart-block were reported from all parts of the world. In some of these the use of atropine is described but, more often than not, precise data are lacking and in many the dose used is either not stated or is too small in amount to be regarded as really effective. It is/
is unnecessary to review these cases in detail, as the universal opinion, culled from a consideration of the available data is, that atropine is not only valueless as a therapeutic agent in complete block, but has no appreciable action on the ventricular rate. COHN and LEVINE (36) in a study of three cases of the Stokes-Adams syndrome found that atropine was not only ineffective, but appeared to aggravate the condition in one case. The position was summed up by RITCHIE (122) in his Gibson Memorial Lecture before the Royal College of Physicians of Edinburgh in 1923, when he said "The intravenous administration of atropine is the most prompt and effective measure in warding off the risks which attend a severe grade of partial 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 dissociation. Here atropine does not increase the ventricular rate although the auricles are accelerated".

As a result of experimental work on animals, various authors came to the conclusion that atropine was without appreciable influence on the idio-ventricular rate. ERLANGER (60), the first to study the physiology of experimental heart block in animals, pointed out as early as 1905 that whereas atropine/
atropine accelerated the auricles it was without influence on the ventricles isolated by transection of the bundle of HIS. In 1913, VAN EGMOND (58) working on cats came to the conclusion that atropine had no appreciable effect on the rate of the ventricle. CULLIS and TRIBE (43) concluded that atropine produced no effect on the ventricles in the presence of complete heart-block, produced by cutting the bundle, in rabbits and cats. For the most part these were all acute experiments and not strictly comparable to the chronic vascular degenerative lesion commonly found in man. It is only natural to suppose that the disturbance produced by cutting or clamping the bundle with the associated interference in the blood supply must to some extent act as a local irritant and thereby produce a somewhat artificial rate of stimulus production in the specialised tissues immediately below the lesion.

As regards the effect of atropine in man it is interesting to find that, even in cases of bradycardia of vagal or reflex nervous origin, atropine occasionally causes little or no acceleration of the heart rate. For instance PETZETAKIS (172) found that certain cases of slow pulse of non-myocardial origin were uninfluenced by atropine and FREDERICQ (72) concluded that reliance should not be placed in the atropine test as a means of distinguishing between different/
different types of bradycardia. In support of this conclusion, it is of interest to refer to the recent work of KAUF (123) who has found that, in contrast to untrained individuals, the hearts of trained athletes did not accelerate after a dose of 1 mgm. of atropine sulphate.

It may equally well be concluded that the atropine test is not reliable as the sole means of distinguishing the slow heart action of complete auriculo-ventricular dissociation from the other forms of bradycardia. It has been shown that in this series of cases, the response to atropine varies with the rate of the independent ventricular rhythm at the moment, a high initial rate of beating yielding the greatest degree of acceleration. It is true that certain cases have been reported in the literature in which the use of atropine was followed by a release in conduction, complete block giving way to partial, (RATHERY & LIAN (175), WILSON (231) etc.) but this did not occur in the cases at present under review. Acceleration was the direct result of an increase in the idio-ventricular rate.

On reviewing the case-reports in the literature, it would appear that not infrequently conclusions have been drawn from the effects obtained by the administration of too small a dose of atropine.
LEWIS and his colleagues (139) found that, in dogs of about 10 kilos, 0.1 mgm. of atropine sulphate had a very decided effect in weakening the inhibitory terminations of the vagus, but that this dose must be increased to 0.2 or 0.4 mgm. before the effects of even weak peripheral stimulation are abolished. To render strong vagal stimulation ineffective, the dose had to be increased to 0.5 to 1.0 mgm. or 0.05 to 0.1 mgm. per kilo of body weight. From similar observations on men, they came to the conclusion that 1/50 gr. of atropine sulphate, given by intravenous injection, is sufficient to produce very decided effects on the heart, nearly, but not quite paralysing the vagi. These workers came to the conclusion that the requisite dose to produce complete paralysis in man is approximately 1/20 to 1/10 grain. Very few cases of complete heart-block in man have been tested with such large doses. Before it can be concluded however, that atropine is ineffective, it is essential that an adequate dose be employed.

LEWIS (139) briefly mentions one case of complete heart-block complicated by the presence of auricular fibrillation. This man received 1/10 gr. of atropine sulphate intravenously and fifteen days later, 1/20 gr. A prompt rise in ventricular rate occurred /
occurred on both occasions. From the chart in this author's publication, it would appear that the ventricular rate rose from 42 to 58, yielding a gain in rate of 16 beats per minute. Incidentally, the response was about equal on the two occasions, indicating that the lower dose was of sufficient quantity to yield a full ventricular response. The gain of beats from an initial rate of 42 in this single individual is in keeping with the response throughout the series of cases at present under consideration. The reaction in Lewis' case has been entered on the Chart (No 7). Similarly DE GRAFF & WEISS (90) have tested four cases of complete heart-block with larger doses of atropine than generally employed. They used 5.0 mgms. in three cases and 3.5 mgms. in another and found "a slight but distinct increase in the ventricular rate". Their results, after the hypodermic dose of 5.0 mgms. have also been incorporated in the same Chart, where it is evident that they are quite in keeping with those obtained throughout this series. RITCHIE (183) in 1927 tested one of the cases included in this series with 1/50 gr. atropine hypodermically. Before injection, the A-V ratio was 70 to 38, and one hour afterwards the respective rates were 92 and 42.

The dose used in this series of cases was
a uniform one of 1/30 grain intravenously. This was found to be sufficient to produce quite decided effects, though it was not of the magnitude of that recommended by LEWIS (139) nor of that employed hypodermically by DE GRAFF & WEISS (90). It is reasonable to suppose that 1/30 grain produces almost complete paralysis and as the same dose was used in each of the ten individuals in this series, the results are therefore comparable.

THE RESPONSE TO ATROPINE IN HEALTH.

CRAWFORD (42) found that the response to atropine in man is influenced by the age of the individual tested, being maximum from twenty to thirty years, to be followed by a gradual decline with a marked fall after the age of fifty. Body-weight must influence the response, and also the method of administration, a more complete and abrupt reaction resulting from a given dose when delivered by the intravenous route. Sex apparently is without influence. The same author also found a diminished response to atropine in cases of chronic heart disease, with the exception of auricular fibrillation. As the patients in the present series ranged from 47 to 84 years of age, and as their weights also varied considerably/
considerably, it is all the more surprising that the degree of correlation between the initial rate and the acceleration produced should be so perfect. Furthermore, it has long been known that in the presence of structural heart disease, the response to atropine is somewhat diminished, (more particularly when aortic regurgitation is the predominant lesion) the normal pacemaker being in control. This observation has been confirmed by Crawford (42). Two of our cases (Cases 3 and 8) suffered from a regurgitant leak at the aortic orifice, but the response of the ventricles to atropine was apparently but little modified in these patients.

THE AURICULAR AND VENTRICULAR RANGES AFTER ATROPINE.

It has been demonstrated above that the ventricular response to atropine depends chiefly upon the rate at the time of injection. Such an observation is rendered the more surprising when the available data concerning the auricular response are analysed. The facts are recorded in the Table No. XVI, in which the auricular rates immediately before and the maximum rates after atropine are shown. On plotting the initial auricular rate against/
against the corresponding range after atropine, it becomes at once evident that no relationship exists between the two. In two cases (No. 8 and 10) auricular fibrillation accompanied complete heart-block and hence comparable figures are not available. The maximum auricular range was 55.4 in Case 3 (representing an increase of 77.0 per cent over the initial rate) and the minimum gain was 19.3 beats per minute (yielding a percentage increase of 35.5). The facts at our disposal therefore indicate that, while ventricular acceleration bears a close relation to the initial rate, this rule does not apply to the auricular response to atropine. This is in agreement with the conclusions of CRAWFORD (42) who found in cases of normal rhythm, that the rate after atropine could not be foretold from the rate existing before the drug was given. This observation would support the natural conclusion, that the auricles in complete heart-block respond to atropine very much after the same manner, as they do, when the normal pacemaker is in full control of the heart beat. On the other hand, it must remain an open question as to the nature and cause of the peculiar ventricular response.

From what has just been written it is not surprising to find that there is no obvious relationship between the auricular and ventricular ranges after/
after atropine. The first varies in an irregular manner from individual to individual even in health, and evidently quite as much in the presence of dissociation. The ventricular range on the other hand is largely determined by the pre-existing rate. This is in contrast to the effect of exertion, in which it has been shown that an inverse correlation exists between auricular and ventricular ranges.

The lack of agreement between the auricular and ventricular ranges after atropine must indicate a fundamental difference between the acceleration of exercise and that produced by atropine. It has already been suggested that the Bainbridge reflex regulates in large part, the balanced response of auricles and ventricles after exercise. After atropine the upper and lower chambers of the heart run their own course, the one is not the reciprocal of the other. SMITH, BURWELL & de VITE (200) found in normal men after an intravenous dose of atropine that the cardiac acceleration was accompanied by a diminution in the output of blood per beat with but little alteration in the volume of blood flow per minute. In all probability a similar state of affairs occurs in complete heart-block. If, after atropinisation, the minute volume of blood flow increased in proportion to the degree of ventricular acceleration/
acceleration, then it would be natural to suppose that, more blood accumulating on the right side of the heart, the Bainbridge reflex would regulate the auricular rate in accordance with the ventricular output. Actually the one does not appear to bear any relation to the other. It therefore seems justifiable to conclude that though the ventricular rate is increased by atropine, the stroke volume is in all probability proportionally reduced.

This conclusion is supported by the fact that in spite of the ventricular acceleration, little or no change occurred in the systolic or diastolic blood pressures. CRAWFORD (42) and SMITH, BURWELL & de VITE (200) detected no constant change in repeated blood pressure readings after atropine, either in health or in the presence of diseased hearts. The absence of constant changes in the blood pressure level in these cases, serves to indicate the remarkable adjustability of the circulatory mechanism in spite of the presence of complete heart-block. From these considerations, it would appear that the auricular response, being more or less peculiar to the individual, is little more than an expression of the degree of vagal tone existing before the injection. A large reaction to atropine predicates a pacemaker of high rhythmicity effectively held in check by a vagus centre of adequate tone.
A small auricular response from an average rate may be taken to represent a less active nerve centre, probably coupled with a reduced rhythmicity of the sino-auricular node.

Considering the nature of the ventricular response, it is obvious that some other mechanism related to the initial idio-ventricular rate must hold sway. This at once suggests that the natural rhythmicity of the centre of stimulus production determines the ventricular response. LEWIS (136) has shown that the natural frequency of the S-A node is greater than that frequency of the A-V node, and there is every reason to suppose that the spontaneous rhythmicity declines as the conducting tract is followed to its termination in the Purkinje tissue. In other words, when the lesion transects the upper part of the A-V node, then the site of effective stimulus production is likely to be relatively high in the conducting tract. A centre of stimulus production immediately below a lesion in the A-V node is likely to have a greater spontaneous rhythmicity than one at the level of the bifurcation of the main bundle. It is known that the A-V node bundle of HIS and its branches, receive vagal fibres (219). When the vagus is paralysed by atropine the response of the ventricles must be limited/
Auricles.

Ventricles.

A. H.
3. ix. '31.

Time in Minutes.
limited by the natural frequency of the controlling centre of impulse production. In other words, the higher the centre, the greater the possible response. It is therefore suggested, that the peculiar nature of the ventricular response to atropine, is primarily determined by the site of the lesion producing the block, an idio-ventricular centre situated in the upper regions of the conducting tract of relatively high natural rhythmicity, yielding a maximum response to atropine and vice versa.

As a converse of this, it would follow that vagal stimulation in complete heart-block is more likely to be effective in those instances in which idio-ventricular rate is relatively high. As will be shown later, there are some grounds for believing that this supposition is correct.

THE COURSE OF THE REACTION TO ATROPINE.

The course of the response is best depicted by plotting the auricular and ventricular rates against time elapsing after the injection. A typical reaction is shown in the accompanying Chart No. 8 (Case 5), and sections of the 27 electrocardiograms recorded in this experiment, from which the auricular and ventricular are calculated, are shown in FIG. I.
Uncomfortable

Auricles

Coupled Rhythm.

Ventricles.

ATROPINE SULPH. 0.0150 I.V.

Time in Minutes.

D.C.

15/10/30
This patient was an arterio-sclerotic subject aged 64 in whom the initial rates were 72.5 and 31.0 for auricles and ventricles respectively. Within five minutes of the intravenous dose of 1/30 gr. of atropine, the ventricle attains its maximum speed of 39.8 beats per minute. Thereafter the gradual decline in rate is recorded at 2 minute intervals. Fifty-four minutes after the injection, the ventricle has almost returned to its original rate. It is interesting to note that a very similar course of events is followed by the auricle, the maximum rates coinciding with the ventricular. The auricular effect, however, apparently persists for a longer time and passes off more gradually. At fifty-four minutes after the injection, when the observations ceased, the auricular rate stood at 79.5, the initial rate being 72.5. It can be seen that the response as it occurs in the auricles is very similar to that portrayed by the ventricles.

Very similar curves of atropine effect were recorded in the other cases. As an additional example, Case 3 may be quoted. The electrocardiograms from which the corresponding Chart (No. 9) has been constructed, are shown in FIG. 2. In some the maximum effect was registered within the first minute, in others 3 minutes after the injection. In general/
FIGURE 1.

Before Atropine:

9 min before

After Atropine:

1 min after

3 " "

5 " "

7 " "

9 " "

11 " "
general the maximum acceleration occurred synchronously in auricles and ventricles and by the end of an hour the ventricles had returned to their original rate, the auricles being a few beats quicker than at the commencement of the observations. That the response should be of such relatively short duration is somewhat surprising in view of the fact that dilatation of the pupil and some dryness of the mouth tended to persist after the cardiac effects had subsided. Some degree of mydriasis was generally obvious twenty-four hours after the test. There is no very satisfactory explanation why recovery should be more gradual in the terminations of the parasympathetic fibres of the third nerve, than in the tenth.

No striking changes occurred in the form of the electrocardiogram after atropine. Extrasystole were infrequent, and when they did occur, have not been included in the estimation of the rate. Coupled rhythm of short duration was only observed once in one individual after atropinisation. In no instance did the degree of block decrease. In certain cases the T waves during the higher rate of beating appeared to increase slightly in amplitude. The P waves were occasionally larger immediately after the injection than in the control records or towards the end of the experiments. Similar changes/
changes in the form of the individual waves have been observed to occur in health after atropine administration.

SUMMARY.

The response of ten individuals suffering from complete heart-block has been tested by the intravenous administration of 1/30 grain of atropine sulphate. Repeated electrocardiograms, taken at intervals before and after the injection, demonstrated that in every case studied, this drug produced an acceleration of the ventricular rate.

The prevailing view, constantly repeated in the literature, that atropine has little or no effect on the frequency of the ventricles is incorrect, and requires modification in the light of the peculiar character of the acceleration. The dose of atropine was sufficient to produce almost complete paralysis of the vagus. The maximum increase in ventricular rate was 47 beats per minute, representing a gain of almost 96 per cent over the initial rate. The minimum acceleration was 1.2 beats per minute, giving a percentage increase of 5.4. In only one case was the gain after atropine within the maximum range recorded/
FIGURE 2.

Before Atropine:

5½ min. before

3½ min. "

2½ " "

After Atropine:

½ min after

1½ min "

2½ min. "

4½ " "

6½ " "

8½ " "
FIGURE 2 (Continued).

10½ min. after

12½ " "

14½ " "

16½ " "

18 " "

21½ " "

23½ " "

25½ " "

27½ " "

29½ " "

33½ " "

36½ " "

39½ " "

42½ " "

45½ " "

48½ " "

51½ " "

54½ " "

FIGURE 2 (Continued).
recorded under similar resting conditions.

The initial ventricular rate is the important factor in determining the amount of acceleration for a given dose of atropine. The coefficient of correlation between the rate before atropine and the amount of ventricular acceleration produced by it is +0.9722 - a very significant relationship.

The law expressing the degree of acceleration for a given initial ventricular rate has been represented by a straight line formula. Actually this is probably not the best expression. It would appear from the available data, that a curve might be the best expression, but the facts are too scanty to allow of its exact determination.

The use of atropine as a means of distinguishing the bradycardia of complete heart-block from other causes, is therefore unreliable. Further work requires to be done on this subject with the object of determining the precise nature of the response to atropine in those cases of slow heart action in which complete heart-block is not present.

To obtain a decided effect on the ventricular rate, it is necessary to use an amount of atropine approaching the full paralysing dose. 1/30 grain of atropine given intravenously in 1 c.c. of normal/
normal saline was found to be sufficient.

In contrast to the ventricular response, the auricular acceleration does not appear to bear any relation to the initial auricular rate. Further the auricular range after atropine does not bear any relation to the ventricular. The amount of auricular acceleration varies irregularly from individual to individual. This is in sharp contrast to the relation between the auricular and ventricular ranges after exertion.

The auricular response probably reflects no more than the degree of vagal tone existing at the moment of injection.

The nature of the ventricular response suggests that the amount of acceleration is determined by the inherent rhythmicity of the specialised tissue at the centre of impulse production. It is suggested that when the lesion producing the block is situated in the uppermost part of the conducting tract, a greater response will occur after atropinisation than when the centre of impulse production lies at a lower level in the specialised tissues.

As a converse of this it may be suggested that vagal stimulation is more likely to be effective in slowing the idio-ventricular rate, when the centre/
centre for impulse production lies in or bordering on the A-V node. In other words, a centre of slow impulse production has, of necessity, a small available range, and vagus stimulation will have little, if any, effect in slowing the rate, just as atropine can produce but little acceleration.

The time relations of the auricular and ventricular reactions to atropine are very similar. The effect appears to pass off in the ventricles before the auricles. No striking changes occurred in the serial electrocardiograms after atropine. The defect in conduction was not restored by the administration of atropine in any of the patients.
THE INFLUENCE OF VAGO-CAROTID PRESSURE.
THE INFLUENCE OF VAGO-CAROTID PRESSURE.

In the previous section it has been shown that atropine accelerates the idio-ventricular rate in complete heart-block. It is therefore not unreasonable to consider at this point the influence of an increase of vagal tone on the rate of the upper and lower chambers of the heart.

The inhibitory effects of vagus stimulation in man were first studied by CZERMAK (48) in 1866 although PARRY (169) had observed in 1799 that firm pressure exerted in the neck over the carotid artery produced a slowing of the heart beat. As a result of the more recent work of HERING (104) it is now universally accepted that inhibition results, not from direct stimulation of the nerve trunk as it lies in the neck, but from reflexes set up by distension of the carotid sinus consequent upon either partial or complete occlusion of the artery immediately distal to its bifurcation. Numerous sensory nerve fibres supply the wall of the vessel at this point, and there is every reason to suppose that distension of the sinus inaugurated a reflex which reaches the heart via the vagus, and produces a fall in blood pressure and a slowing of the heart beat.

In health the effects of vago-carotid pressure/
pressure are generally conspicuous, though on occasions, in perfectly normal individuals some difficulty may be experienced in their demonstration. Numerous workers have shown that appropriate stimulation on either side of the neck may be the means of producing a transient slowing of the whole heart, perhaps cardiac standstill, heart-block, or ventricular escape. In fact the influence of the vagus on the human heart is altogether comparable with that observed in the dog under more rigid experimental conditions. The work of ROBINSON & DRAPER (185) LASLETT (131) RITCHIE (181) & COHN (38) has demonstrated that as a general rule the right nerve is more potent in causing slowing or arrest of the auricular beat (and hence of the whole heart in health) and the left nerve in producing A-V block.

A study of the literature reveals that no systematic attempt has been made to observe the influence of vago-carotid pressure in the presence of complete heart-block in man, though many reports have been made on the influence of the vagus in experimental heart-block. As a result of extensive work in the laboratory it is generally stated that the vagus has no influence on the independent rhythm of the ventricles (ERLANGER (61) (62) (63) (64), KAHN (122), HERING (103), RIHL (179), CULLIS & TRIBE (43))
This conclusion so amply confirmed probably applies with special force to the acute experiment, stimulation being applied to the peripheral end of the cut nerve a few minutes after transection of the bundle of HIS. Some doubt has been cast on these conclusions for FREDERICQ'S (73) work led him to conclude that while complete destruction of the bundle was accompanied by loss of vagal influence on the ventricle, yet after moderate compression (sufficient to induce complete heart-block), the vagus still maintained its inhibitory power over the ventricular rate. The experiments of ERLANGER & BLACKMAN (64) who studied the physiology of complete block in animals, which had survived for several months the operative interference with the conducting tract, are worthy of careful consideration. The dogs used in these researches were afterwards killed and were found to have a lesion of the bundle tissues comparable to that of chronic auriculo-ventricular block as it occurs in man. As a result of several experiments in these animals, ERLANGER & BLACKMAN state that, while stimulation of the peripheral end of the vagus slows the auricles, it is without decided effect on the ventricles, "although the strongest stimulation reduces slightly the/
the rate of the ventricles". The ventricular response to vagal inhibition occurred after 2 or 3 beats, when the auricles had already begun to quicken. It therefore seems justifiable to conclude that vagus stimulation, if of sufficient intensity, may slow the ventricular rate in certain hearts despite the presence of chronic complete block. A full dose of atropine will increase the rate in man, and it is equally reasonable to suppose that an increase of vagal tone may produce at least a slight, though perhaps transient slowing. CRAWFORD (42) has shown that the tone of the vagus centre decreases in later life, particularly after the age of fifty years, that hearts the site of chronic degenerative processes respond less than healthy ones, and that as age advances the heart loses much of its youthful rhythmicity. From this it would appear that a given degree of vagus stimulation is likely to be followed by less conspicuous effects in later life, particularly in the presence of organic heart disease.

There are several isolated instances reported in the literature where vago-carotid pressure has been tested in the presence of complete heart-block in man, with uniformly negative results. RITCHIE (181) examined three cases, using bilateral vagus/
vagus compression repeatedly in one instance, but the
ventricles in each individual remained unaltered in
rate. Likewise KLEEMAN (127) in the course
of an investigation of the action of the vagus on the
heart, examined one case and came to the same conclu-
sion. A search of the literature has revealed only
one case of complete heart-block in man in which the
author refers to a slowing of the ventricular rate
produced by vago-carotid compression in man.
VOLHARD (218) in 1909 in a paper on the relation of
the Stokes-Adams syndrome to heart-block depicts in-
hibition of the ventricular rate by vagus compression.
His curve 21 clearly demonstrates quite decided slow-
ing during the period of vagal stimulation.

METHODS EMPLOYED IN TESTING
THE ACTION OF THE VAGUS.

In these experiments it was found desir-
able to employ the film camera in conjunction with
the string galvanometer in order that a long contin-
uous record might be obtained of the heart rate be-
fore, during and after the vago-carotid pressure.
After the patient had rested on the examination couch
until the heart rate appeared to be steady a contin-
uous strip of film was exposed. After ten or twenty
ventricular beats had been recorded, sufficiently
firm pressure was applied to obliterate the carotid artery on one side of the neck. The duration of the pressure was photographed on the film by an electrical signal. Pressure was maintained for four or five complete ventricular cycles, and after it was released, the exposure was continued for a further ten or twelve ventricular beats in order to secure a record of the recovery period. A fast running film facilitated accurate measurement. At least one right and one left pressure was recorded in each individual. In many patients the experiment was repeated on different days, bilateral pressure was employed in several individuals, and occasionally double ocular pressure was also recorded. No attempt was made to measure the amount of pressure used and doubtless it varied from case to case. The tips of the first, second and third fingers were applied together. The artery was as a rule easily felt but if, as sometimes happened, the fingers slipped off the vessel during the course of the pressure, the experiment was discarded.

In interpreting the results particular emphasis is placed on the third section of the curve - i.e. that portion which represents the after-effects or recovery period. In order to show that vagus stimulation produces an effect on the ventricular/
ventricular rate, it is not enough to demonstrate slowing merely during the period of pressure. If the stimulation be the cause of the decreased frequency, then the rate after pressure is released should approximate to that which existed before the pressure was applied. A natural decrease in the frequency of the ventricular rate should not be confused with that induced intentionally.

Measurement of the control strip revealed that small variations in the ventricular rate do occur even under uniform conditions of bodily rest. The ventricular rate per minute was calculated from successive groups of three or four ventricular complexes. The rate of the three cycles in the group immediately before the pressure was applied was often found to be a trifle faster than that of the preceding two or three groups. In order to apply as rigid a test as possible this reading was discarded, and the slowest rate of the three or four groups preceding the pressure was taken as the control ventricular or auricular rate. As pressure was applied for three or four ventricular cycles, the rate per minute was calculated for these as one group. After the pressure was released the first three beats recorded were disregarded and the rate after pressure calculated for the second or third group of ventricular/
<table>
<thead>
<tr>
<th>CASE NO. &amp; INITs.</th>
<th>VAGAL PRESSURE</th>
<th>AURICULAR RATE</th>
<th>VENTRICULAR RATE</th>
<th>DECLINE</th>
<th>IN RATE</th>
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<tbody>
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<td>RIGHT P.</td>
<td>LEFT P.</td>
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<td>Before pressure</td>
<td>69.8</td>
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<td>During &quot;</td>
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<td>After &quot;</td>
<td>66.8</td>
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<td>After &quot;</td>
<td>Auricular Fibrillation</td>
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<td></td>
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</tr>
<tr>
<td>13</td>
<td>Mrs H.</td>
<td>Before pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>During pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After &quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Mrs Dev.</td>
<td>Before pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>During &quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After &quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ventricular cycles. Accurate measurement of the curves was facilitated by a hand lens, and in certain instances readings were made with a standard pattern comparator.

RESULTS OF VAGO-CAROTID PRESSURE.

Thirteen cases of complete heart-block were tested with right and left sided vago-carotid pressure. In two cases the observations are complicated by the presence of persistent coupled rhythm - each idio-ventricular beat being followed by a premature contraction. In a third subject (Case 7), who suffered from intermittent complete heart-block, the test was only applied during normal rhythm with full conduction of each auricular impulse. Unfortunately vagus pressure was not attempted during the period of complete heart-block. It is interesting to note, however that while right pressure slows the rate of the whole heart, left sided stimulation produced 2 to 1 block with slight quickening of the auricular rate.

The result obtained in ten cases of complete heart-block are presented in the accompanying TABLE No. 18. Unless proof was obtained that the chambers of the heart accelerated after the stimulation was released
released, the result of vagus pressure was regarded as inconclusive, even if the rate during pressure was less than the minimum recorded during the control period. In three of the ten individuals (Cases 1, 12 and 14) definite slowing of both auricular and ventricular rates was observed during the period of vagus stimulation. In Case 1 left-sided pressure was ineffective, but as a result of compression on the right side, the auricular rate fell from 69.8 to 61.0, and the ventricular rate likewise declined from 24.4 to 23.0. The most striking effects were obtained in Case 12. This man's auricular rate decreased by 30.7 beats per minute, from 82.7 to 52.0. At the same time the ventricles slowed in rate by 13.0 beats per minute, the speed being 58.7 before and 45.7 during compression. After the pressure was released the auricular rate increased to 81.2 and the ventricular to 53.8. The effect of left-sided pressure was almost as conspicuous, the auricular rate declining by 21.7 beats and the ventricular by 8.3 beats per minute. Curves demonstrating the effects of right and left vago-carotid pressures in this man are shown in PLATE 1. In each instance the strips of film are continuous, but they have been cut and reduced in size for the sake of reproduction/
reproduction. In the third patient (Case 14) right-sided pressure produced effects more definite than those observed when the left side was compressed. A fall of 3.9 beats per minute occurred in both auricular and ventricular rates during right-sided pressure.

It is not intended to lay much emphasis on the results obtained in the remaining seven cases. Slowing in the auricular rates varying from 15.0 to 0.2 beats per minute was recorded, generally as a result of right-sided pressure. In only three cases of the series did left-sided pressure cause a slowing of the auricular and ventricular rates. It is perhaps sufficient to state that the amount of slowing in the ventricular rate for the seven remaining cases was 0.4, 0.3, 0.5, 0.3, 0.7, 0.3 and 0.3 beats per minute.

It may be doubted whether such a small amount of slowing can be definitely attributed to vagal inhibition, for the figures presented are hardly outside the range of experimental error. Further, it has already been shown that the idio-ventricular centre of stimulus production is endowed with a spontaneous range in rate.

Natural, though small fluctuations occur continuously/
continuously, the rate of contraction waxing and waning within narrow limits from minute to minute. For this reason it must not be assumed that in a given instance such a limited decrease in rate is of necessity attributable to the stimulation applied, even if it be observed on more than one occasion in the same individual. Nevertheless it is justifiable to point out that the change in ventricular rate observed in each of these seven patients is always in the same direction if not for left-sided then right-sided pressure.

It would seem reasonable to conclude that in three individuals vago-carotid pressure slowed the ventricular rate. In one, (Case 12) right and left compression appeared to be about equally effective. In the second (Case 14) right-sided pressure was more effective than left and in the third (Case 1) slowing occurred in response to compression on the right side but not on the left.

In the remaining seven cases it must remain a matter of conjecture whether this method of inducing an increase of vagal tone makes any material difference to the natural fluctuations in the rate of the idio-ventricular centre. The observed decrease did not exceed the spontaneous range of rate, though/
though it was observed to accompany either right or left stimulation in each of the seven individuals. The fact that it was generally possible to slow the auricular rate indicates that some degree of vagal inhibition was induced, but the ventricles, already beating at a slow rate, were largely immune to this form of interference. It has already been shown that the release which occurs on vagal paralysis bears a relation to the initial rate. Had it been possible to apply the opposite effect, — a uniform and powerful degree of vagal stimulation — through this series of cases, then it might be reasonably anticipated that the amount of slowing induced would likewise bear a relation to the initial ventricular rate. Digitalis is a vagal stimulant and the interesting response to this drug is discussed on page 275.

Further information on this aspect of the susceptibility of the ventricles to a relatively sudden increase of vagal tone might be derived from a study of the action of such drugs as pilocarpine, physostigmine or muscarine, all of which are known to be parasympathetic stimulants. The use of full doses of pilocarpine in the presence of organic cardiac disease is however, not without danger, in that/
in that collapse and pulmonary oedema occasionally occur after its use. But, even in healthy men, it often fails to induce slowing and this, when it does occur, is generally slight and always transient. Acceleration of the heart beat is commonly observed (45). The experimental work of CULLIS & TRIBE (43) indicated that this drug failed to induce inhibition after the bundle had been divided. Physostigmine slows the heart and raises the blood pressure in mammals, but in man, serious dizziness and faintness occur before the heart is affected (SOILLMAN (202)). The effect of muscarine on the ventricles has also been tested by CULLIS & TRIBE (43) after the experimental production of complete heart-block in animals. Inhibition was not induced. In man, CUSHNY (45) points out that, instead of a slow pulse, inhibition after muscarine is very frequently absent and that acceleration, accompanied by palpitation and discomfort in the region of the heart may occur after the use of this drug.

For these reasons drugs of the parasympathetic stimulant group were not employed. In therapeutic doses their inhibitory effect on the heart is neither important nor reliable and full doses may be followed by alarming or even dangerous symptoms. Nevertheless, it is known that, at least
in animals, minimal doses augment the effects of
direct vagal stimulation. In further work on this
subject it would seem desirable to repeat the vago-
carotid pressure test after the parasympathetic nerve
endings had been sensitised to a small dose of one
of these drugs. There is no record in the litera-
ture of such a procedure having been applied to the
study of chronic auriculo-ventricular block in man.
By such means, more definite information on the re-
sponse of the ventricles to an abrupt increase of
vagal tone might be obtained. The influence of full
doses of atropine being so conspicuous, it is rea-
sonable to suppose that, by the employment of a suit-
able technique, the counter effect might be demon-
strated with a certainty which has been denied to
the experiments conducted in this series of cases.

SUMMARY.

A study of the literature reveals only
one case of complete heart-block in man, in whom
vago-carotid pressure induced a decided slowing of
the ventricular rate. In acute animal experiments
uniformly negative results after direct vagal stimu-
lation or after such drugs as pilocarpine or muscarine
are/
are also the rule. On the other hand certain exceptions have been noted in the course of experimental work, strong stimulation occasionally causing a slight decrease in the ventricular rate.

The effect of right and left vagal stimulation has been tested on ten cases of complete heart-block in man. In one case pronounced slowing of both auricular and ventricular rates occurred and in two others some degree of slowing was induced.

In the remaining seven cases the results are not sufficiently decisive to permit of definite conclusions. The difficulties encountered in interpreting the results are discussed. As the release after a full dose of atropine bears a close relation to the initial ventricular rate, it might be anticipated that powerful vagal stimulation might have a similar but opposite effect on the ventricles.

Drugs, belonging to the group of parasympathetic stimulants have not been employed on account of the fact that in therapeutic doses their action on the heart is unreliable. Full doses in man are not without danger. A technique, combining minimal doses of one of these drugs with vago-carotid pressure has been outlined. In order to determine precisely/
precisely whether the slow beating ventricle is invariably capable of responding to vagal stimulation further work along the lines suggested would seem desirable.

Theoretically it would appear probable that the converse of the atropine response does hold true, but so far it has not been satisfactorily demonstrated.
THE RESPONSE TO AMYL NITRITE.
THE RESPONSE TO AMYL NITRITE.

In previous sections of the present study the effects of vagal stimulation and paralysis have been described. Amyl nitrite, in virtue of its power of rapidly reducing the arterial blood pressure is naturally associated with the parasympathetic system. Its influence on the action of the heart in the presence of complete block may therefore be conveniently considered at this point.

In 1867 LAUDER BRUNTON introduced this drug to therapeutics as a remedy to be inhaled for the relief of angina pectoris and four years later was able to show (20) that the diminution in blood pressure was not due to a weakening of the heart's action but to a dilatation of the peripheral vessels depending upon a direct effect of the nitrite on the vessel walls. By its dramatic action it has aroused much interest during the years which have elapsed since its introduction and it has formed the subject of much enquiry and investigation.

In health, the inhalation of the nitrite of amyl is followed within a few seconds by a change in the heart rate and a transient but abrupt fall in blood pressure. At first there is often some/
some slight slowing of the heart beat probably of reflex vagal origin from the respiratory passages. Very soon however the heart is greatly quickened. The cardiac acceleration occurs in response to a number of interacting factors. MAYER and FRIEDRICH (156) demonstrated in animals that tachycardia of amyl nitrite was mainly due to depression of the vagus centre, for after section of the vagi, or after atropine, little further acceleration occurred. DOSSIN (53) showed that the remaining acceleration was abolished by division of the accelerator nerves. SOLLMAN (202) states that the depression of the vagus centre is due to the fall in blood pressure, and not to a direct action of the nitrite, for no acceleration occurs if the cerebral blood pressure level is maintained artificially. While reflex vagal inhibition is a prominent feature, the action of amyl nitrite is therefore more complex than that of atropine, and even perhaps than that of adrenaline [SCHERF and ZDANSKY (192)], for beside parasympathetic release and peripheral vasodilatation, a raised tone in the acceleration nerves is also known to occur. BRONK and FERGUSON (19) have recently demonstrated that the inhalation of amyl nitrite increases the discharge of impulses along the sympathetic fibres supplying the heart, a definite/
definite relation existing between the number of nerve impulses and the heart rate. In therapeutic doses the nitrites have no direct action on the heart muscle. [CLARK (30)].

The fleeting nature of the response to amyl nitrite makes accurate analysis of the reaction difficult. In man there is no satisfactory method of obtaining a continuous record of the blood pressure comparable to that yielded by the polygraph or electrocardiograph whereby changes in the rate of the heart may be observed with accuracy throughout the experimental period. Nevertheless VACQUEZ (215) from a study of a considerable number of individuals formed the opinion that the fall in systolic pressure commenced between seven and nine seconds after the start of inhalation and that the lowest level was reached about the fifteenth second. The fall in a given individual may amount to 60 or 70 millimetres if the initial pressure is high, but in health the decrease does not amount to more than 15 or 20 millimetres as a rule. The average effect is about the same in health and disease (202). In cases of abnormally high pressure the absolute fall may be greater than in health, but the percentile fall and the duration of the effect are very much the same. After the blood/
blood pressure has fallen to its minimum level, usually two minutes elapse before the progressive increase commences. The return to the normal level is reached about 8 or 10 minutes after the inhalation is commenced. In association with the changes in blood pressure a great acceleration of the heart occurs in healthy subjects. This may amount to 200 per minute, but only for a few seconds, and it is not uncommon to find that at the height of the reaction, within one minute of commencement, that the heart has doubled in rate.

COTTON, SLADE and LEWIS (40) found that the rise in pulse rate was especially conspicuous in those individuals in whom the pulse is also readily accelerated by exercise, emotion or other physiological cause.

THE RESPONSE IN CASES OF COMPLETE HEART-BLOCK

Although amyl nitrite was introduced by JOSUE and GODLEWSKI (120) in 1913 as a clinical test to elucidate the nature of bradycardia, little work has been done on this subject and no systematic analysis of the results in a consecutive series of cases has been published. VACQUEZ (214) states/
states that the bradycardia of complete heart-block
is equally refractory to atropine and amyl nitrite.
BELLOIR and DUBOS (11) compared the response of
thirty individuals to amyl nitrite and atropine
and were able to establish a constant parallelism
in the rate of the heart after these drugs. In
general a greater, though more transient, accele-
ration occurred after the nitrite than after the
atropine. In complete heart-block no increase
of ventricular rate was observed after the inha-
lation of amyl.

The opportunity has been taken to study
the response of 7 individuals in this series of
cases. After a period of rest, during which re-
peated blood pressure readings were taken,
a continuous record of the heart beat was made
using the film camera in association with the
string galvanometer. After a dozen or more ven-
tricular cycles had been photographed, the patient
was given 3 minims. of amyl nitrite to inhale.
Each subject was instructed to breathe as naturally
as possible and the duration of the period of in-
halation was marked by an electrical signal on the
running photographic film. As a general rule, it
was possible to secure a record lasting from $\frac{1}{2}$ to
$2\frac{1}{2}$ minutes. Blood pressure readings were recorded
as/
<table>
<thead>
<tr>
<th>CASE NO. &amp; INITIALS</th>
<th>AURICULAR RATE BEFORE</th>
<th>AURICULAR RATE AFTER</th>
<th>GAIN %</th>
<th>VENTRICULAR RATE BEFORE</th>
<th>VENTRICULAR RATE AFTER</th>
<th>GAIN %</th>
<th>BLOOD PRESSURE SYSTOLIC MINIMUM BEFORE</th>
<th>BLOOD PRESSURE SYSTOLIC MINIMUM AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mrs T.</td>
<td>66.8</td>
<td>88.4</td>
<td>21.6</td>
<td>32.3</td>
<td>27.6</td>
<td>30.1</td>
<td>2.5</td>
<td>9.1</td>
</tr>
<tr>
<td>3. D. J.</td>
<td>76.6</td>
<td>138.1</td>
<td>71.5</td>
<td>93.4</td>
<td>43.1</td>
<td>44.4</td>
<td>1.3</td>
<td>2.9</td>
</tr>
<tr>
<td>4. W. T.</td>
<td>66.3</td>
<td>76.0</td>
<td>9.7</td>
<td>14.6</td>
<td>33.6</td>
<td>39.8</td>
<td>6.2</td>
<td>18.5</td>
</tr>
<tr>
<td>5. A. H.</td>
<td>67.9</td>
<td>78.4</td>
<td>10.5</td>
<td>15.5</td>
<td>32.6</td>
<td>33.1</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>8. J. E.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. J. D.</td>
<td>105.4</td>
<td>137.6</td>
<td>32.4</td>
<td>30.5</td>
<td>60.0</td>
<td>109.8</td>
<td>49.6</td>
<td>82.0</td>
</tr>
<tr>
<td>13. Mrs H.</td>
<td>72.2</td>
<td>94.1</td>
<td>21.9</td>
<td>30.3</td>
<td>44.4</td>
<td>85.8</td>
<td>41.4</td>
<td>93.3</td>
</tr>
</tbody>
</table>

**TABLE XIX:** To show the response to the inhalation of amyl nitrite in seven cases of complete heart-block.
as rapidly as possible after the inhalation was commenced and the time of each was marked by an appropriate signal on the photographic record. The rates of the auricles and ventricles per minute were then calculated in successive groups. Each group was composed of four or more ventricular cycles and the rate per minute was calculated until the reaction had practically subsided. The details for seven cases of complete block are shown in the accompanying TABLE XIX.

This TABLE shows that in two subjects (Cases 12 and 13) a remarkable gain in ventricular rate occurred after the inhalation of amyl nitrite. In Case 12 the rate rose from 60 to 109.8, a gain of 49.8 beats per minute yielding a percentile increase of 83. In Case 13, the initial rate was 44.4 and at the height of the reaction the ventricles accelerated to 85.8, a gain of 93.3 per cent. At least in this respect these two cases differ conspicuously from the remainder in whom only a trifling degree of acceleration was observed. It is necessary to point out that the block remained complete in each instance in which the response was tested.

In a sense these results challenge the value/
value of amyl nitrite as a test for the presence of complete heart-block. As a rough and ready clinical means of differentiating the forms of bradycardia the drug does however serve a purpose. A failure to respond by an appreciable amount of acceleration is in favour of complete block. On the other hand even a doubling in rate does not exclude the possibility of dissociation. The ease,rapidity and harmlessness of the amyl nitrite test are points in favour of an extended clinical trial.

Before analysing in detail the response to amyl nitrite it is well to point out that there is of necessity less consistency throughout this series of cases than in the atropine test. In the latter instance, an accurately measured and uniform dose was administered, by the intravenous route, to each subject. With a volatile drug, such as amyl nitrite, an unknown amount of the dose will be wasted during expiration and the concentration in the alveolar air must therefore have varied considerably in different individuals. Only by the use of a special breathing apparatus, with inspiratory and expiratory valves, could these discrepancies in the drug's administration be avoided. The difficulties are not/
not insurmountable but it was considered sufficient for our purposes that a definite effect was produced in each individual. Some throbbing in the head, or a transient giddiness were as a rule experienced within half a minute of the start of inhalation, and a definite flush over the face and neck made it obvious that the drug was acting in the peripheral circulation. Nevertheless, the precise amount of the nitrite absorbed being unknown, the results cannot be compared on a strictly quantitative basis.

It is, however, permissible to compare the auricular acceleration with the corresponding ventricular in the different individuals throughout the series. By plotting the auricular gain (either as a percentage of the initial rate or as the actual gain) against the ventricular, it becomes evident that for this group of cases there is no agreement between the two. The same fact was true of the response to atropine. Auricles and ventricles apparently react quite independently one from the other. On the other hand it has been shown that in the response to exertion, an inverse correlation of high degree exists between the auricular and ventricular ranges. But this does not hold good for either/
### TABLE XX:

<table>
<thead>
<tr>
<th>CASE NO. &amp; INITIALS</th>
<th>VENTRICULAR RATE PERCENTAGE GAIN</th>
<th>TIME ELAPSING</th>
<th>BLOOD PRESSURE PERCENTAGE FALL</th>
<th>TIME ELAPSING</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mrs T.</td>
<td>9.1</td>
<td>43 secs.</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3. D.C.</td>
<td>2.9</td>
<td>16 &quot;</td>
<td>26.8</td>
<td>80 secs.</td>
<td></td>
</tr>
<tr>
<td>4. W.T.</td>
<td>18.5</td>
<td>20 &quot;</td>
<td>38.5</td>
<td>70 &quot;</td>
<td></td>
</tr>
<tr>
<td>5. A.H.</td>
<td>1.5</td>
<td>66 &quot;</td>
<td>37.0</td>
<td>65 &quot;</td>
<td></td>
</tr>
<tr>
<td>8. J.B.</td>
<td>5.8</td>
<td>75 &quot;</td>
<td>6.0</td>
<td>50 &quot;</td>
<td>Nervous individual Only slight flush.</td>
</tr>
<tr>
<td>12. J.D.</td>
<td>83.0</td>
<td>46 &quot;</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>14. Mrs H.</td>
<td>93.3</td>
<td>40 &quot;</td>
<td>34.0</td>
<td>65 &quot;</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE XX:** To show the percentage increase in ventricular rate and the percentage fall in blood pressure induced by the inhalation of amyl nitrite.
either atropine or amyl nitrite.

It may be that the lack of uniformity in the dose of the drug absorbed accounts in part for the fact that in this series of cases the amount of ventricular acceleration does not bear a close relation to the initial ventricular rate. The number of patients tested is too small to render comparison with the effect of atropine any more than approximate. Apparently the mechanism underlying the ventricular response to amyl is different to that controlling the atropine reaction. The scanty number of cases, and the unavoidable discrepancies associated with the administration of amyl nitrite make it unsafe to draw precise distinctions between the reactions to these two drugs.

In the following TABLE NO.XX the percentage gain in ventricular rate is compared with the percentage fall in blood pressure for each individual in whom reliable readings were secured. The time elapsing from the start of inhalation to the maximum effect on the heart rate has been accurately calculated from the electrocardiogram. It was however only possible to secure two or three blood pressure readings in each experiment, and while the figures/
figures from which the percentage fall is calculated are naturally the lowest recorded this may well have been exceeded and have passed unobserved.

VAQUEZ (215) has shown that the low blood pressure level is maintained for nearly two minutes. As all the readings were secured within that time they may be regarded as approximately correct. In one instance at the end of 50 seconds (Case 8) the systolic pressure had only fallen by 6 per cent as compared with the resting value. This result is exceptional when it is compared with the other cases in the series, but it is quite in keeping with the observation of RICHARD (178) that nervous and anxious patients may react atypically. This author reports that, the individual of highly strung temperament may, presumably as the result of excitement, exhibit an actual rise of pressure after the administration of nitrite. The four other cases exhibited a percentage fall of pressure ranging from 38.5 to 26.8.

The time elapsing from the start of inhalation until the maximum heart rate was attained varied a good deal in the different subjects. The shortest interval was 16 seconds, the longest 75 seconds. There is no obvious relationship between the/
the amount of acceleration and the time elapsing until the maximum rate was reached. Similarly, the magnitude of the fall in systolic pressure does not appear to bear a relation to the corresponding gain in ventricular or auricular rate. This might be anticipated, for the reason that the fall in blood pressure is not necessarily made good by an increase in rate. The volume flow of blood per minute depends more upon the amount ejected per beat than upon the ventricular rate alone. In complete heart-block, with a more or less fixed ventricular rate, the fall in pressure must ultimately be made good by an increase in the stroke volume of the ventricles.

No studies have been made on the circulation rate after the administration of nitrites in pathological cases, but some interesting experiments in normal individuals have been reported by LINDHARD (142) and by GAISBOCK and JARISCH (75). It has been found that amyl nitrite inhaled for two minutes produced a 100 per cent increase in the pulse rate, a 25 per cent increase in the cardiac output and only a slight decrease in blood pressure. On the other hand, by the inhalation/
inhalation of the drug for a longer period, the
blood pressure fell considerably, due presumably
to a decreased systolic discharge and a failure to
compensate by increase in rate. This probably re-
sults from a relative stagnation of blood in the
periphery, the consequence of extreme vaso-dilation.
The venous return to the heart will therefore be
decreased. The ventricles are thus starved of
their full quota of blood on account of the temporary
accumulation in the periphery. As the vessel walls
recover their tone, rapid compensation will be
effected by the active heart muscle.

Of the five cases in which it was possible
to secure fairly accurate blood-pressure readings
a decided fall in pressure occurred in four. Case
13, reacted to the vaso-dilation like a normal per-
son in that the ventricular rate increased by 93.3
per cent. So far as the available blood pressure
readings allow of comparison, it is of interest to
note that the percentage fall in systolic pressure
viz. 34 was no greater in this woman than in the
other subjects tested. In cases 4 and 5, the per-
centile fall in blood pressure was somewhat greater
than in case 13, though only the slightest ventric-
cular acceleration occurred. It seems justifiable
to conclude that, in those instances in which the
Ventricles/
ventricles fail to gain appreciably in rate compensation for the fall in blood pressure is accomplished in some measure by a greater ventricular output per beat. This must be the usual means of adaptation in complete heart-block.

THE COURSE OF THE RESPONSE TO AMYL NITRITE.

It has been shown above that the reactions of these cases of complete block to amyl fall into two groups,

(1) those in which the ventricular acceleration is slight not exceeding 18.5 per cent of the resting rate

(2) and those in which a very decided gain in ventricular rate occurs, even up to 93 per cent.

There were four individuals whose reaction placed them in the first group and two individuals in the second.

In describing the response to amyl nitrite it is convenient to select a representative experiment from each group. In case 4 the gain in ventricular rate amounted to 6.2 beats per minute.

The auricular and ventricular rates have been plotted against time elapsing from the start of inhalation. This case is representative of the first group/
group composed of Cases 1, 3, 4 and 5. Of the two individuals (Cases 12 and 13) in whom amyl nitrite produced a great acceleration of the idioventricular frequency, the reaction in the latter subject has been selected as being suitable for comparison with the first group.

The chart No. 10, (Case 4) shows that though the blood pressure falls from 180 to at least 130, there is but little change in the ventricular rate. The maximum gain of 6.2 beats per minute occurs 20 seconds after the commencement of inhalation. This may be, perhaps at least in part, due to excitement and some associated respiratory embarrassment. The maximum gain in auricular rate does not occur until 52 seconds have elapsed. The fall in blood pressure in the absence of ventricular acceleration must be corrected by a greater ventricular systolic discharge.

In chart No. 11, (Case 13) a totally different type of reaction to amyl nitrite is depicted. Auricular and ventricular acceleration occur within 3 seconds of commencing the inhalation and reach a maximum at the fortieth second. A portion of the long continuous film record, from which Chart has been constructed is presented in PLATE II. The strips numbered 1, 2, 3 have been cut/
The graph shows the changes in systolic blood pressure, auricular rate, and ventricular rate over time in seconds. Amyl nitrite was inhaled at the point marked on the time axis, which caused a significant drop in blood pressure and an increase in heart rates.
cut and mounted to show the immediate response to the inhalation of amyl nitrite. The start of inhalation is marked by the signal in the lower part of Strip 1 and the cessation in Strip 2. Strip 4 which is the final portion of the film, ends at 174.0 seconds from the first inhalation of amyl nitrite. The intervening section of the record between the end of Strip 3 and the commencement of Strip 4 has not been included in order to facilitate reproduction and to economise space.

Despite the persistence of complete dissociation the ventricular rate is so extremely labile that within 40 seconds it almost doubles in rate. On the other hand, during the same period, the auricle only increases by 30 per cent. Despite the increase in ventricular rate, the blood pressure fell by 34 per cent, as compared with 38 per cent in the previous case. If it be assumed that each of the individuals received a similar quantity of amyl nitrite, it might therefore be argued that an increase of rate is not essential in order to maintain an adequate pressure level. Indeed, we know from the exercise tests, that a greater rate could be attained in response to exertion, than that which was observed after amyl when the pressure was reduced. It has also been pointed out how after exertion/
exertion, a minimal ventricular response is accompanied by a maximum auricular and vice versa. It has already been suggested that this phenomenon is related to an increased venous return and that the excessive auricular rate results from an augmented Bainbridge reflex. No such relationship is found to exist after the administration of amyl nitrite, probably for the reason that in contrast to exertion, the venous return is temporarily greatly diminished, at least until the height of the reaction is reached.

Finally it should be pointed out that these patients suffered no ill-effects from the absorption of amyl nitrite. Subjective symptoms were surprisingly slight, though all complained of some throbbing in the head for a few seconds. The blush was often less marked than in healthy subjects. Two individuals (Cases 3 and 8), who also suffered from free aortic regurgitation, were amongst those tested. Neither experienced any untoward symptom. There were no striking changes in the electrocardiograms. The P, R, and T waves remained constant in form throughout the period of observation, except in one individual (Case 1) in whom the R waves declined temporarily in height and the QRS interval widened slightly, the change in form being of the type/
type associated with partial block of a branch of the bundle of HIS.

SUMMARY.

It has been possible to test the effect of the inhalation of amyl nitrite on seven cases of complete dissociation. By employing the film camera in association with the string galvanometer, a continuous electrocardiogram permitted accurate enumeration of the auricular and ventricular rates over the period of changing blood pressure.

In two subjects a remarkable increase in ventricular rate followed the administration of amyl nitrite. In case 12, the ventricular rate increased by 83.0 per cent, and in case 13 by 93.3 per cent. By contrast the corresponding auricular gain was in the neighbourhood of 30 per cent in each of these cases. Amyl nitrite did not relieve the block, which remained complete throughout the period of observation.

In the remaining five cases, while the auricles accelerated by various amounts, the ventricular gain was slight, ranging from 1.5 to 18.5 per cent.
As the precise amount of amyl nitrite inhaled must have varied in the different subjects the results are not strictly comparable throughout this series. Nevertheless a decided effect on the vasomotor mechanism was invariably produced. A definite facial blush was always observed and a throbbing headache commonly complained of. The variation in dosage implies less consistency in these results than in the reaction to atropine.

There does not appear to be any relation between the auricular and ventricular ranges after the administration of amyl nitrite. Auricles and ventricles apparently react independently to the fall in systolic pressure produced by this volatile nitrite.

Similarly there does not appear to be a definite relation between the initial rate and the associated acceleration in this series of cases. In the reaction to atropine the degree of ventricular acceleration is a function of the pre-existing rate. A larger series of cases and more precise methods of dosage will be required before it can be definitely stated that, in this respect, the amyl nitrite reaction differs materially from that of atropine.
atropine. As these drugs differ considerably in their pharmacological actions, it is probably true that the high degree of correlation between the initial rate and degree of acceleration found to exist in the atropine response, does not hold good for amyl nitrite.

It is also probably true to say that, in the presence of complete dissociation, amyl nitrite either causes a very marked increase of rate (2 cases) or only a trifling amount (5 cases), whereas atropine produces an acceleration in proportion to the rate at the moment. Employed as a rough and ready clinical test in bradycardia this would imply that while a failure to accelerate after the inhalation of amyl nitrite is in favour of complete heart-block, yet acceleration in itself is compatible with the presence of complete dissociation. In other words a negative response favours complete-block, but a positive does not exclude it.

In the two individuals in whom the ventricles showed a conspicuous acceleration, the quickening occurred almost instantaneously and reached a maximum respectively 46 and 40 seconds after the commencement of inhalation. The auricles accelerated/
accelerated synchronously but to a less extent.

The mechanism of adaptation to a sudden reduction in systolic blood pressure is discussed. If the idio-ventricular rate remain more or less constant throughout the period of changing blood pressure, then in order to compensate the volume output per beat must be augmented. No estimations of the circulation rate after nitrites in pathological states have been reported in the literature least of all in the presence of complete heart-block.

No changes occurred in the form of the electrocardiographic deflections except in one patient, and no untoward symptoms were observed even in two cases complicated by free aortic regurgitation.
The RESPONSE to ADRENALIN.
The RESPONSE to ADRENALIN.

One of the sympathomimetic amines, adrenalin produces striking reactions in the vascular system of the body. Analysis of the response to this drug indicates that its action consists of a highly specific stimulation of the myoneural junctions of the sympathetic system, peripheral vasoconstriction with an associated rise in arterial pressure, and some cardiac acceleration being the predominant features.

LYON (148) has shown that in man the character of the reaction to adrenalin differs considerably in different subjects. The response, as it affects the cardio-vascular system and the metabolism, may be slight, moderate or marked in degree, rapid or slow in its onset, transient, or persistent in its duration. Further "the type of reaction depends to a great extent on the rate of absorption of the drug and also on the 'sensitiveness' of the patient". While adrenalin stimulates the accelerator mechanism of the heart, its pronounced pressor effects result in an augmentation of vagal reflexes /
reflexes. Under ordinary conditions an abrupt increase of blood pressure calls forth reflexes arising in the wall of the first part of the aorta and in the carotid sinus. Reaching the heart by way of the vagus, these reflexes induce some degree of inhibition. After a dose of adrenalin the heart rate is therefore an expression of at least two interacting forces, direct augmentation of sympathetic origin on the one hand and reflex vagal inhibition on the other. It is believed that, at least in certain instances, adrenalin also stimulates the vagal centre directly, and if the pre-existing inhibitory tone is high this may result in an actual slowing of the heart (MEEK & EYSTER (157)). On the other hand, when the vagus tone is low considerable quickening of the heart may result (116).

In this connection it is of interest to consider the effect of direct sympathetic stimulation in the presence of complete heart-block. The earliest experiments found in the literature are those of HERING (103) who, writing in 1905, reported that while vagus stimulation had little effect on the ventricular rate, sympathetic stimulation was/
was followed almost immediately by definite acceleration of the ventricles. ERLANGER (63) obtained similar results. Having produced chronic complete block in dogs, ERLANGER & BLACKMAN (64) demonstrated an increase of 22 per cent in ventricular rate, and 15 per cent in auricular, on strong sympathetic stimulation in these animals. It is therefore not surprising to find that adrenalin produces an augmentation of the rate and force of the independent ventricular beat at least under experimental conditions. CULLIS & TRIBE (43), VAN EGMOND (58), ROUTIER (190), HARDY & HOUSAY (95) and CLERC & PEZZI (33) are all agreed that the administration of adrenalin after the production of complete heart-block in various animals causes an increase in the rate and force of the auricular and ventricular contractions. On the other hand, there is an isolated observation by KAHN (121) who noted the appearance of heart-block in healthy dogs after the intravenous administration of adrenalin.

Three years elapsed before the results obtained in the experimental laboratory were confirmed in cases of heart-block in man. In 1916
DANIELOPOULU & DANULESCU (49) reported on the clinical use of adrenalin in complete block. These authors found that after a dose of 1.5 mgms. the auricles quickened from 84 to 91 and the ventricles from 30.5 to 40.5. After 2 mgms. the respective rates increased from 91 to 120 and from 25.75 to 43.5. In a case of partial block with a 2 to 1 frequency full conduction was temporarily restored.

LUTENBACHER (145) administered 0.25 mgm. of adrenalin by the intravenous route and noted an immediate acceleration of auricles and ventricles in a patient suffering from complete block. Before the drug was given the rates were 75 and 29. Adrenalin produced a distinct acceleration, the auricular rate reaching 150 and the ventricles rising to 60 per minute. This effect was followed by some irregularity of the ventricular rhythm, with pauses of sufficient duration to account for transient syncopal attacks. For this reason, LUTENBACHER recommends caution in the use of the drug and refers to the fact that on several occasions he has observed an extreme slowness of the ventricles on the days following the injection. In the light of modern knowledge it would seem more justifiable /
justifiable to infer that the intravenous route was largely responsible for the dangerous symptoms noted. Subcutaneous dosage is much the safer method of administration. DE GRAFF & WEISS (90) have reported observations on five patients suffering from complete heart-block. Adrenalin was used subcutaneously in doses of 1 to 5 mgms. and in each instance an acceleration of the ventricular rate was induced. In one patient no rise occurred in the auricular rate, and on three occasions the acceleration was preceded by a decrease in the rate of the auricles. The fact that the auricles accelerate relatively less than do the ventricles, is attributed by these authors to reflex vagal inhibition acting on the sino-auricular node as a result of an elevation of the arterial blood pressure. Ventricular extra-systoles were noted to occur frequently after the injection of adrenalin, not only by these authors but also by LUTEMBACHER (145) & ARRILACA (4).

Some conflicting results are found in the literature. For instance, STRISOWER (211) has recorded an instance where, after 0.5 mgms. of adrenalin, the ventricles not only increased in rate /
rate but normal rhythm was temporarily restored. A month later the patient again came under observation and was found to have a partial block with 2 to 1 rhythm. A further dose of adrenalin abolished the block for a few seconds. In the case reported by KORNS & CHRISTIE (130) adrenalin appeared to be the cause of a transition from partial to complete. In association with the increase in the degree of block, the auricular and ventricular rates accelerated, and the rhythm of the auricles became irregular. PARKINSON & BAIN (168) have described a case in which, when the block was partial, adrenalin facilitated conduction, but when complete, the drug was without effect. Just as the underlying mechanism in the production of partial heart-block varies greatly in the different types of this disorder, so also does the effect of adrenalin on the conducting pathway vary with a number of factors. In partial block, the result of organic disease of the bundle, adrenalin may well produce at least temporary increase of block, either as a result of reflex vagal inhibition or more probably by the additional burden imposed on the /
the tract in consequence of an increase in the rate of auricular beating. Similarly in partial block of toxic origin, the bundle is often unduly susceptible to vagal influences. Reflex inhibition may then overcome the local tendency of adrenalin to facilitate conduction. On the other hand in chronic complete block of organic origin it is of necessity impossible to believe that adrenalin can restore in the slightest degree the functional link between the auricles and ventricles. The explanation of recovery of conduction after adrenalin may be attributed to the nature of the dissociation. Restoration of conduction may well occur in intermittent complete block after the use of the drug (though not necessarily on account of its use) or in that form of block described by MOBITZ (159) (160) as "dissociation with interference".

It is only necessary to mention briefly the remarkable effect of adrenalin in the prevention of Stokes-Adams seizures, as this aspect of the use of the drug is not of immediate concern to us. PHEAR & PARKINSON (173) and FEIL (68) have /
have reported cases in which repeated seizures were abolished by an increase in the rhythmicity of the ventricular centre so that temporary arrest of the ventricular beat no longer occurred.

The VENTRICULAR RANGE after ADRENALIN.

From the preceding review of the literature, it is evident that no systematic study of the effects of adrenalin in complete heart block-in man has been published. DE GRAFF and WEISS (90) in reporting their five cases came to certain conclusions regarding the power of the drug to increase the rate of the human ventricles but, apart from their short review of the subject and a few case reports, which are often of a meagre nature, little detailed information is available. In the following pages an attempt is made to discover the nature of the reaction and to determine the factors which govern the response of the heart to this drug.

Twelve cases of complete heart-block have been tested with varying doses of the drug. A technique similar to that employed in the atropine experiments was used with the exception that the adrenalin was administered subcutaneously generally on the outer aspect of the left forearm about three inches below the bend of the elbow. Electrocardiograms were recorded at intervals of two minutes /
minutes for approximately one hour after the injection, and in the majority of the experiments blood pressure readings were made in the intervals between the exposure of the photographic plates. A period of rest, varying from 30 to 60 minutes, during which the blood pressure and heart rates were recorded, served as a control for the adrenalin reaction. Twenty-eight experiments were performed on twelve patients, the dose of adrenalin varying from 0.25 c.c. to 1.0 c.c. of 1/1000 solution (P.D. & Co.). As the drug decomposes rapidly on exposure to light and air, every care was taken to insure the use of a preparation of full potency. The slightest discoloration of the solution is evidence of oxidation, and as the drug deteriorates in keeping a fresh and reliable supply was used in each test.

In every experiment the rate of the auricles and ventricles was increased by the injection of adrenalin, generally within five minutes of its administration. In spite of the local vaso-constrictor effect at the site of injection, absorption from the subcutaneous tissue commences immediately, probably by way of the lymphatics (148) and /
and the drug comes into action with surprising rapidity. LYON (147) found that as a general rule
the rise of blood pressure after a subcutaneous dose of adrenalin commenced within two minutes, and that
after 9 minutes only about 50 per cent of the dose remains at the site of injection.

For various reasons the reaction observed to occur after adrenalin is not uniform throughout this series of cases. Atypical results, which demand separate consideration, were obtained in Case 2 (congestive heart failure present), in Case 4, (developed a transient bundle branch-block during the height of the reaction) in Case 7 (one of intermittent complete-block) and in Case 12 (transient recovery of conduction under adrenalin). Comparable results were obtained in the remaining eight individuals (Cases 1, 3, 5, 6, 8, 10, 11, and 13) in whom the response to adrenalin was observed under uniform conditions. In the accompanying table, the rates of the auricles and ventricles immediately before the injection of 0.5 c.c. of 1/1000 solution of adrenalin hydrochloride, and the maximum rates attained after the injection are recorded for eight cases of complete heart block.

**TABLE**
<table>
<thead>
<tr>
<th>CASE NO. &amp; INIT.</th>
<th>AURICULAR RATE</th>
<th>VENTRICULAR RATE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RATE before ADRENALIN</td>
<td>MAXIMUM RATE after ADRENALIN</td>
<td>GAIN IN AURICULAR RATE</td>
</tr>
<tr>
<td>1. Mrs T. (a)</td>
<td>70.4</td>
<td>105.0</td>
<td>34.6</td>
</tr>
<tr>
<td>&quot; &quot; (b)</td>
<td>75.3</td>
<td>92.6</td>
<td>17.3</td>
</tr>
<tr>
<td>3. D.C.</td>
<td>72.8</td>
<td>77.6</td>
<td>4.8</td>
</tr>
<tr>
<td>5. A.H.</td>
<td>58.0</td>
<td>69.8</td>
<td>11.8</td>
</tr>
<tr>
<td>6. J.W.</td>
<td>51.5</td>
<td>66.8</td>
<td>15.3</td>
</tr>
<tr>
<td>8. J.B.</td>
<td>58.0</td>
<td>69.8</td>
<td>11.8</td>
</tr>
<tr>
<td>Auricular fibrillation</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10. Mrs O.</td>
<td>&quot;</td>
<td>&quot;</td>
<td>-</td>
</tr>
<tr>
<td>11. Mrs D. (a)</td>
<td>90.0</td>
<td>95.0</td>
<td>5.8</td>
</tr>
<tr>
<td>&quot; (b)</td>
<td>95.1</td>
<td>99.3</td>
<td>0.7</td>
</tr>
<tr>
<td>13. Mrs H.</td>
<td>76.1</td>
<td>82.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Table: To show the maximum effect of a subcutaneous dose of 0.5 c.c. adrenalin on the auricular and ventricular rates in eight cases of complete heart-block. Two cases, complicated by auricular fibrillation are also included.
A glance at the Table is sufficient to show that the degree of acceleration varies considerably in different cases and that the magnitude of the reaction as it affects the auricles and ventricles is dissimilar in a given case. With a single exception (Case 1, (a) ) the ventricular gain in rate expressed as a percentage of the initial rate is greater than the corresponding auricular, thus confirming the observations of DE GRAFF & WEISS (90).

Closer study of the results obtained for the ventricles reveals that in general less acceleration occurs in those instances in which the resting ventricular rate is high, than in those in which the rate is low before the injection is given. For instance in Case 1 (b) the initial ventricular rate was 25.0 per minute and the maximum recorded was 39.1 representing a gain of 14.1 beats per minute or an increase of 56.4 per cent. On the other hand in Case 11 (b) the respective rates before and after the injection were 51.0 and 52.4 respectively, an increment of 1.4 beats per minute or only 2.7 per cent. By plotting initial rate against the corresponding gain, a remarkable relationship /


- **Square (□)**: Observed values (0.50 c.c.)
- **Circle (○)**: Calculated response.

**Axes:**
- **X-axis**: Initial Ventricular Rate
- **Y-axis**: Gain in Rate

**Values:**
- 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52
relationship becomes at once evident. This is shown in Chart 12 in which the results obtained in ten experiments are inserted.

It is obvious that the rate of the ventricles at the time the drug is administered is an important factor in determining the response to a given dose. The plottings lie along a curve which gradually approximates to the base line as the rate 50 is approached, and moves away from the base line with increasing rapidity as lower initial rates are encountered. In other words the slower the ventricles the greater is their response to a dose of adrenalin and vice versa. This peculiar feature of the adrenalin reaction has not been previously described and is in sharp contrast to that noted under the influence of atropine.

The lie of the plottings suggests that the effect may be represented by a descending exponential curve. This has been tested by plotting the exponential values for the observed increment against the corresponding initial rate. If the observed increments be of the order of a falling exponential curve, then on plotting their corresponding exponential values against the initial rate, the /
\[ e^{-y} = 2.35x - 4.51. \]
the points will fall along a straight line. The data are presented in TABLE XXII and are plotted in the accompanying Chart (No. 13). Let $x$ = the initial rate and $y$ = the observed increment at that rate. The value $e^{-y}$ is taken from exponential Tables (201).

**TABLE XXII.**

<table>
<thead>
<tr>
<th>$x$</th>
<th>$y$</th>
<th>$e^{-y}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.2</td>
<td>13.1</td>
<td>2698</td>
</tr>
<tr>
<td>25.0</td>
<td>14.1</td>
<td>2441</td>
</tr>
<tr>
<td>38.5</td>
<td>4.7</td>
<td>6250</td>
</tr>
<tr>
<td>30.6</td>
<td>11.0</td>
<td>3329</td>
</tr>
<tr>
<td>27.4</td>
<td>9.8</td>
<td>3753</td>
</tr>
<tr>
<td>32.9</td>
<td>6.8</td>
<td>5066</td>
</tr>
<tr>
<td>26.6</td>
<td>16.3</td>
<td>1959</td>
</tr>
<tr>
<td>45.2</td>
<td>5.3</td>
<td>5886</td>
</tr>
<tr>
<td>51.0</td>
<td>1.4</td>
<td>8693</td>
</tr>
<tr>
<td>41.7</td>
<td>3.9</td>
<td>6770</td>
</tr>
</tbody>
</table>

The value $e^{-y}$ plotted against $x$ yields a series of points which approximate to a straight line. The fit is not perfect but is sufficiently good.
### Table XXIII.

<table>
<thead>
<tr>
<th>ADRENALIN DOSAGE</th>
<th>0.25 c.c.</th>
<th>0.75 c.c.</th>
<th>1.0 c.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INITIAL VENTRIC RATE</td>
<td>GAIN in RATE</td>
<td>GAIN as PERCENTAGE of INITIAL RATE</td>
</tr>
<tr>
<td>CASE NO. &amp; INITS.</td>
<td>------------</td>
<td>------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1. Mrs T.</td>
<td>26.6</td>
<td>14.9</td>
<td>56.0</td>
</tr>
<tr>
<td>3. D.C.</td>
<td>40.4</td>
<td>4.1</td>
<td>10.2</td>
</tr>
<tr>
<td>5. A.H.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6. J.W.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11. Mrs D.</td>
<td>43.0</td>
<td>2.1</td>
<td>4.9</td>
</tr>
<tr>
<td>13. Mrs H.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table: To show the effect of various doses of adrenalin at different ventricular rates.
good to indicate that the response to adrenalin for varying initial rates closely resembles a decreasing exponential curve. In other words the reaction approximates to a series of decreasing exponentials for increasing initial rates. The regression line, drawn to the formula \( y = 2.35x - 4.51 \), yields optimum values for \( e^- \) at a given initial ventricular rate \((x)\). Values for \( y \), obtained from exponential tables, have been plotted in Chart 12, where they form a curve, which expresses the theoretical increment for a given initial rate.

The influence of the size of the dose on the Ventricular Response.

The results so far examined were obtained with a uniform dose of 0.5 c.c. of adrenalin administered subcutaneously. It is of interest to discover the effect of smaller and larger doses on the response of the ventricles. Doses of 0.25, 0.75 and 1.0 c.c. were tested in those subjects who had on other occasions received 0.5 c.c. and the results are arranged in TABLE XXIII.
- ○ = Optimum Value for 0.5 cc.
- ● = Observed """"
- ★ = 1.0 cc.
- ▲ = 0.75 cc.
- □ = 0.25 cc.
By again plotting the initial rate against the observed gain for each dose, a remarkable result becomes at once evident. This is shown in Graph in which, by way of contrast, the reactions to 0.5 c.c. adrenalin are also included. The continuous curve indicates the optimum response to 0.5 c.c., and it is at once evident that in spite of varying the dose the effect remains remarkably constant. The points representing doses other than 0.5 c.c., fall sufficiently close to the curve to indicate that the exponential expression representing the effect of 0.5 c.c. also records the effect of 0.25 c.c., 0.75 c.c. and 1.0 c.c.

The data, just presented may be interpreted in a number of ways. It seems clear that within a range extending at least from 0.25 to 1.00 c.c. the degree of the reaction depends not on the size of the dose, but on the initial rate. In other words, the state of the heart at the moment determines its response and, within the usual therapeutic range, the size of the dose is virtually immaterial. It therefore appears that 0.25 c.c. (or perhaps less) will produce as much ventricular /
ventricular acceleration as 1.00 c.c. at a given rate.

The Nature of the Action of Adrenalin on
the Ventricular Pace-maker.

In certain respects the observations just described are in accord with the laws governing the activity of enzymes. It is well known that the action of enzymes depends upon their rate of diffusion, and adsorption of substrate on their surfaces. This is followed by the chemical re-action. BAYLISS (9) has aptly employed the following illustration.

"Imagine a number of snails in the neighbourhood of a strawberry. As soon as a snail, in the course of its wanderings, becomes sensible of the presence of food it proceeds towards it. This is the preliminary diffusion ...... The next stage that of adsorption, follows rapidly as the animal attaches itself to the fruit. If nothing more happens there is no chemical reaction. The final, chemical stage is the devouring of the food and its subsequent hydrolysis. It is obvious that the rate of this final stage is proportional to /
to the number of snails "adsorbed". It will also be noted that it is not in linear ratio to the number at work. The more there are, the more they interfere with one another, and, when the strawberry is completely covered, the advent of more snails will not further increase the rate of disappearance, since the newcomers cannot get at the fruit. The strawberry here represents the enzyme. We may imagine that, instead of the fruit, we have a powerful chemical substance which induces the disintegration of the snails representing the substrate, which is adsorbed on its surface.

"The exponential ratio of the concentration of the enzyme to its activity receives a satisfactory explanation on this adsorption theory as will be plain from the above illustration".

What is true of enzyme action also applies in some measure to the response of the idioventricular rhythm to a dose of adrenalin. To draw a comparison it is only necessary to regard the snail, of Bayliss' illustration, as a minimal dose of adrenalin. Up to a point the reaction will be intensified as the dose is increased, but the relationship between the two is not a simple linear expression /
expression, and a stage is ultimately reached when a further increase of dose produces no appreciable effect in the degree of reaction. The independence of the response to the size of the dose (within a certain range) suggests that a surface action is involved, and that the adrenalin (like the snails of Bayliss' illustration) is being adsorbed on some (? enzyme) surface, as an essential condition of its action. Such a surface could adsorb only up to a certain maximal amount of adrenalin, and any excess of the drug would be without further action on that surface. As a similar state of affairs, the action of the enzyme invertase on cane sugar may be instanced (BAYLISS (10)). With very low concentration of sugar, the rate of the hydrolysis in the presence of the enzyme varies in a logarithmic way with the concentration of sugar. The sugar is adsorbed on the enzyme surface, but there is not enough to cover it completely, and the reaction

$$E + S \rightarrow ES$$

is governed by the law of mass action. When, however, the sugar concentration is increased beyond a certain limiting value, the surface is completely covered /
covered, and the rate of hydrolysis becomes independent of the sugar concentration, so that addition of still more sugar has no effect on the reaction.

That this peculiar effect of adrenalin is not limited to the ventricles is borne out by the observations of LYON (146) on its action on the blood-pressure. LYON has suggested that the reaction obeys WEBER'S law, i.e. "the effect is proportional to the natural logarithm of the stimulus". This implies that in so far as blood-pressure is concerned, a given dose of the drug does not produce a uniform response under varying conditions. It was found that the amount of the rise of blood pressure after uniform doses of adrenalin, depended upon the level of the blood pressure at the moment of injection, a small rise occurring if the initial pressure were high and vice versa. A study of the response of the ventricles in complete heart-block reveals that the reaction to adrenalin is similar in nature to that observed by LYON under experimental conditions though it is not necessarily governed by WEBER'S law. (See CLARK 31.)
<table>
<thead>
<tr>
<th>CASE NO. &amp; INITIALS</th>
<th>ADRENALIN DOSAGE</th>
<th>INITIAL AURIC. RATE</th>
<th>GAIN in RATE</th>
<th>GAIN as PERCENTAGE of INITIAL RATE</th>
<th>INITIAL AURIC. RATE</th>
<th>GAIN in RATE</th>
<th>GAIN as PERCENTAGE of INITIAL RATE</th>
<th>INITIAL AURIC. RATE</th>
<th>GAIN in RATE</th>
<th>GAIN as PERCENTAGE of INITIAL RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mrs T. (a)</td>
<td>0.25 c.c.</td>
<td>80.8</td>
<td>22.0</td>
<td>27.2</td>
<td>81.8</td>
<td>41.2</td>
<td>58.5</td>
<td>69.6</td>
<td>45.0</td>
<td>65.2</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.75 c.c.</td>
<td>81.8</td>
<td>41.2</td>
<td>58.5</td>
<td>69.6</td>
<td>45.0</td>
<td>65.2</td>
<td></td>
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<td>78.1</td>
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<td>59.0</td>
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Table: To show the effect of various doses of adrenalin at different auricular rates.
The Response of the Auricles.

It has been shown above that the ventricles increase in rate after an injection of adrenalin and that the amount of acceleration induced depends upon the preexisting rate. Further, for doses ranging in size from 0.25 to 1.0 c.c. the gain in rate is uniform, provided the initial rate is constant. The peculiar character of the ventricular response to adrenalin makes it desirable to enquire into the behaviour of the auricles under similar conditions. In complete heart block the ventricles are functionally isolated from the auricles, and are therefore no longer under the dominating influence of the normal pacemaker - the sino-auricular node.

In each of the individuals studied, adrenalin produced some auricular acceleration. The amount varied considerably in different cases. The responses of the auricles to 0.5 c.c. in eight instances are shown in Table and to 0.25, 0.75 and 1.0 c.c. in Table XXIV.

TABLE XXIV/
By employing similar methods of analysis it is found that there is not such a close relation between the amount of auricular acceleration and the initial auricular rate. The response appears to vary considerably not merely from a given resting auricular rate but also to some extent for the amount of the drug employed. The points when plotted show a somewhat wider "scatter" than those expressing the ventricular ratio. It would therefore appear that the reaction of the auricular tissue differs to some extent from that displayed by the ventricular. Actually this disparity is perhaps more fictitious than real.

It may very well be that the auricular response to adrenalin is not inherently different from that of the ventricles, but that the reaction in the former is modified or distorted by certain extraneous influences playing upon the sino-auricular node. It has already been pointed out that in normally beating hearts the reaction to this drug is profoundly influenced by inhibitory vagal reflexes. There is no reason to believe that the normal reflexes arising in the carotid sinus or arch
\[
\text{Percentage Ventricular Acceleration vs. Percentage Auricular Acceleration.}
\]

- ○ = 0.5 cc. Adrenalin
- ○ = Doses of 0.25, 0.75, 1.0 cc.
arch of the aorta are appreciably disorganised in the presence of complete heart block, and it may therefore be assumed that the rise of pressure, consequent upon the injection of adrenalin, will call forth inhibitory reflexes acting on the sino-auricular node. The rhythmicity of the pace-maker and the degree of vagal tone must be important factors in modifying the natural tendency of the auricles to accelerate in response to adrenalin.

The Relation of the Auricular to the Ventricular Response.

Though it has not been possible to demonstrate a high degree of correlation between the gain in rate of the auricles and their initial level, yet nevertheless there is a distinct relation between the auricular gain in rate and the associated ventricular acceleration. The fact can be demonstrated in a number of ways.

Perhaps the simplest method is to plot the respective increments, each as a percentage of the pre-existing rate, one against the other. This has been done in Chart 15. Study of this diagram reveals that the percentage increments for auricles /
auricles and ventricles after adrenalin are not proportionate. For instance, when the ventricles accelerate by, say 50 per cent, the auricles do not quicken by the same amount, but rather less. If the magnitude of the reaction was similar in auricles and ventricles then the points would fall along the line A. Actually they appear to fall along the line B. This implies that as the percentage ventricular acceleration increases, the corresponding auricular gain lags more and more behind. It has already been shown that the greatest gain in ventricular rate occurs from the lowest initial levels. This must mean that under such conditions, when the rate and force of ventricular systole are greatly increased, a mechanism comes into play which has the effect of limiting the auricular response. In other words it would appear probable that the widening interval separating the lines A and B, represents the effect of increasing reflex vagal tone. As the magnitude of the ventricular reaction increases so also does reflex vagal tone. The probable mechanism is that as the ventricular rate and the blood pressure rise, inhibitory /
Initial Ventricular Rate.

Ventricles

Auricles

Percentage Acceleration.

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52
inhibitory vagal reflexes limit the auricular response. The more the ventricles gain in rate, the greater is the lag in the auricular response.

The same phenomenon may also be demonstrated by contrasting the percentage gain in rate of auricles with that of the ventricles when each is plotted against the initial ventricular rate as shown in Chart 16. The respective plottings lie along two distinct curves, that for the ventricles being almost a perfect exponential relationship to the pre-existing rate. At high initial rates the curve for the auricular acceleration lies nearer the base line than the ventricular. As low initial rates are approached the auricular curve displays a slight shift to the left indicating that the auricular response tends to be restricted.

This is confirmed by again plotting the exponentials of the percentage gains in rate for the two chambers of the heart. The ventricular exponentials, as previously shown, are grouped almost in a straight line. The auricular exponentials are less perfect in their arrangement, their lie being slightly curved.

It /
It is suggested that the reason for the dissimilarity between the two curves is due to vagal influences. These arise in the carotid sinus and aortic wall as a result of sudden elevation of the arterial pressure, and have the effect of retarding the auricular rate. The greater the degree of ventricular acceleration the more does the auricular response lag behind. If the auricular inhibition be the result of increased blood pressure, then it would seem correct to suppose that in complete heart block, the pressor effect of adrenalin is largely controlled by the ventricular response. Support for this view is obtained from the studies of Euler and Liljestrand (65) on the effect of adrenalin on the circulation rate. The drug was found to cause, not merely an increase of the systolic output but a doubling of the volume flow per minute in spite of but little change in the mean arterial pressure. The circulation rate was increased out of proportion to the oxygen requirements of the tissues. This implies that adrenalin acts as a whip to the heart, and that its main effects on, at least certain of the peripheral vessels (e.g. the lung or elsewhere), must be dilator rather /
FIGURE 3.

Before Adrenalin:

11 min before

After Adrenalin:

1 min after
FIGURE 3 (Continued).

32 mins after

34 " "

36 " "

38 " "

40 " "

44 " "

50 " "

55 " "
rather than constrictor. The observations described in these cases of heart-block support this view, for the reason that the greater the ventricular response the more do the auricles lag behind. The ventricles presumably have a large share in regulating the blood pressure and consequently reflex vagal auricular inhibition.

The Course of the Reaction to Adrenalin.

An examination of the course of the reaction to adrenalin in complete-block does not reveal any striking difference from that which has been noted to occur in the normally beating heart. Just as the reaction may be slow or rapid in onset, or transient or persistent in duration, in different healthy individuals, so also in those suffering from complete block, the character of the response varies within wide limits.

It is not necessary to depict in detail the reaction observed in each individual. To demonstrate the extremes observed it is sufficient to select two individuals, one in whom the initial ventricular rate was low and the other in whom the usual resting rate was high. Case No.1 and 13 have /
Rate Per Minute

Blood Pressure

Auricles

Ventricles

Adrenalin 0.75cc.

Time in Minutes

10 20 30 40 50 60 70

Systolic Blood Pressure

180 160 140 120 100 80 60 40 20 10

110 100 90 80 70 60 50 40 30 20 10

H. T.

6'11' 28
have been chosen as examples and the course of the reaction as it affects the systolic blood-pressure and the auricular and ventricular rates is depicted in the accompanying Charts (No. 17 and 18).

Case 1 (Chart 17) had, after lying at rest for over 30 minutes a ventricular rate of 29.2, an auricular of 70.4, and a systolic pressure of 138 Mm Hg. A very prompt reaction immediately followed the dose of adrenalin. Within four minutes, the auricles reached their maximum rate of 105 per minute from which they gradually declined. It can be seen that three minutes after the auricular rate attains its observed maximum, the blood pressure reaches its highest point, and three minutes later the ventricular rate, after a more gradual acceleration, touches its greatest level. It is worth noting the different time reactions in auricles and ventricles. The highest peaks in the auricular and ventricular rates do not occur at the same moment. Actually the auricular rate has attained its greatest value and is declining during the period when the ventricles are gaining rate most rapidly. From the Chart it would appear that the remarkably
Chart 18.

Blood Pressure

Auricles

Ventricles

Time in Minutes

Adrenalin 0.75 cc.

18-11-30.
remarkably abrupt acceleration of the auricles between the second and fourth minutes is permitted by a transient fall in blood pressure. As the systolic pressure increase, the rise in auricular rate is stemmed. The ventricles meantime continue to accelerate. According to Murray Lyon's researches (147) this period corresponds with the time at which the greatest amount of the adrenalin is actually in the blood stream and when the amount passing from the blood to the tissues is maximum. Thereafter the blood-pressure declines, reaching its pre-existing level about 30 minutes after the injection. It is noteworthy that the auricular and ventricular acceleration persists for some time after the blood pressure reaction has passed off.

In Case 13, on the other hand, the initial rates were relatively high, and even after prolonged rest the systolic pressure was 184 mm. when the adrenalin was administered. The electro cardiograms, from which the auricular and ventricular rates are calculated, are shown in Fig. 3 Chart 18 demonstrates the course of the reaction in /
in this patient. The response in this woman was of longer duration but of less intensity than that observed in Case 1. The blood pressure standing at a higher initial level, than in the previous individual, gains less and the ventricular reaction is also slight. The auricles do not exhibit an early abrupt acceleration but fluctuate in rate from minute to minute.

Just as no untoward inconvenient symptoms followed the administration of atropine or amyl nitrite, so also the subcutaneous injection of adrenalin produced no distress amongst these patients. In the usual subcutaneous doses the drug may be given in cases of complete block without harm resulting. LEVINE (134) has employed the drug as a diagnostic test for angina pectoris, on account of the ease with which precordial pain is induced among those who suffer from this cardiac disability. No suspicion of angina occurred in any of these cases of block, although two suffered habitually from precordial pain on exertion. Extra-systoles were occasionally observed. It should be pointed out that they were not included in the estimation of heart rate. Finally in not a single instance among these eight patients did adrenalin alter the degree of block.
ATYPICAL RESPONSE to ADRENALIN.

It has been pointed out in previous pages that only eight individuals to whom adrenalin was administered, yielded a reaction which was more or less similar throughout the group. A response differing in certain respects from that observed in this group was recorded in four patients (Cases, 2, 4, 7, and 12).

In this section it is proposed to examine briefly the reaction in these four individuals. In Case 2, a mild degree of congestive heart failure existed on the two occasions when this man's reaction to adrenalin was tested. He received two doses of respectively 0.25 c.c. and 0.5 c.c. After each the amount of ventricular acceleration exceeded that which would be expected for the corresponding initial heart rate, and the reaction was a trifle slower in onset, perhaps as a result of the decreased circulation rate and slower absorption of the drug. It is difficult to explain why a heart labouring under the burden of a gross defect in circulation should respond by an excessive acceleration.
acceleration, unless it be that, incapable of increasing its systolic output, an attempt is made to compensate for this by an unusual gain in rate.

In Case 4, the gain in rate was not as high as might be anticipated at the pre-existing rate. Electrocardiograms showed that this man towards the height of the reaction developed a bundle branch block which persisted until after the end of the experimental period. This abnormal rhythm seemed to form a sufficient reason for relegating this patient to the group in whom the response was atypical.

Case 7 is of some little interest in that this man suffered from intermittent complete heart-block. It was possible to test his response to adrenalin on two occasions, on the first of which the block was complete, whereas on the second occasion the block was of the 2 to 1 type with a P-R interval of 0.2010 sec. The electrocardiogram (Fig. 4) recorded immediately before the first test shows complete heart block with a defect in the bundle branch conduction, with the main deflections downward in lead 1 and upward in lead 3.
Until recently this record would be classified as an example of a defect in the left branch of the bundle but the work of Wilson and his collaborators (230) would suggest that more probably the right branch was the sight of the defect. Records from lead 3 were made repeatedly during the course of the 64 minutes following the injection. Between five and seven minutes after the dose the form of the ventricular complex underwent a complete alteration in form becoming almost the mirror image of that previously existing. This is shown in Fig. 5. The block of the "left" branch has been replaced by a block of the "right" (or vice versa, according to Wilson's theory). This persisted throughout the experiment and the final records in lead 1, 2 and 3 are in marked contrast to those existing before the adrenalin was injected. Compare Fig. 6 and 8.

Alterations in the ventricular complexes in complete heart-block occasionally occur spontaneously and have been described and analysed in detail by Gilchrist & Cohn (87). We observed gradual transitions in the form of the QRS waves in /
in cases of complete heart-block so that while left
ventricular effects might predominate at one time,
in a few seconds right sided influences took their
place. An example of a spontaneous and temporary
change in the form of the ventricular complex is
shown in Plate 3. (Case 8, of the present series)
We came to the conclusion that the phenomenon was
due to two interacting centres of impulses produc-
tion one on either side of the heart. This theory
assumes the presence of a bilateral bundle lesion,
not necessarily of an organic nature, with rhythmic
centres below the defect. "In this case, the
simultaneous discharge of impulses from each centre
will result in a composite complex of normal out-
line. By a disturbance of this time relationship
the centre of impulse production in advance of the
other assumes control and the resulting complexes
are of the form associated with a preponderance of
right or left-sided effects as the case may be".
The other possibility, originally proposed by
COHN (35) is that abrupt transitions in the form
of the ventricular complexes might be interpreted
as the onset of partial bundle branch-block in one
branch /
branch with simultaneous recovery of conduction in the other branch. A change in the form of complexes after adrenalin was noted on two occasions in one heart-block patient by DE GRAFF & WEISS (90).

In health, according to CLOUGH (34) epinephrine does not alter the P-R conduction time in man, probably for the reason that, though an increase in accelerator tone facilitates conduction, the reflex vagal stimulation induced by adrenalin, will tend to counterbalance the pure sympathetic effect. In the case under consideration, it is unlikely that vagal tone induced the change in the form of the ventricular complexes for it persisted long after the blood pressure had returned to its pre-existing level. It would therefore seem more probable that the change in the conduction defect from one side of the heart to the other resulted from a change in the time relationship between two pace-makers.

This might result from exhaustion of one branch or centre as a consequence of an increased rate of stimulus production. An increase in the refractory period of the associated bundle-branch may ultimately be dependent on a blood supply inadequate for /
for the immediate needs of the over stimulated tissues.

By the following day the rhythm of the heart in this patient (Case 7) had changed spontaneously, 2 to 1 block now replacing the complete, which had previously been present. It is of interest to note that the partial recovery of conduction was accompanied by not only a further change in the form of the ventricular complexes but also by a peculiar inversion of the P waves in all leads. This is shown in the electrocardiogram (FIG. 6) taken immediately before the injection of 1.0 c.c. adrenalin. Two minutes later conduction was abolished, the block became complete, the ventricular complexes changed in form and the P waves became upright (FIG. 7). The block remained complete for 18 minutes the main ventricular deflection being upright. 20 minutes after the injection, conduction was restored, the ventricular complex changing its shape in association with the alteration in rhythm. In lead 3 the main deflection was upright during complete-block, and downward throughout the period of 2 to 1 block. Nevertheless leads /
leads 1, 2, 3 (FIG. 8) taken an hour after the injection, show that though 2 to 1 block persists, yet the form of the complexes is different from that observed during the 2 to 1 block, which was present before the injection was given.

Several other individuals showed transient and often abrupt changes in the form of the ventricular complexes a few successive cycles after adrenalin administration, and not at other times, though several hundred electrocardiograms were recorded. Atropine, for instance did not affect the form of the ventricular waves in a single instance. It therefore seems reasonable to suppose (in spite of the fact that Case 7 suffered from spontaneous changes in conduction) that the alterations observed to occur after adrenalin, were in all probability due to adrenalin. To carry this argument a stage further, it may be tentatively suggested that the spontaneous alterations in conduction, which occurred on more than one occasion, might well be determined by some subtle alteration in accelerator tone and in the local blood supply. This man's heart seemed unduly susceptible to adrenalin but whether /
whether this or some other closely related substance of bodily origin determined the apparently spontaneous onset of complete block must remain a mystery. It is known that adenosine may produce a transient block in man (115) and perhaps one explanation of intermittent complete heart-block is ultimately to be found in the addition to the blood stream of a subtle chemical substance of bodily origin.

The response of Case 12 to adrenalin is briefly discussed under functional A-V dissociation.

**SUMMARY.**

Twelve cases of complete heart block have been tested with repeated subcutaneous doses of adrenalin in an attempt to discover the factors which govern the response of the heart to this drug. A review of the literature indicates that in man a detailed study of the influence of adrenalin on the independent auricular and ventricular rhythms of complete block has not previously been made.

After a subcutaneous dose the drug comes into action with surprising rapidity. Acceleration of auricles and ventricles may occur within /
within two to four minutes of the injection.

The amount of ventricular acceleration induced bears a striking relationship to the rate existing immediately before the injection. High initial rates are followed by little or no gain in rate, slow rates by pronounced acceleration. This means that the state of the heart at the time of the drug's administration determines the heart's response.

By plotting the observed increment against the corresponding initial rate, it is found that for a group of eight cases the reaction approximates to an almost perfect series of decreasing exponentials for increasing ventricular rates.

Within a certain range of dosage, the amount of adrenalin injected makes little or no difference to the ventricular response at a given ventricular rate. The optimum response to 0.5 c.c. adrenalin for various initial rates has been calculated and compared with the reaction observed after doses of 0.25, 0.75, and 1.0 c.c. in the same subjects. The gain in rate after these doses is to all intents similar to that recorded after 0.5 c.c. This implies that the response of the heart is determined /
determined, not by the size of a dose in the usual therapeutic range, but by the rate of the heart existing at the time of the injection. In other words, for a given initial rate 0.25 c.c. of adrenalin will produce as much acceleration as a dose four times that amount.

This phenomenon is discussed in the light of the known laws which govern enzyme action. The independence of the size of the dose to the response recorded suggests that a surface action is involved, and that adrenalin is being adsorbed on some (? enzyme) surface, as an essential condition of its action.

The observation that the initial rate determines the degree of acceleration finds support in blood pressure studies. Lyon has suggested that the reaction to adrenalin obeys Weber's law, in that the amount of elevation in the systolic blood pressure, after uniform doses of adrenalin depended upon its level at the moment of the injection.

It has not been found possible to demonstrate as close a correlation between the initial auricular rate and its increment after adrenalin, as /
as that observed in the case of the ventricles. The auricular response is modified to some extent particularly in those cases in which the magnitude of the ventricular response is maximum, that is when the initial ventricular rate is relatively low.

It would appear probable that reflex vagal influences, induced by a marked ventricular reaction, limit the auricular response. The amount of limitation is apparently determined largely by the initial ventricular rate.

This would imply, at least in complete heart-block, that the blood pressure reaction is in great measure determined by an increase in the rate and force of ventricular systole, rather than by a peripheral vaso-constriction. At all events considerable dilation of the smaller vessels must occur in certain situations e.g. in the lung fields.

The course of the reaction to a subcutaneous dose of adrenalin varies as much in complete block as it does in the normal beating heart. The maximum auricular and ventricular reactions are not necessarily synchronous. As a general rule the auricles attain to the height of their reaction before the ventricles have completed their acceleration. An increased frequency of both chambers of /
of the heart persists after the blood pressure rise has returned to its pre-existing level. No untoward symptoms resulted from the use of the drug. Release from the block was not observed in any of the experiments performed upon these eight patients.

Reactions differing from those just described, were encountered in four patients. An acceleration, somewhat in excess of that anticipated for a given initial ventricular rate, was observed in one case, in the presence of congestible heart failure. Two cases developed signs of a defect in bundle branch conduction under the influence of adrenalin. This was probably not the direct result of an increase in reflex vagal tone. One of these cases was a man who suffered from intermittent complete block. Tested with adrenalin during complete block no change in the rhythm occurred but branch defect changed from one side of the heart to the other. Tested during 2 to 1 rhythm, complete block was induced. The direction of the main ventricular deflection varied according to the presence or absence of conduction through the main stem of the bundle. During half-rhythm, the ventricular complex in lead 3 was directed downwards, whereas during complete dissociation its direction was upwards.
upwards. The fact that this man's heart was unduly susceptible to adrenalin suggests that in cases of intermittent complete heart-block, the temporary failure of conduction, leading to transient complete dissociation, may perhaps be associated with the formation within the body of some subtle and complex chemical substance analogous to adrenalin or adenosine.