T H E S I S.

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

BY

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SUBMITTED FOR

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

March 1933.

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P R E F A C E .

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 ven-
tricles 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 sug-
gests 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 ack-
nowledge a debt I cannot pay to Professor Murray
Lyon for all the facilities granted me in the Clini-
cal 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.   Profes-
sor Ritchie has also invited me to see certain pa-
tients and given me facilities for their investiga-
tion.   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 signi-
ficance 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 ex-
tending 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 physi-
cians of HARVEY'S generation was of inconvenient
pattern, often inaccurate and generally unreliable.
As a consequence of this, the significance of varia-
tions in the pulse rate was not appreciated.

The water clock, or clepsydra of the an-
cient 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 record-
ing instruments of a convenient portable nature
were invented towards the end of the fifteenth cen-
tury 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 physiologi-
cal state of the pulse, is an irregular and falla-
cious practice".

It is literally true that in the precise
study of the pulse, medicine lagged behind the clock.
FLOYER (70) published in 1707, the first serious
study on the rate of the pulse in health and dis-
eases 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 charac-
teristic 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 ef-
fect.   On account of these influences he came to
the conclusion that the natural healthy pulse was
best observed by counting "the morning pulses be-
fore eating, exercise, or other external influences
disturbed it".

As was true of WITHERING'S original ac-
count 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 inves-
tigation which it well merited.   CUSHNY (46) has
recorded that the indiscriminate use of digitalis
continued for a hundred years after its introduc-
tion to therapeutics, without any endeavour to ana-
lyse its efficiency in different diseases of the
heart.   To a large extent the same fate befell
FLOYER'S attempt to focus attention on the varia-
tions 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 1732.   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 in-
stant 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
mniute: and breathing voluntarily three or four
times faster than usual, has quickened it 13 or 14
beats: The pulse is quickened by coughing, swallow-
ing, reading loud, or by any motion that is perform-
ed by the soul.   From hence it appears, that the
motion of the heart is changed mediately or imme-
diately, by every change made in the affections, ac-
tivity or power of the soul."   HALLER (93)
HEBERDEN (101) and FALCONER (66) likewise dis-
cussed 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 FALCONER (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. ADAMS (2)/

6a.

WILLIAM STOKES.
1804 - 1878.

William Stokes. F.R.S
D.C.L.

(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 $7\frac{1}{2}$ 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 stimu-
lantium 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 impor-
tant contributions on slow pulse made by his collea-
gues, 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 brady-
cardia was no more than a symptom requiring investi-
gation. ".... 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 conva-
lescent, 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 vas-
cular 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 STANNIUS
(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 im-
pulse to ventricular contraction was passed on from
the auricle by means of a slender neuro-muscular
bundle situated in the region of the septum. GASKELE
amplified and confirmed the work of HIS and short-
ly afterwards clinical confirmation of the experi-
mental 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 ba-
lance 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 BAILLIE 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 min-
ute, 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 se-
cond.   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 elabora-
tion of such instruments as the polygraph and
electrocardiograph/

electrocardiograph more detailed knowledge has be-
come 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 per-
iods of time and under greatly varying conditions.
This apparatus, depends upon sufficient amplification
of the action current of the heart to actuate a sen-
sitive relay which in turn activates an electro-
magnetic 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 fol-
lowed their usual mode of life.

THE/

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 func-
tionally isolated from the controlling influence of
the sino-auricular pacemaker, as a result of the in-
ability of the conducting tract to transmit the im-
pulse 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 dis-
sociated.   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 chang-
ing/

changing circumstances, the ventricles are of neces-
sity deprived of the experienced leadership provided
by the sino-auricular node.   Without the resource-
fulness of the skilled pilot, the ventricles may well
pursue a dangerous and treacherous course.   Never-
theless, as will be demonstrated in the following
pages, despite the disadvantages imposed by dissocia-
tion whether functional or organic, the ventricles,
at least in the human heart, are capable of remark-
able 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 re-
produce so perfectly the experimental findings of
the physiologist as does complete heart-block.   Pro-
bably for this reason, auriculo-ventricular disso-
ciation is wellknown and its diagnosis seldom mis-
taken.   No other condition **produces** such a slow
pulse as may complete heart-block, and if indepen-
dent auricular activity be demonstrated by graphic
records, thus excluding the other forms of bradycar-
dia, the diagnosis can be precisely established.
Nevertheless complete block is an uncommon manifes-
tation 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 popu-
lation may be derived from the fact that in a conse-
cutive series of 5000 patients submitted to electro-
cardiographic 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 con-
secutive series of 9000 patients electrocardiographed
at the National Heart Hospital in London.   Consider-
ing 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 lar-
ger 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 precedures 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.

AUTHORS	MALES	FEMALES	TOTAL
Cowan & Ritchie (41)	22	1	23
Downie (54)	13	7	20
Ellis (59)	30	13	43
Goodall (87a)	15	5	20
White and Viko (224)	19	8	27
Willius (228)	14	8	22
This series	9	4	13
TOTAL	122	46	168
Per cent of total	72·6	27·4	100·0

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/
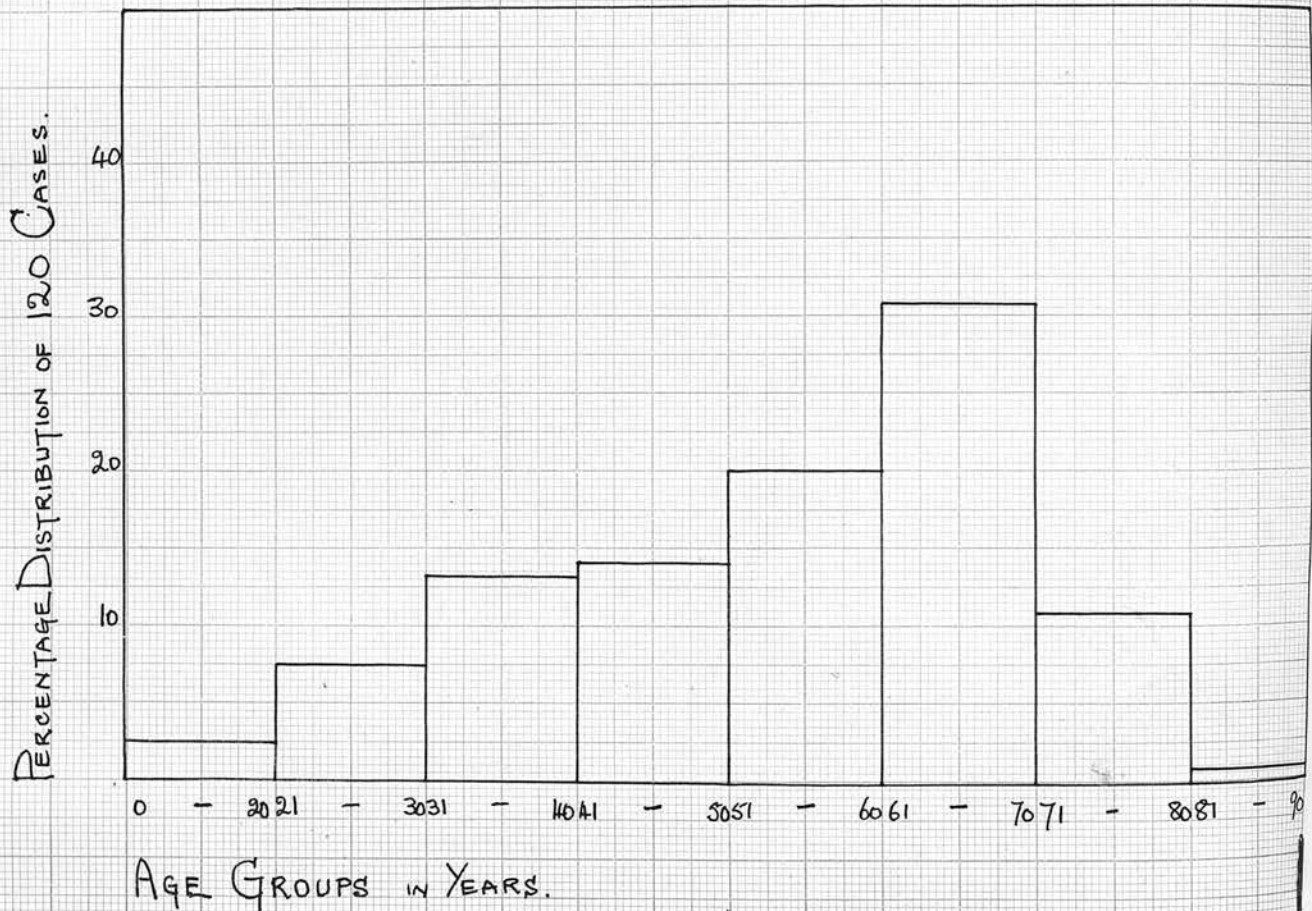
TABLE II.

AGE GROUP	CASES REPORTED BY DOWNIE( ) ELLIS( ) AND WILLIUS( )	THIS SERIES	TOTAL	PER CENT OF TOTAL
Under 20 years	3	0	3	2·5
21 – 30 years	9	0	9	7·6
31 – 40 years	16	0	16	13·5
41 – 50 years	14	3	17	14·3
51 – 60 years	21	3	24	20·2
61 – 70 years	33	3	36	30·2
71 – 80 years	10	3	13	10·9
81 – 90 years	0	1	1	0·8
TOTAL	106	13	119	100·0

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 mor-
tem 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 great-
er 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 collect-
ed 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 discover-
ed most frequently in the seventh decade is of inter-
est, for this is the age period at which arterio-
sclerotic/

1.

PERCENTAGE DISTRIBUTION OF 120 CASES.

40

30

20

10

0 — 20 21 — 30 31 — 40 41 — 50 51 — 60 61 — 70 71 — 80 81 — 90

AGE GROUPS IN YEARS.

sclerotic changes are most prone to manifest them-
selves. According to WARTHIN (220) age 60 marks
the period when "sclerosis of the arteries becomes
the chief collaborative factor in hastening or ex-
aggerating the parenchymatous involution of senes-
cence" with its important effects on the heart, kid-
neys and brain. Vascular disease is apparently the
most frequent etiological factor in the production
of complete heart-block and at those ages when scle-
rotic 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 clini-
cally in New England found that it occurred most fre-
quently (44 per cent) in the sixties. While com-
plete heart-block may occur at any age, and while
it is not necessarily a manifestation of arterial
disease, it is perhaps significant that the great-
est incidence of the disorder falls at that time of
life when coronary artery disease becomes increas-
ingly 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 as-
pects of the condition.   Amongst the lesions found
have been gummata, areas of calcification, oblitera-
tive disease of the branches of the coronary arteries
fibrosis of the conducting tract, neoplasms and va-
rious 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 com-
plete heart-block.

A CLINICAL CLASSIFICATION FOR PERMANENT
COMPLETE HEART-BLOCK.

The difficulty encountered in assign-
ing a cause for certain of the cases included in the
present series has suggested that they might be con-
sidered 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 it-
self may serve to correct our notions and prove a
refreshing stimulant for further endeavour.

To have a classification based on pre-
cise 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 stu-
dies for local fibrotic change is probably the com-
monest 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 causa-
tion, the first or degenerative group is taken to re-
present chronic vascular disease with associated fi-
brosis and local myocardial degneration.   The neces-
sary criteria to establish such a diagnosis are often
slender enough.   They may be taken to be, the pre-
manence of the block over a period of months or years,
the/

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-sclero-
tic heart disease may exist without precise signs
during life, and hence a number of cases may be in-
advertently excluded from this group on account of
the absence of regognisable vascular disease else-
where 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 justi-
fiably 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 justi-
fy 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/

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 III.

THE DEGENERATIVE VASCULAR GROUP.

Case No., Initials, and estimated age at onset of complete block.	Total duration of symptoms to death or to October 1932.	Probable duration of Cardiac symptoms before onset of block.	Stokes-Adams Seizures Usual type.
2. W.W. age 70	1 year 6 months	4 months	Transient giddiness Consciousness lost for only an instant.
4. W.T. age 62	3 years 2 months	Seizures antedated onset of other Cardiac symptoms by about 2 yrs.	Giddiness, weakness, and faintness without actual loss of consciousness.
5. A.H. age 64	4 years 9 months	2 years 11 months	Loss of consciousness.
10. Mrs C. age 82	4 years 2 months	2 years 3 months	Typical severe seizures. Electrocardiograms of attack.
11. Mrs D. age 71	2 years 6 months	1 year	Loss of consciousness.

TABLE III. To show the duration of cardiac symptoms and the probable duration of complete heart degenerative vascular origin.

IIIa.

Number and frequency of Stokes-Adams seizures.	Remarks.
A single attack.	Died in congestive heart failure. Post-mortem; generalised vascular disease, cerebral, renal and cardiac.
One attack at inter-vals of 3 to 6 weeks About 30 to 35 in all	Alive. Able to go about in comparative ease.
One severe faint unconscious for 2 minutes or more.	Alive. Suffers from chronic bronchitis and emphysema. Able to go about in comfort and capable of performing light duties.
352 fully developed seizures April 1930-January 1932.	Died. Hypostatic congestion. Post-mortem; Coronary sclerosis. interstitial myocarditis, generalised arterio-sclerosis.
Two severe faints in succession.	Died. Suffered from diabetes. Exact mode of death not known - ? congestive heart failure; no post-mortem.

25b.

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 intermit-
tent 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 inter-
vals for a greater or longer period and normal
rhythm then alternates with complete heart-block.
While syphilis may have played some part in the pro-
duction of the attacks of complete heart-block in
this man, the fact that the dissociation was inter-
mittent in type does not justify us in assuming that
in this case syphilis was necessarily the causative
factor of importance.   Indeed subsequent histologi-
cal 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 justi-
fied 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.

AUTHOR	No. of SYPHILITIC CASES.	TOTAL No. of CASES.
DOWNIE (54)	4	27
ELLIS (59)	2	43
GOODALL (87a)	1	20
WILLIUS (228)	0	22
This Series.	? 2	14
TOTAL	9	126
Percent of Total.	7.1	100

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 etiologi-
cal 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 justifica-
tion 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, recog-
nising 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 patho-
logist may on occasions find no lesion of the con-
ducting 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 com-
plete may be readily induced.   Whether this results
reflexly through vagal influences or by direct ac-
tion on the bundle tissues is not within our pro-
vince to discuss at the moment.   Similarly asphy-
xia (136) or the administration of fatal doses of
diphtheria toxin may be followed by the development
of auriculo-ventricular block.   It may also be in-
duced 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 af-
fecting 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 infec-
tion and indeed often heralds a fatal termination.
Electrocardiographic proof of the presence of dis-
sociation in the course of the disease has been pre-
sented by various authors (199) and more recently
MARVIN & BUCKLEY (151) have described two cases
in detail.   In one, subsequent histological exami-
nation 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 contract-
ed 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 spe-
cialised cells in the conducting tract, and the sur-
rounding oedema and infiltration, are ultimately re-
placed 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 le-
sion 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 fi-
brotic 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 appa-
rently 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 im-
pairment 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 in-
fection.   Even complete heart-block has been re-
corded during the course of acute rheumatism (41).
In lobar pneumonia according to DE GRAFF and his
colleagues (89) defects in conduction are not un-
common and may appear for the first time during con-
valescence.   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 demonstrat-
ed 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-
sise/

emphasise the association of the block with a re-
cent throat infection.

It would seem reasonable to suppose that
if block may appear as an acute and perhaps tem-
porary 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 da-
mage 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 in-
fection, 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.

As/

TABLE V.

THE "TOXIE" OR UNKNOWN GROUP.

CASE NO., INITIALS, AND ESTIMATED AGE AT ONSET OF COMPLETE BLOCK	TOTAL DURATION OF SYMPTOMS TO DEATH OR TO OCTOBER 1932	PROBABLE DURATION OF CARDIAC SYMPTOMS BEFORE ONSET OF BLOCK	STOKES-ADAMS SEIZURES USUAL TYPE	NUMBER AND FREQUENCY OF SEIZURES	PREVIOUS ILLNESSES	REMARKS
1. Mrs T. age 50	9 years	? 2 months	Severe faints, Coma Several injuries sustained in attacks.	3 or 4 per year, about 30 in all	Severe attack of tonsillitis age 49, immediately before present illness.	In good health at present able to do all household work.
3. D.C. age 61	18 years	9 years	Dizzy, fainted.	One, (?) at onset	(?) syphilitic infection about age 20-25. Subacute rheumatism at age 30 and several attacks since.	Able to go about and undertake light exertion.
6. J. Whd. age 46	3 years	same duration	Giddy turn with sense of weakness.	One, (?) at onset	Severe diphtheria as a child, followed by paralysis of both legs. Ultimate recovery.	Alive. Only able to go about with difficulty.
8. J.B. age ? 31	1 year 2 months	? slow pulse ? block for 16 years	None	None	Scarlet fever, and measles at age 5. Slow pulse at age 31. Rheumatic fever at age 40.	Unable to do much. Rheumatic heart disease, aortic and mitral regurgitation.
12. J.D. age 46	7 years 6 months	2 years	Transient giddy attacks without loss of consciousness	Three or four in all; separated by long intervals.	No rheumatic fever, diphtheria, or any other acute infection known. No arterio-sclerosis.	Able to go about and undertake light duties.
13. Mrs H. age 51	6 years 3 months	same duration	Attacks of loss of strength and giddiness without unconsciousness.	Two or three a fortnight with intervals of two or three months freedom	"Influenzal throat" about 2 months before onset of symptoms. Severe attack of rheumatic fever at age 18. Off work for 12 months.	Able to go about and undertake all kinds of exertion with little incapacity.

(3)

(4)

TABLE V. (contd.)   SUB-GROUP   (INTERMITTENT COMPLETE BLOCK)

CASE NO., INITIALS, AND ESTIMATED AGE AT ONSET OF COMPLETE BLOCK	TOTAL DURATION OF SYMPTOMS TO DEATH OR TO OCTOBER 1932	PROBABLE DURATION OF CARDIAC SYMPTOMS BEFORE ONSET OF BLOCK	STOKES-ADAMS SEIZURES USUAL TYPE	NUMBER AND FREQUENCY OF SEIZURES	PREVIOUS ILLNESSES	REMARKS.
7. R.R. age 57	10 weeks	Same period	Typical Stokes-Adams seizures. Electro-cardiograms of attacks	About 250 seizures in 10 weeks of which 168 or more occurred in the last 24 hours of life	Gonorrhoea at age 31. Syphillis in youth. Tabes dorsalis.	Died in a Stokes-Adams seizure No lesion of the bundle found on histological examination.
9. J.B.G. age 77	10 months	Same period	Typical Stokes-Adams seizure.	About 30 in 10 months.	Subacute cystitis with an acute exacerbation at time of onset of repeated seizures	Alive. Arterio-sclerosis slight. Able to move about in the house. Feeble.

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 (in two intermittent 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 na-
ture, these two cases are best considered as a sub-
group 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 pre-
sence 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 para-
lysis of both legs from which he ultimately recovered.
Case 8 suffered from rheumatic heart disease (mitral
and aortic endocarditis) when he came under observa-
tion 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 per-
sistence was probably not of organic origin.   Ex-
perimental methods demonstrated that adrenalin was
capable of relieving the dissociation.   This case is
quite exceptional and may be classified as a func-
tional 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 infec-
tion, 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 an-
tecedent 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 scle-
rosis.   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 se-
vere 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 symp-
toms.   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 repres-
ent a type of dissociation presenting distinct fea-
tures.   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 distur-
bance 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 suffi-
cient to turn the scale with the result that the
stimulus in its downward path enters an area of re-
fractory tissue and fails to bridge the gap.   It is
justifiable to assume that some temporary and ex-
traneous influence acting on the conducting tissues,
- perhaps in a state of increased susceptibility
owing to the presence of an associated organic le-
sion of one kind or another - must be the determin-
ing factor in the production of the attacks of com-
plete 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 di-
sease (Case 9).   In Case 7 no provoking cause for
the onset of complete heart-block was discovered.
Examination revealed no active infection.   The auri-
cular 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 play-
ed 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 con-
clude 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 con-
ducting pathway and complete block ultimately re-
sults 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 ap-
parently sufficient to account for the dissociation
in his cases.

SUMMARY.

Complete heart-block is a rare manifesta-
tion 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/

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 indi-
viduals the lesion was believed to be
primarily the result of sclerotic vas-
cular 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 suf-
fered from tabes dorsalis.   The block
was of the intermittent type and there
was peripheral evidence of slight ar-
terio-sclerosis.   One other man, in
whom syphilis was suspected also gave
a history of repeated attacks of sub-
acute rheumatism.   In the past the
importance of syphilis as an etilogi-
cal factor in the production of com-
plete 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 determin-
ing the onset of dissociation.   One
was an example of a functional disso-
ciation of unknown etiology.   The re-
maining five cases each gave a history
of a severe infection - tonsillitis,
diphtheria, scarlet fever or rheuma-
tism.

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 his-
tory 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 de-
generative 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 sug-
gest that, if it be significant, there may likewise
be some other distinctions in regard to symptomato-
logy. Physiologically it is of common experience
that the response to a given stimulus varies some-
what with the age of the tissue tested. In clinical
medicine however clear cut experiments are the ex-
ception rather than the rule. Accurate deduction is
handicapped by a multiplicity of factors and compli-
cated interactions obscure the individual's response
Complete heart-block must of necessity be of rela-
tively 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 circu-
latory inefficiency.

In considering the reaction of the indi-
vidual to the sudden onset of an independent ventri-
cular 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 ap-
pear 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 genera-
lised 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 fail-
ing 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 sug-
gest that they are not of considerable significance.
In fact it has been possible in more than one in-
stance to demonstrate by means of the electrocardio-
graph, 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 dura-
tion 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 re-
corded 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 be-
comes complete. An adequate circulation then de-
pends upon the immediate developement of an inde-
pendent idio-ventricular rhythm. Delay in the
iniation of stimulus formation at a new focus, be-
low 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 indepen-
dent 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 individu-
als 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 at-
tacks 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/

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 suf-
fered 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 con-
dition if we admit that a fainting attack is of suf-
ficient 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 con-
clusion/

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, par-
ticularly 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 demon-
strated 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 dis-
order of rhythm. Of the twelve individuals who ad-
mitted or frankly complained of this symptom it is
found that seven suffered from general cardiac symp-
toms 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 coin-
cided with the advent of the first Stokes-Adams sei-
zure. 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 detioration 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 manifesta-
tion of a similar tendency.   The natural downward
course of the disease does not appear to be appre-
ciably 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 sei-
zures, 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 ad-
vice.   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 there-
fore appear that, the block itself plays a minor
part in the production of general symptoms, the in-
capacity resulting from a progressive myocardial
deteriotation.

Of the five individuals in the degenera-
tive/

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 experien-
ced.

Considering first the three individuals
mentioned above (CASES 1, 3 and 12) it is found
that, just as in the degenerative group, the symp-
toms, 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 estab-
lished 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 per-
form 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 heartblock 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 approxi-
mately 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 estab-
lished 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 on-
set of cardiac symptoms, the block has remained per-
manent for the past 18 months. His symptoms have
likewise consisted of dyspnoea and fatigue and cul-
minated in an attack of congestive heart failure
eight months after the onset of the heart-block.
The fact that this man developed auricular fibrilla-
tion 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 bradycardia 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 predominating with auricular fibrillation, it would appear probable that the mere presence of complete heartblock 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 sub-
jects (CASES 1, 3, 6, 9, 12 and 13) have been afflic-
ted 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 under-
take 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 (re-
peated at intervals over periods of 4 and 6 years
respectively) have confirmed the presence of perma-
nent dissociation, have suffered little or no ap-
preciable 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.

GROUP	CASE NO.	CASES ALIVE AT THIS DATE (OCTOBER 1932) AGE AT ONSET	DURATION OF BLOCK	CASES NOW DEAD CASE NO.	AGE AT ONSET	DURATION OF BLOCK.
Degenerative Group	4	62	3 yrs. 2 months.	2	70	1 year 2 months.
	5	64	1 yr. 10 months	10	82	1 year 11 "
				11	71	1 year 6 "
Average of Degenerative Group		63	2 yrs. 6 months.		74	1 year 7 months.
"Toxic" or Unknown Group.	1	50	8 yrs 10 months			
	3	61	8 " 0 "			
	6	46	3 " 0 "	None are dead (Oct. 1932)		
	8	?31	?16 " 0 "			
	12	46	5 " 6 "			
	13	51	6 " 3 "			
Average of "Toxic" group (omitting case 8)		51	6 yrs. 4 months	-	-	-
Intermittent	9	77	0 yrs.10 months	7	57	0 year 2½ months.

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

complete heart-block was first diagnosed with
certainty. Had it been possible to continue ob-
servations 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 individu-
als, its total duration is likely to be shorter in
them than amongst those in whom it becomes estab-
lished 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 degene-
rative 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-emminent 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 re-
sult 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 rela-
tively 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 altera-
tions 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 fac-
tors. 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.

S U M M A R Y.

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 con-
dition 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 re-
vealing. 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 func-
tional integrity of the myocardium as a whole than
upon the mere dissociation of auricular and ventri-
cular/

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 atten-
tion 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 com-
plete 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 illus-
trated 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 accelera-
tor tone, and serve to indicate the ceaseless activi-
ty 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. Exer-
cise and rest, alterations in environmental tempera-
ture 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 respec-
tively. 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 indivi-
dual.

THE/

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 influ-
ences 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) ex-
perience 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 beat-
ing 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/

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 VII.

CASE NO. & INITS.	RESTING RATES		AURICULAR	VENTRICULAR	AVERAGING RESTING RATES	
	AUR.	VENT.			AURICULAR	VENTRICULAR
1. Mrs T. 1	75.3	22.2				
2	72.1	22.0				
3	75.3	25.0				
4	81.8	23.8	Max.aur.Rate 81.8	Max.Vent.Rate 29.2		
5	69.0	21.0	Min.aur.Rate 69.0	Min. " 21.0		
6	77.0	26.7	Aur. Range 12.8	Vent. Range 8.2	74.9	24.9
7	70.4	29.2				
8	80.8	25.6				
9	77.7	27.6				
10	69.8	24.4				
2. W.W. 1	74.1	36.1				
2	71.8	36.8	Max.aur.Rate 78.8	Max.Vent.Rate 36.8		
3	69.9	34.8	Min. " 69.9	Min. " 33.8		
4	71.5	33.8	Aur. Range 8.9	Vent. Range 3.0	73.7	35.4
5	78.8	35.7				
6	76.2	35.0				
3. D.C. 1	72.0	42.8	Max.aur.Rate 78.0	Max.Vent.Rate 42.8		
2	78.0	40.4	Min.aur.Rate 72.0	Min. " 38.5	77.6	40.6
3	72.8	38.5	Aur. Range 6.0	Vent. Range 4.3		
4. W.T. 1	63.1	23.6	Max. aur.Rate 63.1	Max.Vent.Rate 23.6		
2	59.3	22.9	Min. " 55.2	Min. " 22.1		
3	55.2	22.1	Aur.Range 7.9	Vent.Range 1.5	58.8	23.0
4	57.6	23.6				

TABLE VII (contd.)

CASE NO. & INITS.	RESTING RATES		AURICULAR	VENTRICULAR	AVERAGING RESTING RATES	
	AUR.	VENT.			AURICULAR	VENTRICULAR
5. A.H. 1	72.5	31.0				
2	67.3	34.8	Max.aur.Rate 72.5	Max.Vent.Rate 36.0		
3	66.3	30.7	Min. " 58.0	Min. " 30.6		
4	58.0	30.6	Aur.Range 14.5	Vent.Range 5.4	64.4	32.3
5	59.0	36.0				
6	63.5	30.6				
6. J.W. 1	57.7	28.5	Max.aur.Rate 57.7	Max.Vent.Rate 28.5		
2	48.4	27.2	Min. " 48.4	Min. " 25.0	53.1	27.0
3	51.5	27.4	Aur.Range 9.3	Vent.Range 3.5		
4	54.2	25.0				
8. J.B. 1	A.fib.	29.7				
2	"	32.6	Auricular	Max.Vent.Rate 33.0		
3	"	31.7	Fibrillation	Min. " 29.7	A.fib.	31.7
4	"	33.0		Vent.Range 3.3		
5	"	31.4				
10. Mrs C. 1	A.fib.	26.7	Auricular	Max.Vent.Rate 26.8		
2	"	26.8	Fibrillation	Min. " 26.5	A.fib.	26.7
3	"	26.5		Vent.Range 0.3		
11. Mrs D. 1	94.6	42.8				
2	84.5	40.3	Max.aur.Rate 98.6	Max.Vent.Rate 51.0		
3	89.8	43.0	Min. " 84.5	Min. " 40.3		
4	90.0	45.5	Aur.Range 14.1	Vent.Range 10.7	90.4	44.4
5	86.0	43.6				
6	98.6	51.0				

TABLE VII (contd.)

CASE NO. & INITS.	RESTING RATES		AURICULAR	VENTRICULAR	AVERAGING RESTING RATES	
	AUR.	VENT.			AURICULAR	VENTRICULAR
12. J.D. 1	91.3	49.3				
2	73.1	55.2	Max.aur.Rate 91.3	Max.Vent.Rate 55.2		
3	79.2	48.7	Min. " 73.1	Min. " 46.6		
4	84.6	49.8	Aur.Range 18.2	Vent.Range 8.6	82.4	49.5
5	83.6	46.6				
6	82.8	47.1				
13. Mrs H. 1	71.3	39.8	Max.aur.Rate 77.3	Max.Vent.Rate 42.6		
2	77.3	42.6	Min. " 71.3	Min. " 39.8	74.8	41.4
3	76.1	41.7	Aur. Range 6.0	Vent. Range 2.8		
Average of Series:—			Auricular Range 10.9	Ventricular Range 4.7	72.2	34.3
			As percentage of average resting auricular rate 15.1	As percentage of average resting ventricular rate 13.7		

TABLE VII. To show the recorded auricular and ventricular rates on different days in eleven individuals under approximately uniform conditions of bodily rest. For the whole series the average resting auricular rate is 72.2 and the ventricular is 34.3 per minute. The average resting auricular range is 10.9 and the ventricular 4.7 under these conditions.

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 de-
termination) 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 uni-
form 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 approp-
riate 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 maxi-
mum 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 sup-
pose 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 im-
plies 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 ventri-
cles 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 aver-
age 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.

S U M M A R Y/

S U M M A R Y

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.

2.

All cases — degenerative and "toxic".

$y = 0.51x + 3.08$
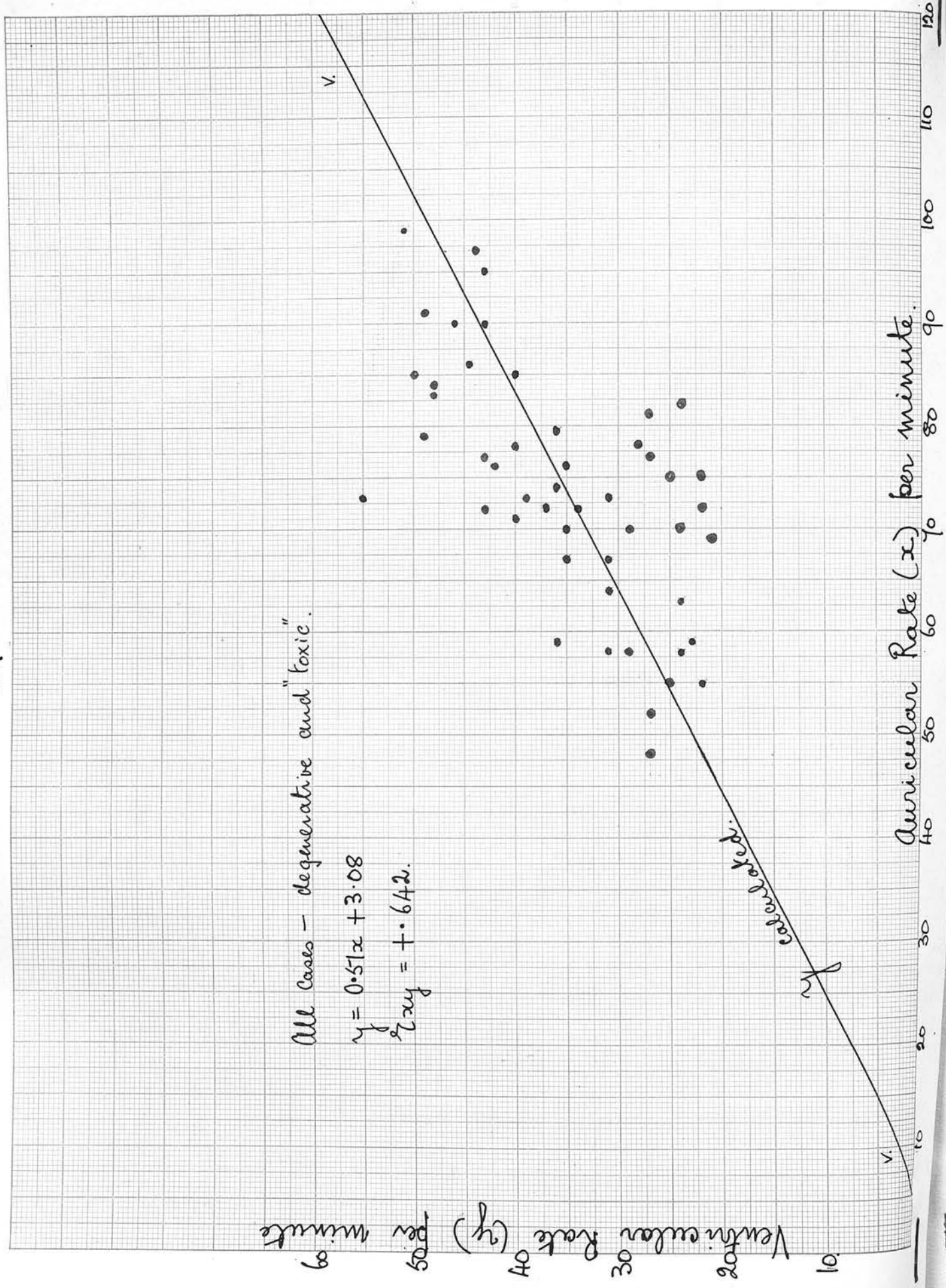
$r_{xy} = +.642$

calculated.

Ventricular Rate (y) per minute

Auricular Rate (x) per minute.

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 con-
ceivable that likewise the actual resting auricular
and ventricular rates may bear some definite propor-
tion the one to the other. The accompanying GRAPH,
No. 2 in which corresponding auricular and ventricu-
lar rates, have been plotted against each other, de-
monstrates 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 ven-
tricular rates in nine individuals are recorded in
TABLE 7.

        Applying the law of least squares, where:-

$$y = \text{the ventricular rate}$$
$$\text{and } x = \text{the auricular rate}$$
$$\text{and } a = \frac{\sum(x) \ x \sum(xy) - \sum(x^2) \ x \sum(y)}{[\sum(x)]^2 - n\sum(x^2)}$$

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

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 3.08 and 0.51.   Substituting we have $y = .51x + 3.03$.

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,   then $\sigma x = \sqrt{\dfrac{(x^2) - (\bar{x})^2}{n}}$

and $\sigma y = \sqrt{\dfrac{(y^2) - (\bar{y})^2}{n}}$

and where $\zeta = $ coefficient of correlation then $\zeta xy = \dfrac{\bar{xy} - (\bar{x}\ \bar{x}\ \bar{y})}{\sigma x\ \ x\sigma y}$

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/

Ja.

Degenerative Cases.

$y = 0.53x + 3.63$

$r_{xy} = + .9012.$

Auricular Rate (x) per minute

Ventricular Rate (y) per minute

calculated.
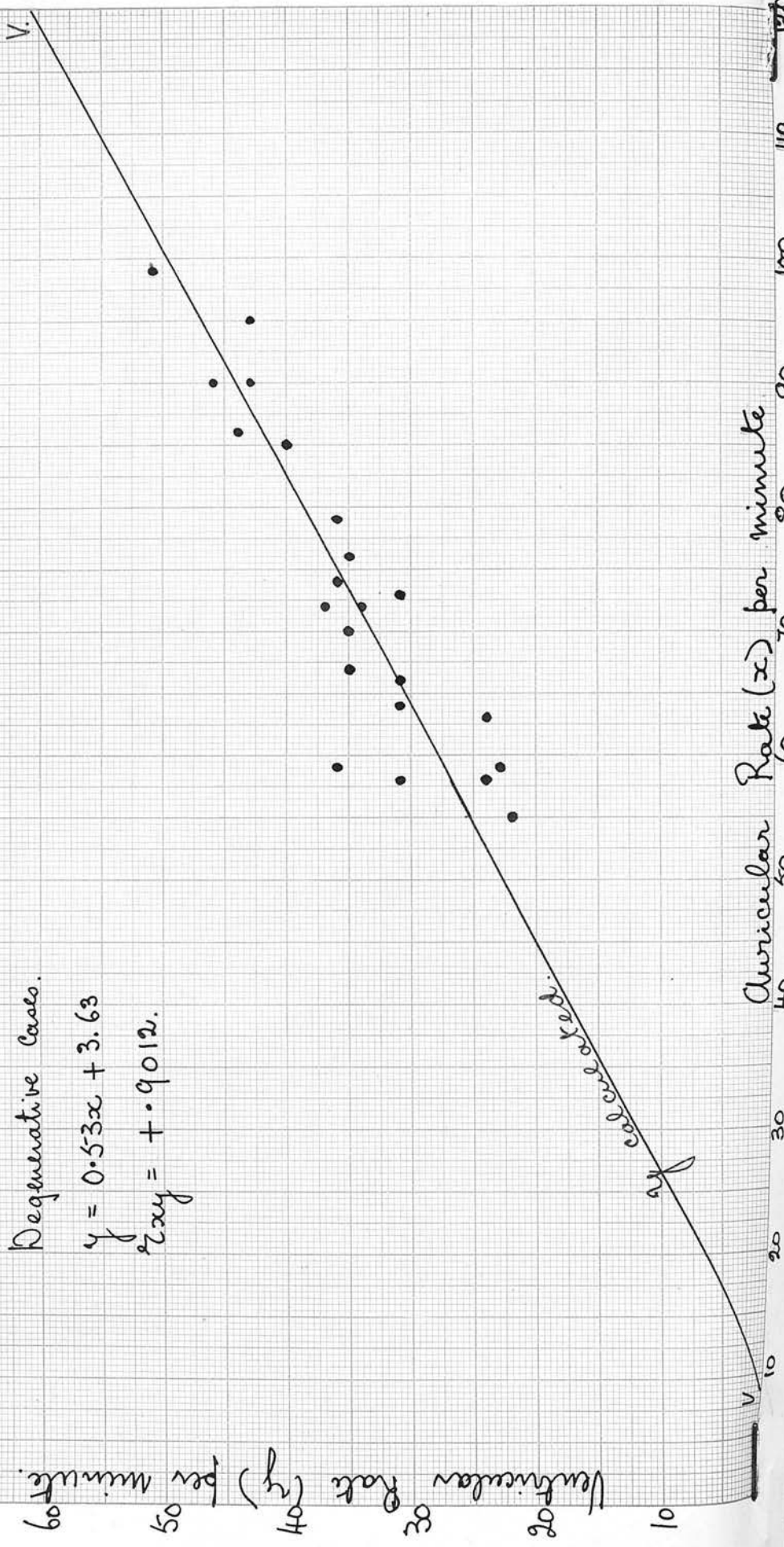
Reference has already been made to a sug-
gested clinical classification of cases of complete
heart block.   It was found possible to divide the
cases into two broad groups a degenerative, and a
"toxic" or unknown variety.   The degenerative were
on the average older individuals and the block oc-
curred apparently as a manifestation of a more or
less generalised cardiac fibrosis.   Each group had
certain features in common, the "toxic" being com-
posed of a variety of cases of a mixed type, as
heterogeneous in their etiology as in their func-
tional capacity.   The amount of "scatter" depicted
in the chart of the whole series, suggested that
probably by replotting the two groups of cases se-
parately a more perfect correlation between auri-
cular and ventricular rates might be demonstrated
for one or other.

In GRAPH $3_a$the observed auricular and
corresponding ventricular rates of the four degenera-
tive 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 cal-
culated value y =.53x + 3.63.

GRAPH/

V.

"Toxic" Cases.

$y = 0.48x + 3.02$

$y_{xy} = +.4970.$

Ventricular Rate (y) per minute.

Auricular Rate (x) per minute.

V. y calculated.

V.
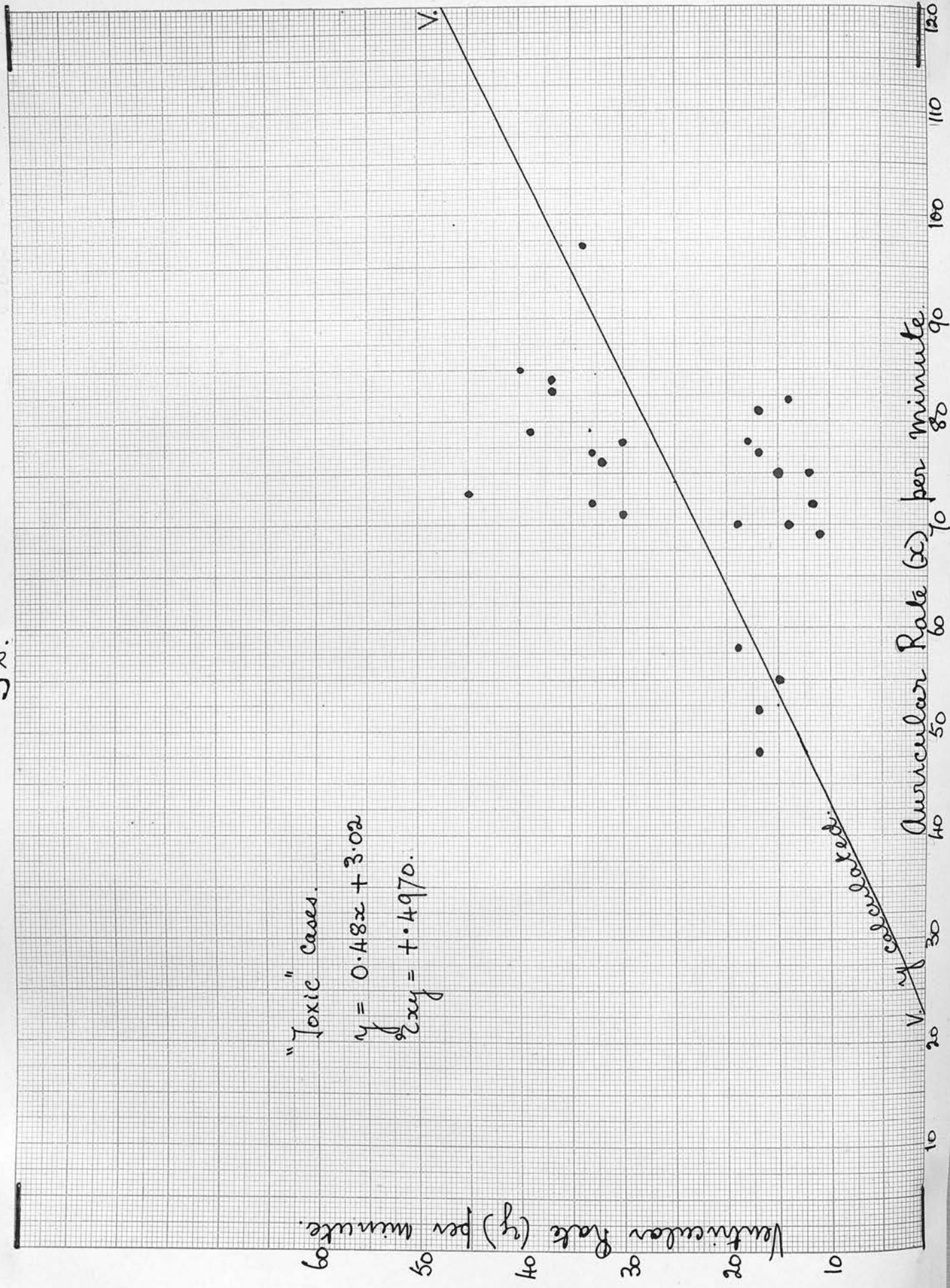
GRAPH 3bis composed of the readings obtained from the individuals included on a basis of clinical classification in the "toxic" or unknown group. A glance at the plottings is sufficient to demonstrate a sharp contrast when this chart is compared with that of the previous group. The "scatter" is over 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. Further, 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:- VIII

GROUP	NO. OF CASES.	CHART	COEFFICIENT of CORRELATION xy	CALCULATED VALUE of y. $(y = bx + a)$
Whole series.	9	2	+.6420	$0.51x + 3.08$
Degenerative Group.	4	3a	+.9012	$0.53x + 3.63$
"Toxic" Group.	5	3b	+.4970	$0.48x + 3.02$

SUMMARY/

S U M M A R Y.

The mathematical analysis of the avail-
able data demonstrates that a fair degree of posi-
tive correlation exists between the auricular and
ventricular rates under resting conditions for all the
cases.   Moreover, this treatment indicates a fur-
ther justification for the proposed clinical subdi-
vision 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 rela-
tively wide degree of dispersion in this group in-
dicates 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 com-
plete heart-block is rather less than half a given
auricular rate.

THE RELATION OF VENTRICULAR RATE TO CERTAIN BODILY MEASUREMENTS.

TABLE IX.

CASE NO.	VENTRICULAR RATE RESTING MIN. RATE.	MAX. RATE.	RANGE	AGE YRS.	HEIGHT in INCHES.	WEIGHT in POUNDS.	SURFACE AREA SQ. M.
1. Mrs. T.	21.0	29.2	8.2	55	65	131	1.640
2. W.W.	33.8	36.8	3.0	72	68	136	1.725
3. D.C.	38.5	42.8	4.3	64	67	161	1.831
4. W.T.	22.1	23.6	1.5	65	71	178	2.000
5. A.H.	30.6	36.0	5.4	64	64½	119	1.572
6. J.W.	25.0	28.5	3.5	48	68	151	1.805
8. J.B.	29.7	33.0	3.3	47	65	137	1.670
11. Mrs.D.	40.3	51.0	10.7	71	61	163	1.729
12. J.D.	46.6	55.2	8.6	50	63	114	1.521
13. Mrs.H.	39.8	42.6	2.8	57	64	175	1.860

THE RELATION OF VENTRICULAR RATE TO CERTAIN BODILY MEASUREMENTS.

It has been shown above that, under condi-
tions 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 fea-
tures 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 maxi-
mum 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/

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 Œconomy" 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:-

$$e.g. \quad \sqrt[4]{72^3} \quad : \quad 65 \quad :: \quad \sqrt[4]{60^3} \quad : \quad x$$

$$\therefore \quad 24 \cdot 717 \quad : 65 \quad :: 21 \cdot 558 \quad : \quad x$$

$$\therefore \qquad x = \frac{24 \cdot 717 \times 65}{21 \cdot 558}$$

$$= 74 \cdot 52$$

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 fac-
fors, a clear cut agreement between theoretical and
observed rates over a wide range can hardly be ex-
pected. 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 de-
rived from a large series of basal metabolic duties
could find no relationship between stature and
heart rate in adult men and women, nor indeed be-
tween body weight and heart rate. They were, how-
ever, 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 be-
tween the heart weights and body weights. It there-
fore 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 assurety 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 king-
dom.

In man the heart-ratio probably varies
considerably in different individuals, as is sugges-
ted 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 assess-
ing the heart-ratio during life, although some ap-
proximation to the truth might be derived from x-ray
studies of the cardiac area. Radiological observa-
tions on the precise size of the heart, even by
modern methods, are liable to be fallacious. With
a technique designed to minimise the distortion pro-
duced 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. Further,
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 doubt-
ed 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 rela-
tively 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 sym-
pathetic, are as a general rule incapable of in-
fluencing the autonomic ventricular rhythm in com-
plete heart-block. This implies that in the pre-
sence of complete heart-block, while the auricles
are capable of responding to vagal and sympathetic
influences, the ventricles are functionally isolat-
ed 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 com-
pare the ventricular rate in complete heart-block
with bodily measurements, particularly in relation
to the metabolic rate or surface area of the indi-
vidual. We have seen that there is in health a
slight/

slight but significant correlation between metabo-
lism and heart rate. It it be true that the ventri-
cular 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 meta-
bolism.

VENTRICULAR RATE in RELATION to SURFACE AREA.

It has been shown that in man, the meta-
bolic 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 re-
cumbent position about two to three hours after a
light meal. Auricular and ventricular rates were
recorded synchronously.

On/

4.

$y \text{(auricles)} = 5.88 - 0.286x$

$r_{xy} = -.387.$

$y \text{(ventricles)} = 5.19 - 0.18x$

$r_{xy} = -.236.$

Heart Rate per minute

Auricular.

Ventricular.

Surface Area (x) in sq. cm.
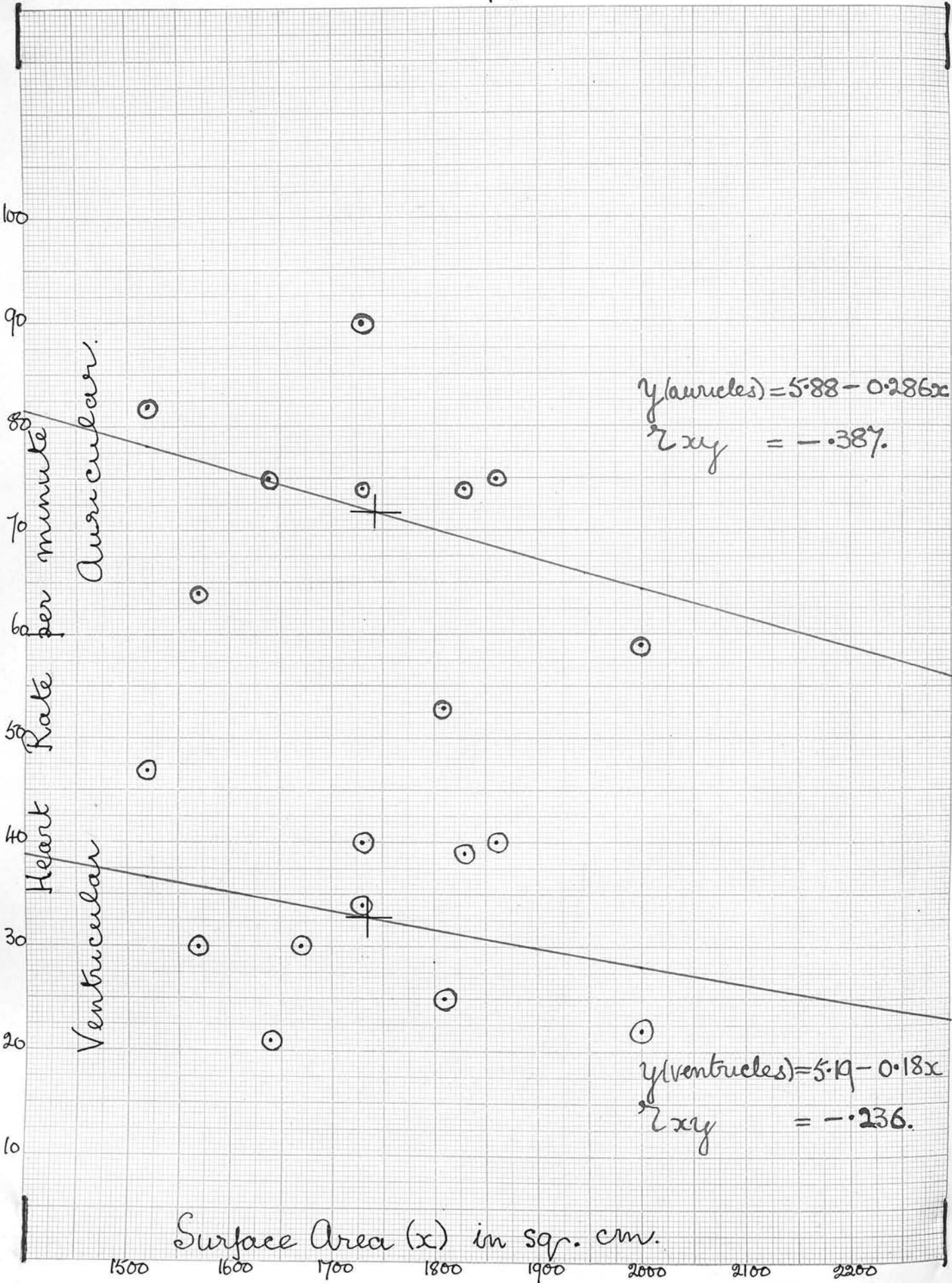
On subjecting the data presented in TABLE
IX to mathematical analysis, it is found that only
a slight inverse correlation exists between the
ventricular rate and the surface area of the body.
The coefficient of correlation is - ·236. The re-
gression line V-V drawn to the equation y=5·19 -
0·18x represents 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 sur-
face area) is - ·387, rather better than that exist-
ing 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 ventricu-
lar 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 com-
plete 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 auri-
cular 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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were under detailed observation. Others gained a
few pounds. The initial weight has been selected
as a uniform one throughout this series of
individuals./

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 + •1003,
so low as to be negligble. As regards auricular
rate and body weight, the coefficient is a trifle
higher and inverse, being - •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 re-
corded under the same resting conditions have been
compared with the corresponding heights. The indi-
viduals studied were all adults, the extremes of
height being 61 and 71 inches. On plotting the
data presented in TABLE IX, a distinct relation-
ship 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/

a.

V.

$y(\text{auricles}) = 6.13 - 2.58x$
$r_{xy} = -.7890.$

$y(\text{ventricles}) = 5.56 - 1.73x$
$r_{xy} = -.5840.$

y(ventricles) calculated.

y(auricles) calculated.

Heart Rates per Minute. (y)

Auricular.

Ventricular.

100

90

80

70

60

50

40

30

20

10

Height (x) in Inches.

V.   a.

30   40   50   60   70   80   90   100.
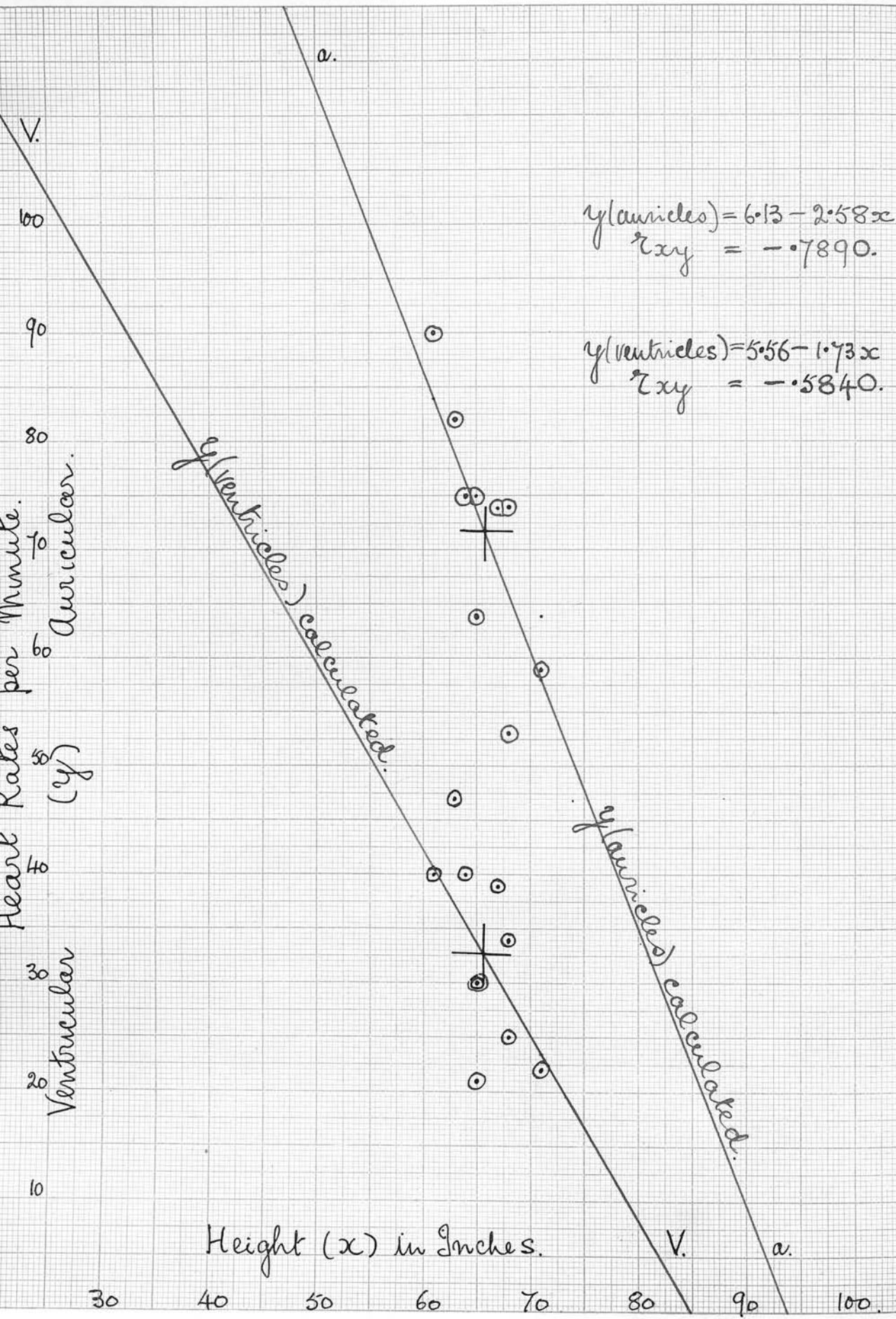
correlation exists in relation to auricular rate.
The coefficients of correlation are, - •584 for the
ventricles and - •789 for the auricles . The corres-
ponding regression lines, V-V and a-a, drawn to the
equations y (ventricles) = 5•56 - 1•73x and y =
(auricles) = 6•13 - 2•58x, are presented in Chart 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 or correlation of only - •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 re-
lationship does exist. The group of cases is how-
ever 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 corre-
lation between heart rates and other bodily variates
are grouped in the accompanying TABLE X.

VARIATES	COEFFICIENT OF CORRELATION.
Ventricular Rate and Surface Area Auricular Rate and Surface Area	- ·236 - ·387
Ventricular Rate and Body Weight Auricular Rate and Body Weight	+ ·100 - ·117
Ventricular Rate and Height Auricular Rate and Height	- ·584 - ·789

TABLE X to show the relation between
ventricular rate and certain bodily variates.

RELATION/

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.

	MIN. RATES.	MIN. of SERIES.	MAX. of SERIES.	RANGE.
Mrs. T.	21·0			
Mrs. C.	26·5			
Mrs. D.	40·0			
Mrs. H.	39·8	21·0	40·0	19·0
Average	31·8			

MALES.

	MIN. RATES.	MIN. of SERIES.	MAX. of SERIES.	RANGE.
W.W.	33·8			
D.C.	38·5			
W.T.	22·1			
A.H.	30·6			
J. Whd.	25·0			
J.B.	29·7			
J.D.	46·6	22·1	46·6	24·5
Average	32·3			

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./

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 diffe-
rent 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 asso-
ciation 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 ventricu-
lar and auricular rates under uniform conditions of
bodily rest have been compared with certain anatomi-
cal measurements. It has been found that no signifi-
cant 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 dis-
covered there are no figures in the literature to
show whether this correlation is peculiar to com-
plete heart-block. By contrast it would be desir-
able 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 in-
verse 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 indi-
viduals 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, ex-
hibiting 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 inde-
pendent 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 de-
gree of correlation between the metabolism of the
individual and the rate of the independent ventricu-
lar/

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 in-
dividual (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 ven-
tricular 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 condi-
tions.

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 com-
parable figures for the range throughout the series,
it is desirable to study the maximum range for each
individual.

For our present purposes the maximum natu-
ral range in either ventricular or auricular fre-
quency 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 pro-
tein, the ventricular rate is greater than that ob-
served after a standard exercise test.   Similarly,
the lower rates observed under uniform resting con-
ditions 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 digi-
talis administration do not concern us for the mo-
ment.   It seems more justifiable to consider that
range represented by the difference between the maxi-
mum 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 electrocardio-
graph 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 per-
mitted.

The minimum rate, used in the estimation of
ventricular range was that observed under prolonged
conditions of bodily rest.   This rate was been sel-
ected 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 indivi-
duals 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 sleep-
ing ventricular rate throughout the whole series of
cases.   The effect of sleep on the ventricular rate
is discussed elsewhere.

<div align="center">

THE   NATURAL   MAXIMUM   AURICULAR   AND
VENTRICULAR   RANGES.
</div>

Under the conditions described above it
is found that the maximum natural range of rate for
auricles and ventricles varies a good deal in dif-
ferent individuals.   The results obtained are pre-
sented 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 com-
pared with those other cases in which the rate of
auricular/

TABLE XII.

CASE NO.	AVERAGE RESTING RATE		MINIMUM RESTING RATE		MAXIMUM RATE AFTER EXERCISE		MAXIMUM NATURAL RANGE IN RATE — AURICULAR		MAXIMUM NATURAL RANGE IN RATE — VENTRICULAR	
	AUR.	VENT.	AUR.	VENT.	AUR.	VENT.	ACTUAL GAIN	PER CENT. GAIN	ACTUAL GAIN	PER CENT. GAIN
*1. Mrs T.	74.9	24.9	69.0	21.0	129.6	33.0	60.6	87.8	12.0	57.1
2. W.W.	73.7	35.4	69.9	33.8	88.4	36.8	18.5	26.5	3.0	8.9
*3. D.C.	74.3	40.6	72.0	38.5	128.7	57.4	56.7	78.8	18.9	49.1
*4. W.T.	58.8	23.0	55.2	22.1	97.4	46.2	42.2	76.5	24.1	109.0
*5. A.H.	64.4	32.3	58.0	30.6	116.3	36.0	58.3	100.5	5.4	17.8
*6. W.Whd.	53.1	27.0	51.5	25.0	131.0	30.6	79.5	158.5	5.6	22.4
8. J.B.	A.Fib.	33.7	A.Fib.	29.7	A.Fib.	43.2	A.Fib.	—	9.5	22.0
"	"	26.7	"	26.5	"	27.3	"	—	0.8	3.0
10. Mrs C.	90.4	44.4	84.5	40.3	111.1	51.0	26.6	31.5	10.7	26.6
11. Mrs D.	82.4	49.5	73.1	46.6	123.8	82.9	50.7	69.4	36.3	77.9
*12. J.D.	74.8	41.4	71.3	39.8	110.0	90.0	38.7	54.2	50.2	126.1
*13. Mrs H.										
Average in whole series.	71.9	34.5	67.2	32.2	114.1	48.7	38.0	56.6	16.0	49.7
Average for 7 marked with *	69.0	34.2	64.3	31.7	119.5	53.7	55.2	86.2	21.8	70.7

auricular activity was governed by the normal pace-
maker.   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 ven-
tricles was greater after exercise than immediately
before and likewise even greater than the minimum
rate recorded for the individual under average rest-
ing conditions.   Exercise also accelerated the auri-
cular 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 correspond-
ing minimum rates, then it is found that while the
auricles accelerated by 56·6 per cent the ventricles
accelerated/

aceelerated 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 re-

spective 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 per-

centage increase over minimum resting rate of 86•2

and 70•7 respectively.   This suggests that the avail-

able 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 auri-

cular range against the corresponding ventricular

range.   It then becomes evident that in general

those individuals who exhibit a great range of auri-

cular rate have by contrast only a small range of

ventricular rate.   Similarly those whose ventricles

exhibit a large range have relatively less auricu-

lar acceleration.   The facts are best demonstrated

by expressing the auricular and ventricular ranges

as percentages of the minimum resting rate and plot-

ting one against the other.   This has been done in

the /

6.

Graph with axes:
- Vertical axis (left): Percentage Circulation Deceleration. (x) — scale from 10 to 170
- Horizontal axis (bottom): Percentage Ventricular Acceleration. (y) — scale from 10 to 200

y calculated

$y = -0.92x - 5.66$

$\Sigma xy = -.765$

118a
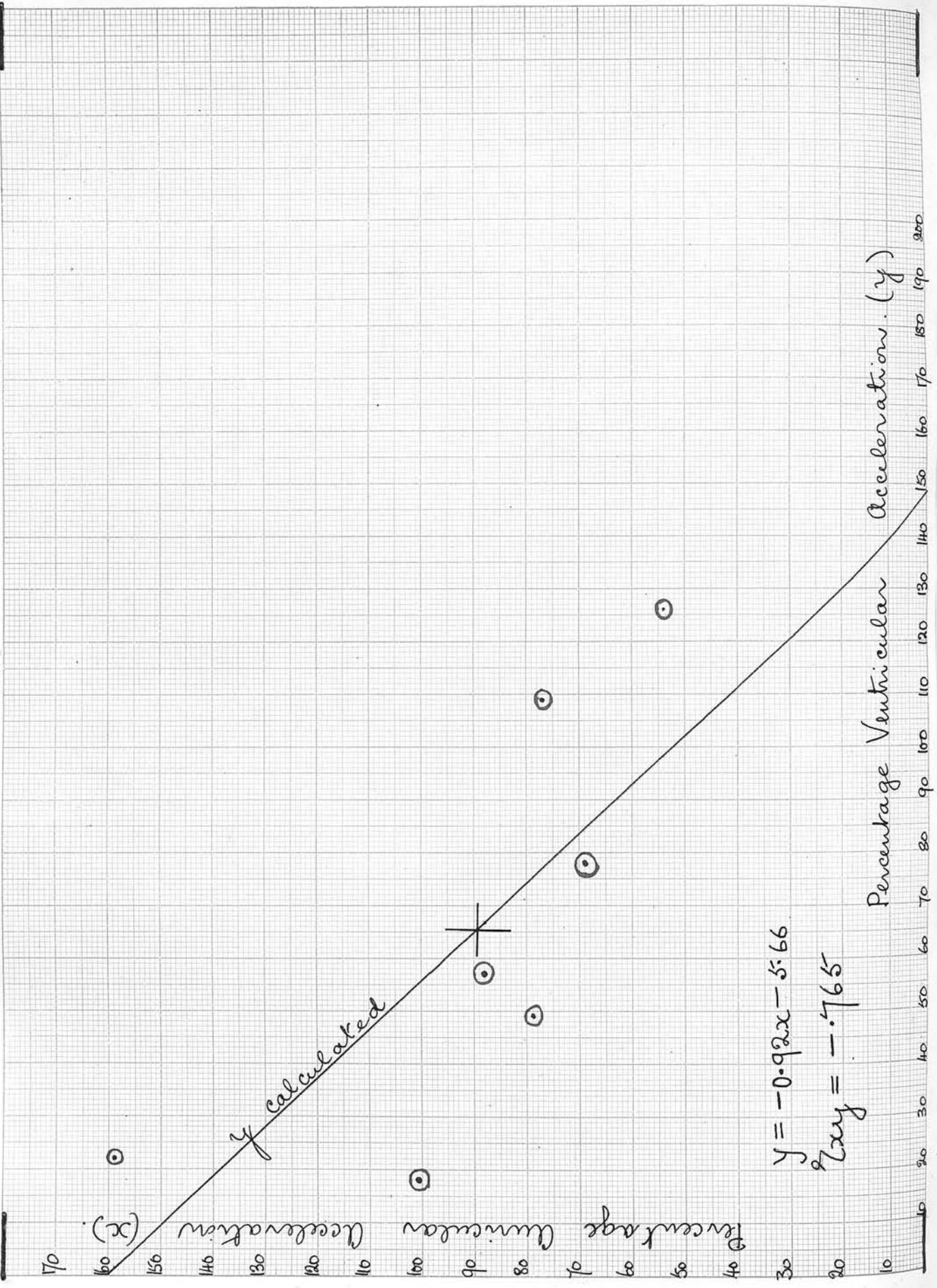
Graph 6
here

the accompanying GRAPH (No. 6).   This demonstrates
quite conclusively that the auricular and ventricular
ranges are not of the same order of magnitude through-
out this series of cases.   Incidentally it points
out how fallacious conclusions drawn from averages
may be.   Were the ranges of a uniformly similar or-
der 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 $y = -0.92x - 5.66$ re-
presents the percentage ventricular range (y) for a
given auricular (x).   From this it is evident that
an increase of approximately 150 per cent in auri-
cular rate is accompanied by only a 10 per cent rise
in ventricular, whereas a 50 per cent gain in auri-
cular rate coexists with a 100 per cent gain in ven-
tricular.   In other words under a standard test of
the natural maximum range of the auricular and ven-
tricular 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 ventri-
cular acceleration the less the auricular.   That a
close/

Graph 6

close relationship exists between the two sets of
ranges is evident from the coefficient of correla-
tion, which is - •765.   The observations are, of
course rather few to treat mathematically and it may
be that a straight line formula is not the best ex-
pression of the relationship between the auricular
and ventricular ranges.   Nevertheless the available
figures indicate the existence of an inverse correla-
tion.   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 num-
ber 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 metabolities 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 pres-
sure 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 ex-
cessive auricular acceleration is all the more like-
ly. 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 dys-
pnoeic after the exercise test than those in whom
the ventricular increase was maximum and the auricu-
lar 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 in-
fluence 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 pres-
sure.   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 con-
ditions 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 proportion-
ate to the minimum rate throughout the series?

The ventricular range has been measured
in nine individuals (including the two cases com-
plicated 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 an-
other with a similar rate of 21·0 the range is 12
(57%).   Taking the group as a whole, it is imposs-
ible to predict the range in rate for a given ventri-
cular 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 in-
dividuals.

This conclusion finds support from simi-
lar observations on the response of the heart in
healthy people.   The degree of acceleration produced
by a given amount of work varies enormously through-
out a series of healthy subjects.   It even varies a
little in repeated observations on the same indivi-
dual.   The range in rate of the heart of the normal
healthy individual cannot be predicted from the ini-
tial rate before exercise.

THE/

THE RELATION OF VENTRICULAR RANGE TO AGE.

It is difficult to find any distinct re-
lationship between ventricular range and other fac-
tors. 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 im-
possible to measure accurately or record quantitative-
ly. 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 phleg-
matic as in those of more impressionable and vivacious
temperament.

VENTRICULAR/

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 XIII.

CASE NO.	OBSERVED RANGE AUR.	OBSERVED RANGE VENT.	FUNCTIONAL EFFICIENCY GROUP	AVERAGES RANGES FOR EACH GROUP AUR.	AVERAGES RANGES FOR EACH GROUP VENT.
13. Mrs H.	38.0	50.2	1.	38.0 and	50.2
1. Mrs T.	60.6	12.0	2a		
3. D.C.	56.7	18.9			
4. W.T.	42.2	24.1			
12. J.D.	50.7	36.3		52.6 and	22.8
5. A.H.	58.3	5.4	2b		
6. J.Wd.	79.5	5.6		68.9 and	6.8
8. J.B.	a.fib.	9.5			
2. W.W.	18.5	3.0	3.		
10. Mrs C.	a.fib.	0.8		22.5 and	4.8
11. Mrs D.	26.3	10.7			

group. This woman had only slight distress on sev-
ere exertion and the presence of complete heart-block
was only detected by a routine examination.

Group 2 is composed of patients with or-
ganic heart disease unable to carry out their ordin-
ary 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 dis-
comfort, their capacity for exertion is greatly lim-
ited. 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 avail-
able 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 indivi-
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/

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 ven-
tricular range.   This may be appreciated by study
of the accompanying table in which the cases are ar-
ranged in descending order of pulse-pressure.

TABLE   XIV.

CASE No. and INITIALS.	PULSE PRESSURE.	VENTRICULAR RANGE.	B.P. in mm. Hg. SYSTOLIC and DIASTOLIC.
4. W.T.	146	24.1	220/74
2. Mrs. T.	109	12.0	165/56
6. J.W.	94	5.6	158/64
10. Mrs. C.	90	0.8	170/80
11. Mrs. D.	85	10.7	200/115
2. W.W.	82	3.0	180/98
5. A.H.	78	5.4	162/84

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 in-
fluenced 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 me-
thods.   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 na-
tural ventricular range, reference has been made to
four instances in which the ventricular rate was
counted in the early morning hours while the indivi-
dual slept.   In the preceding pages the minimum
rate used in the calculation of the ventricular range
was that found to occur under uniform resting condi-
tions 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 in-
fluence 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 stu-
dies 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 occasion-
ally rates as low as 38 or 39.   From the tables
published by these workers it is found that for 51
healthy adults the average minimum heart rate during
sleep was 52.75 ($\pm$ 7.5), and that the corresponding
minimum rate while awake was 61.15 ($\pm$ 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 McMICHAEL
.(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 reduc-
tion in temperature and metabolism, and of a decrease
in reflex excitability.   The other is due to posi-
tive 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 electro-
cardiograph 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 asso-
ciated 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 **re**mained 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   XV.

CASE No. and INITIALS.	AVERAGE RATES COUNTED by HAND.		No. and HOUR of DETERMINATIONS.	DIFFERENCE BETWEEN AWAKE and ASLEEP RATES.	MINIMUM RESTING RATES (from E.C.G's)	DIFFERENCE BETWEEN MIN. RESTING RATE and SLEEP RATE*
	Asleep	Awake.				
10. Mrs. C.	22·4	23·1	10. (2 a.m. & 2p.m.)	0·7	26·5	4·1
12. J.D.	45·6	56·0	6. (11p.m.&11a.m.)	10·4	46·6	1·0
13. Mrs. H.	39·0	45·6	6. (4 a.m. &4p.m.)	6·6	39·8	0·8

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 satisfac-

tory 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 dur-

ing sleep the customary fall in heart rate does not

occur in the presence of myocardial insufficiency.

The probablilty is that a similar conclusion holds

good in cases of complete heart block - a reduced

range of ventricular rate during sleep being asso-

ciated 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 ab-

solutely constant for the individual.

SUMMARY/

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 $-.765$.

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 cor-
relation 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 ex-
hibits a minor fluctuation comparable to that ob-
served 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 ventri-
cular 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/

EXPERIMENTAL METHODS.

The patients were brought from their beds
in a wheeled chair to the electrocardiograph depart-
ment 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 surround-
ings and workers in the laboratory. The room tem-
perature 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 solu-
tion 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 insert-
ed 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 intravenous-
ly. 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 solution of atropine was injected. In this way the possibility of the registration of a transient acceleration 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 minute, or a minute, succeeding records were made and after the first three exposures, further electrocardiograms 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 patient'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 re-
corded 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 waa not found to be
necessary.

Every patient in this series of cases of
complete heart-block was tested with atropine, ac-
cording 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 (Case2
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 uni-
form series. In each instance a definite accelera-
tion of ventricular rate was observed.

The effect of the dose of 1/30 grain of
atropine/

TABLE XVI.

CASE NO. & INITS.	AURICULAR RATE PER MINUTE		GAIN IN RATE AURICLES	PERCENTATE GAIN IN RATE AURICLES	VENTRICULAR RATE PER MINUTE		GAIN IN RATE VENTRICLES	PERCENTAGE GAIN IN RATE VENTRICLES
	BEFORE	MAX.RATE AFTER			BEFORE	MAX.RATE AFTER		
1. Mrs T.	75.3	101.6	26.3	34.7	22.2	23.4	1.2	5.4
3. D.C.	72.0	127.4	55.4	77.0	42.8	62.3	19.5	45.6
4. W.T.	63.1	80.1	27.0	42.3	23.6	26.4	2.8	11.9
5. A.H.	72.5	92.3	19.8	27.3	31.0	39.8	8.8	28.4
6. J.Whd.	57.7	77.0	19.3	33.5	28.5	30.3	1.8	6.3
8. J.B.	Auricular fibrillation pressure ?				30.7	41.0	10.3	33.5
10. Mrs C.	"				26.7	31.3	4.6	17.2
12. J.D.	91.3	135.0	43.7	48.0	49.3	96.3	47.0	95.9
13. Mrs H.	77.3	100.5	23.2	30.0	42.6	76.4	33.8	79.4
14. Mrs D.	64.6	87.0	22.4	25 7	29.1	32.8	3.7	11.3
I	II	III	IV	V	VI	VII	VIII	IX

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 exa-
mined - the figures derived from those patients who
each received a 1/30 grain intravenously being pre-
sented in the table. The maximum gain in ventricu-
lar rate occurred in Case 12. The patient's vent-
ricular 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 min-
utes 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 ven-
tricular, 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 emphaaises 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.

CASE NO.	MAXIMUM RATES AT REST		MAXIMUM RATES AFTER ATROPINE FROM TABLE		VENTRICULAR GAIN OVER MAXIMUM RESTING RATE.
	AURICLES	VENTRICLES	AURICLES	VENTRICLES	
1. Mrs T.	81·8	29·2	101·6	23·4	—
3. D.C.	78·0	42·8	127·4	62·3	19·5
4. W.T.	63·1	23·6	80·1	26·4	2·8
5. A.H.	72·5	36·0	92·3	39·8	3·8
6. J.Whd.	57·7	28·5	77·0	30·3	1·8
8. J.B.	Aur. fib.	33·0	Aur. fib.	41·0	8·0
10. Mrs C.	Aur. fib.	26·8	Aur. fib.	31·3	4·5
12. J.D.	91·3	55·2	135·0	96·3	41·1
13. Mrs.H.	77·3	42·6	100·5	76·4	33·8
14. Mrs Dev.	-	?30·0	87·0	32·8	?2·8

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 indivi-
duals, 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 an-
other (Case 14) the upper limit of the spontaneous
variations in rate could not be determined with suf-
ficient accuracy to allow of strict comparison. In
this case the heart-block was complicated by an ir-
regularity in the idio-ventricular rhythm - with the
result that distinct, but transient variations in rate
made the upper limit of the ventricular range diffi-
cult 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/

7.

⊙ = Case reported by Lewis (139)
⊠ = Cases reported by de Graff and Weiss (90)
⊠ = This series.

$y = 1.62x - 1.04.$

$\Sigma xy = +.9722.$

y calculated.

INITIAL VENTRICULAR RATE. (x)

GAIN IN RATE. (y)

20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50
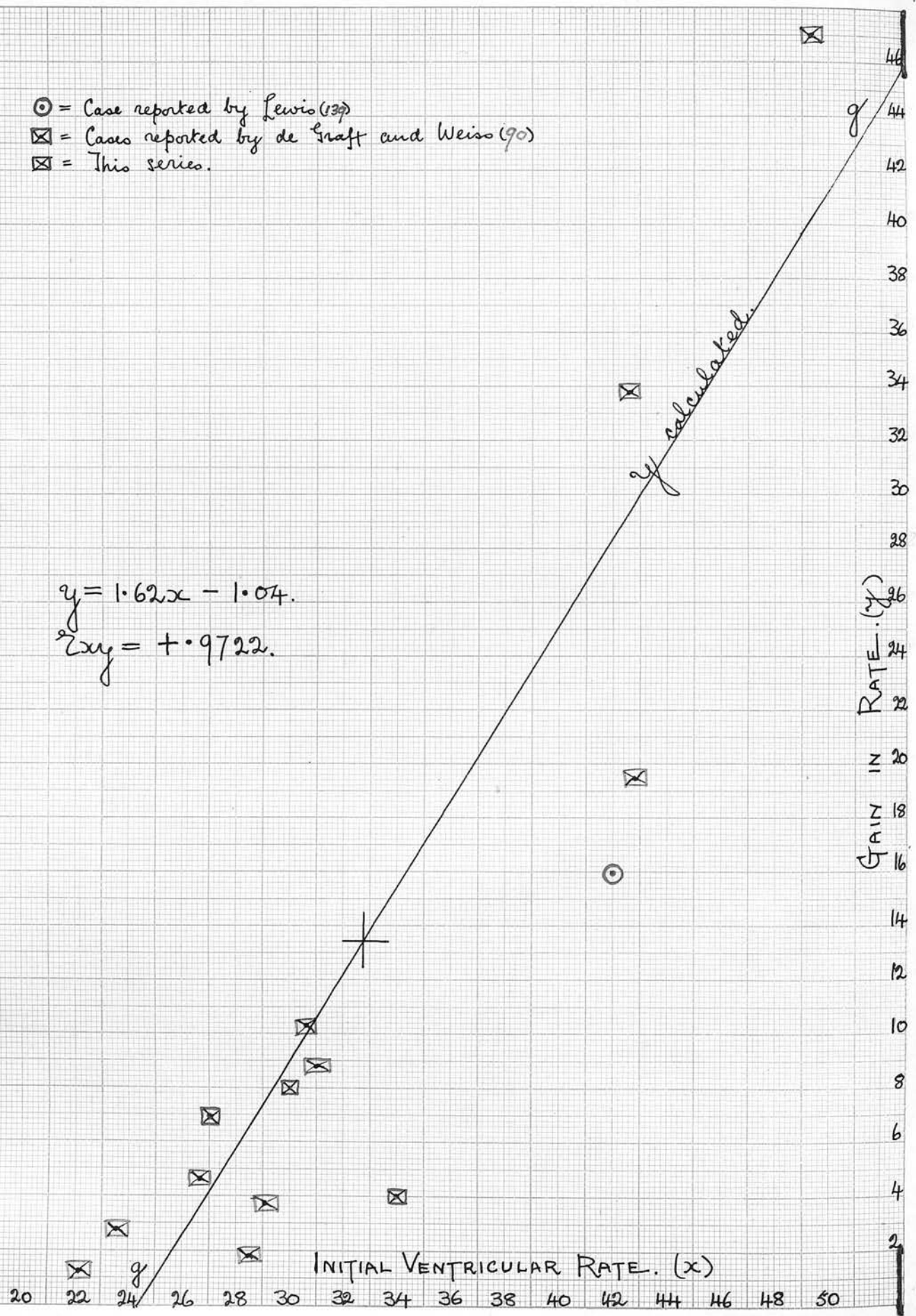
more stringent test associated with the spontaneous ventricular range, it may be said that the acceleration produced by atropine, definitely exceeded the maximum natural fluctuation in 8 out of 10 instances.

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 coeffecient
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 deter-
mine 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 ob-
vious 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 vent-
ricles 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 com-
plete 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 neighbour-
hood 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 atro-
pine has little or no effect on the ventricular rate
requires modification.   The fact that at the slower
idio-ventricular rates atropine yields a minimae
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 num-
erous 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 ins-
tances 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 (182) in his Gibson Memorial Lecture before
the Royal College of Physicians of Edinburgh in 1923,
when he said "The intravenous administration of atro-
pine 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 dissocia-
tion.   Here atropine does not increase the vent-
ricular rate although the auricles are accelerated".

As a result of experimental work on ani-
mals, 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 in-
fluence 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 com-
plete 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 im-
mediately below the lesion.

As regards the effect of atropine in man it
is interesting to find that, even in cases of brady-
cardia 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 ath-
letes 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 yield-
ing the greatest degree of acceleration. It is true
that certain cases have been reported in the litera-
ture 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/

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 ven-
tricular 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, in-
dicating that the lower dose was of sufficient quan-
tity to yield a full ventricular response. The gain
of beats from an intial rate of 42 in this single
individual is in keeping with the response through-
out the series of cases at present under considera-
tion. 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/

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 dis-
sociation. 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 al-
ready been suggested that the Bainbridge reflex re-
gulates in large part, the balanced response of auri-
cles 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 af-
fairs occurs in complete heart-block. If, after
atropinisation, the minute volume of blood flow in-
creased 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, BUR-WELL & 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 rhthmicity effectively held in check by a vagus centre of adequate tone.

A/

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/

8.

AURICLES.

VENTRICLES.

RATES PER MINUTE.

ATROPINE SULPH. gr. 1/30.

TIME IN MINUTES.

A. H.
3. IX. 31.
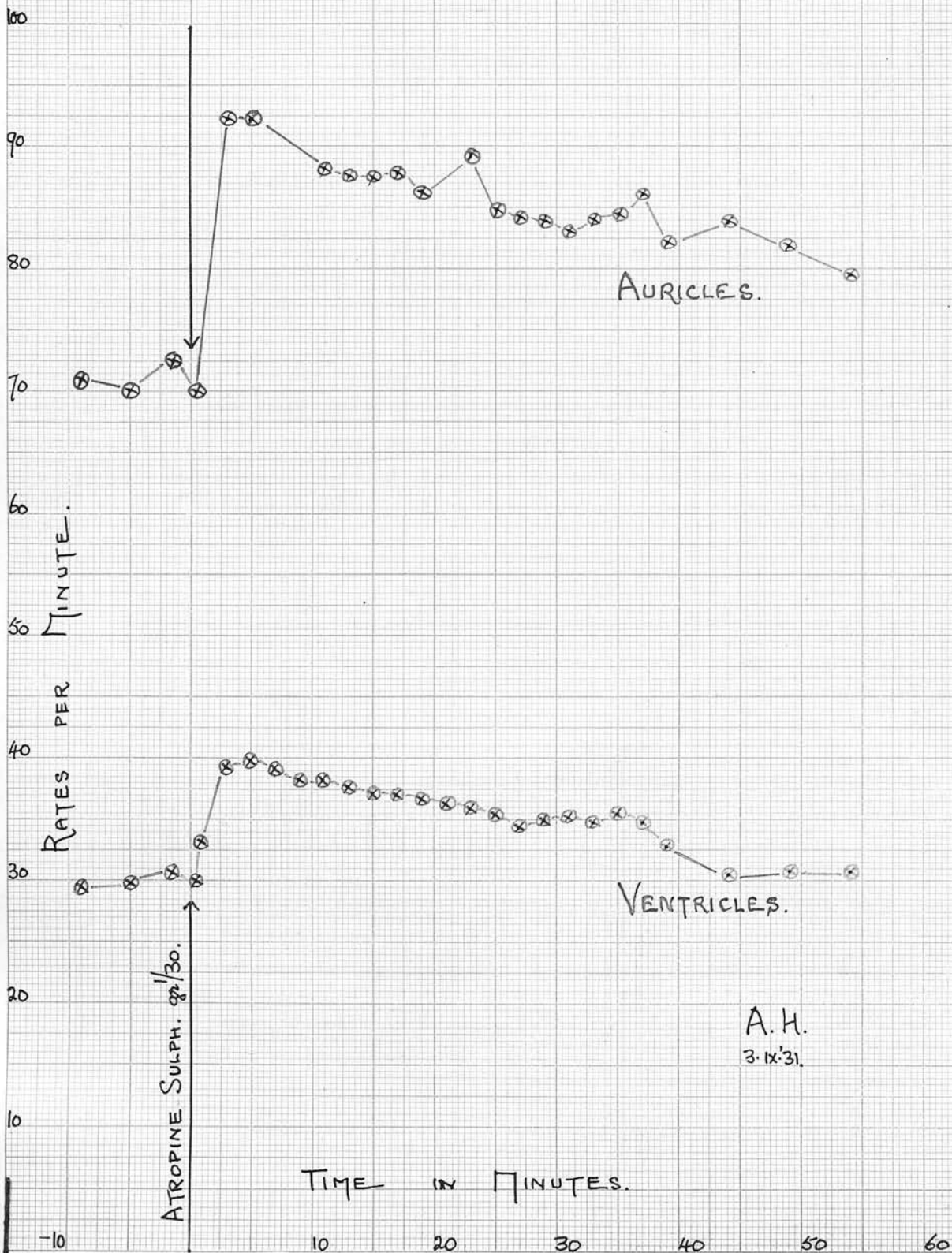
limited by the natural frequency of the controlling centre of impulse production. In other words, the higher the centre, the greater the possible response. It is therefore suggested, that the peculiar nature of the ventricular response to atropine, is primarily determined by the site of the lesion producing 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 be- lieving that this supposition is correct.

THE COURSE OF THE REACTION TO ATROPINE.

The course of the response is best depict- ed 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 v entricular are calculated, are shown in FIG. I. This/

9.

161 α

Atropine Sulph. gr. 1/30 I-V.

Minute.
Rates per Minute.
Time in Minutes.

⊗ = Coupled Rhythm.

Auricles

Ventricles.

Uncomfortable.
Mouth very dry
Restless.
given sip of cold water.
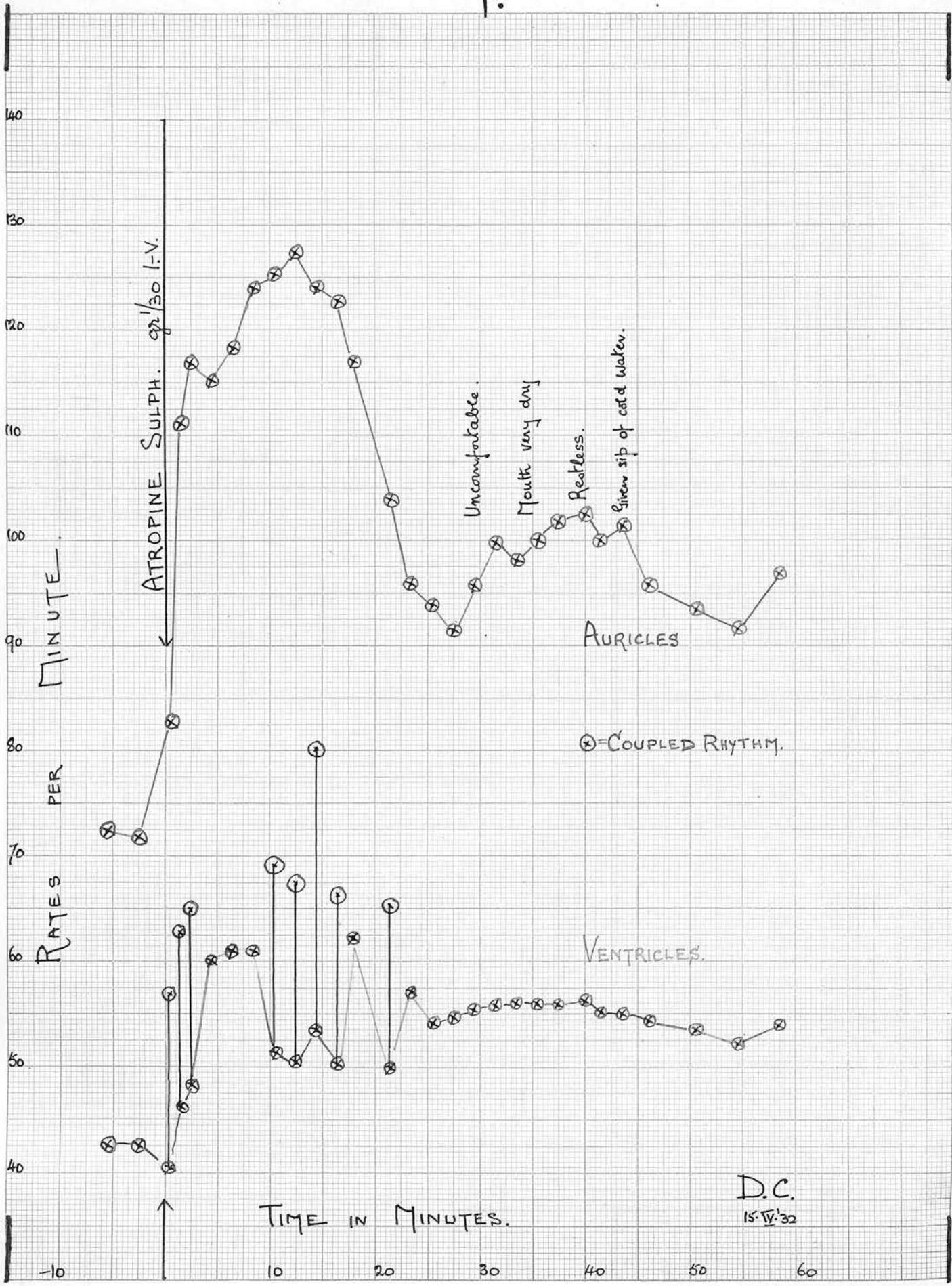
D.C.
15. IV. '32

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 atro-
pine, 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, apparent-
ly 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 auri-
cles is very similar to that portrayed by the vent-
ricles.

Very similar curves of atropine effect were
recorded in the other cases. As an additional exam-
ple, 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 :-

162a

9 min before

5 " "

1½ " "
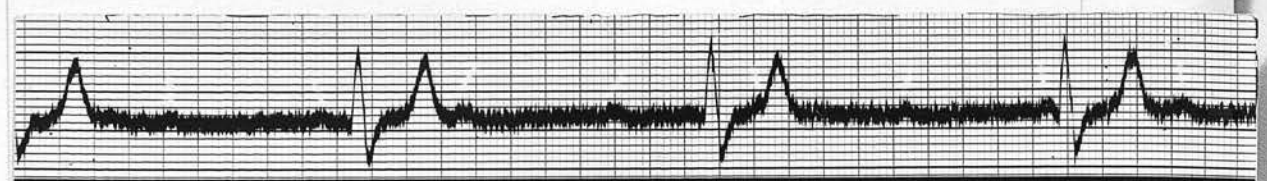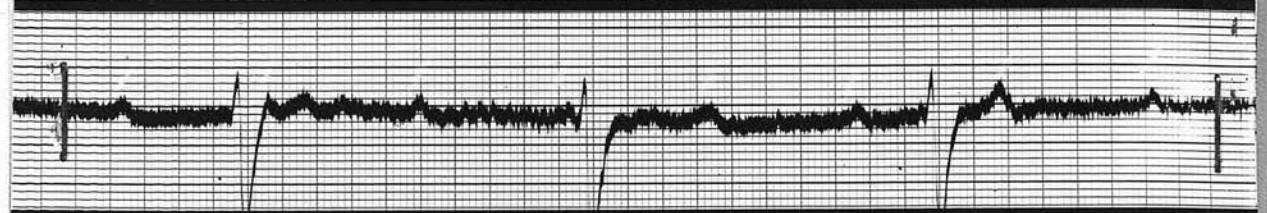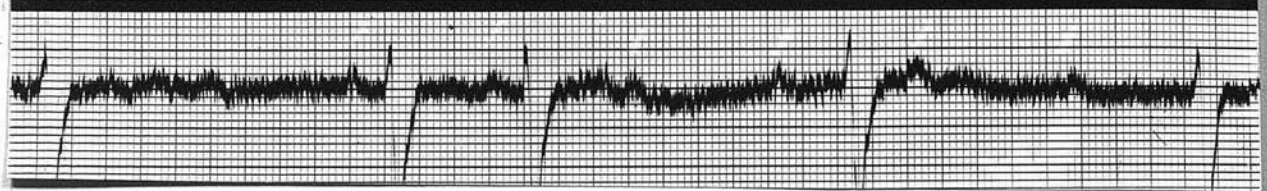
After Atropine :-

1 min after

3 " "

5 " "

7 " "

9 " "

11 " "

FIGURE 1 (Continued).

162 6.
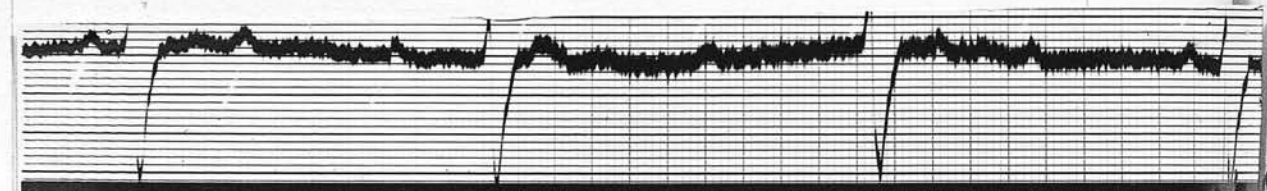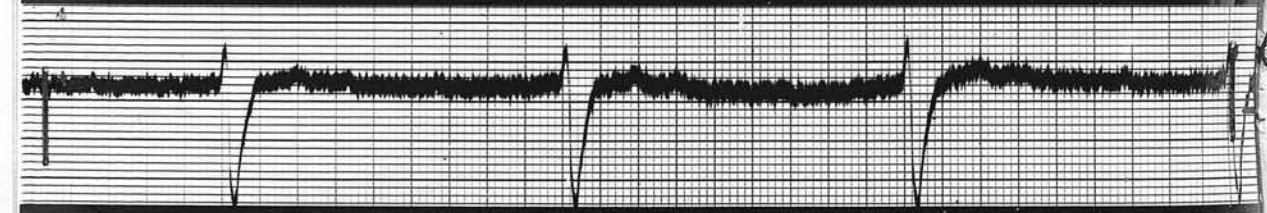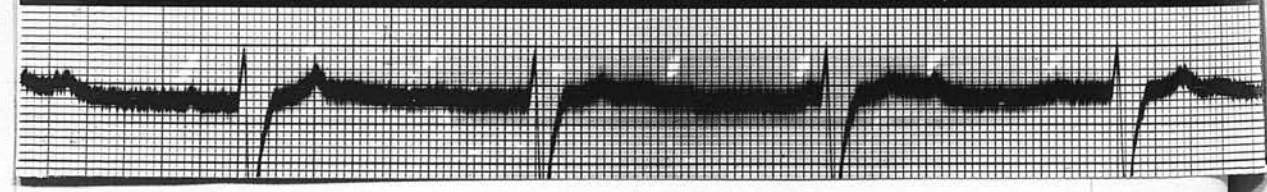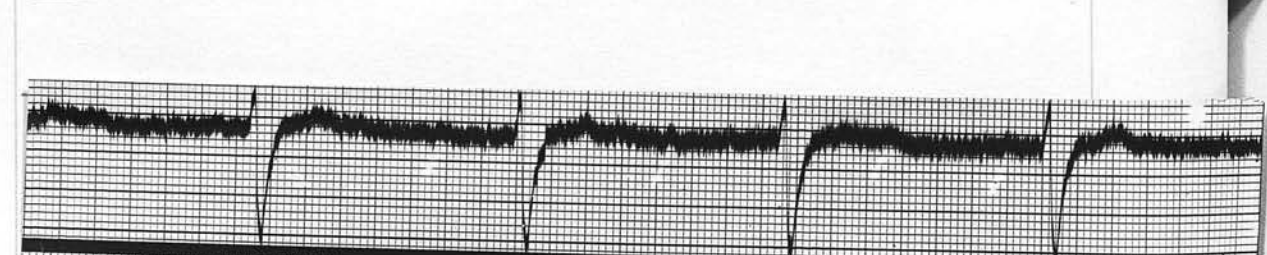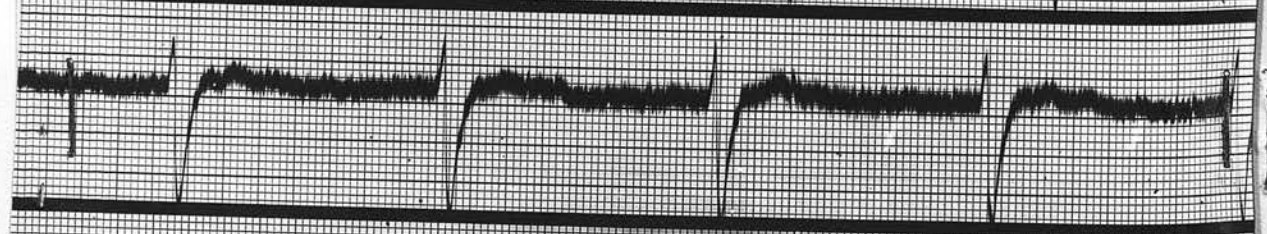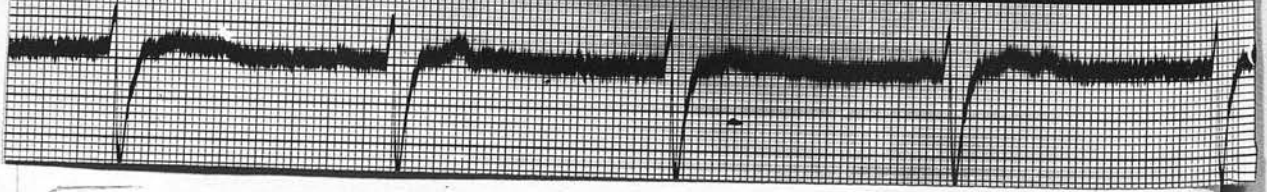
11 min after

13 " "

15 " ".

17 " "

19 " ".

21 " "

23 " "

25 " "

FIGURE 1 (Continued).

27 " "

FIGURE 1 (Continued).
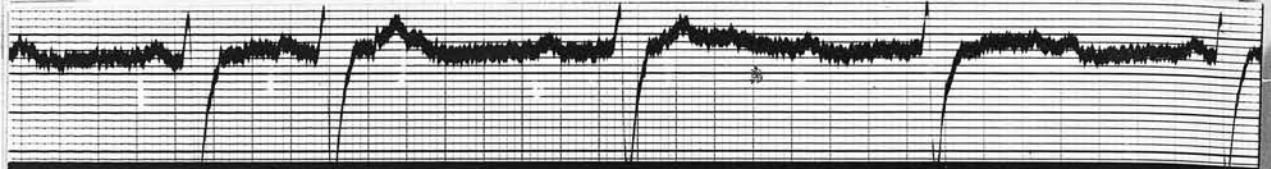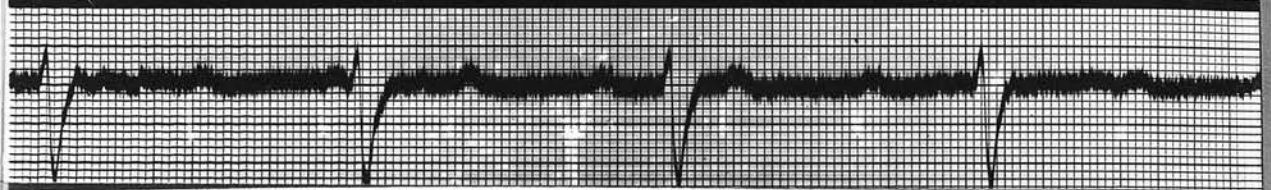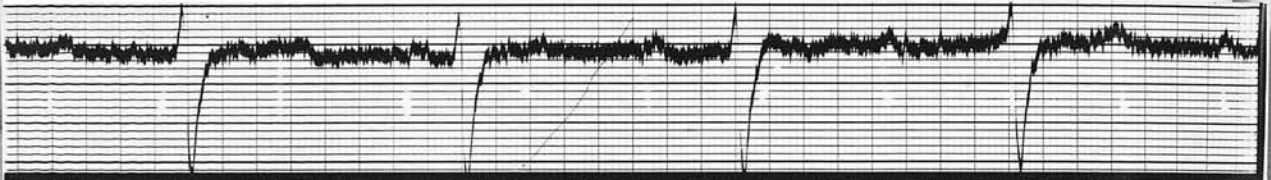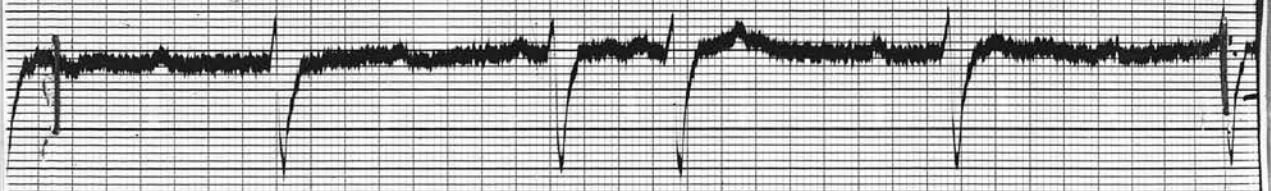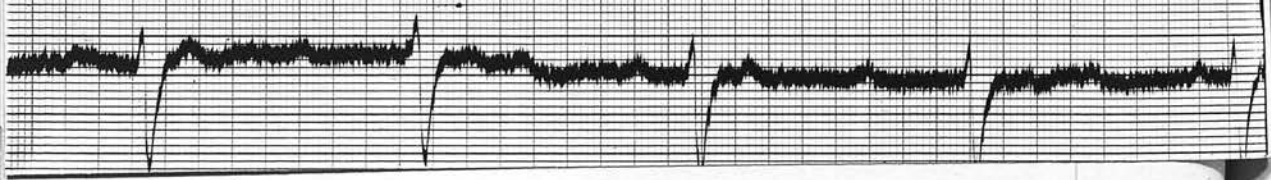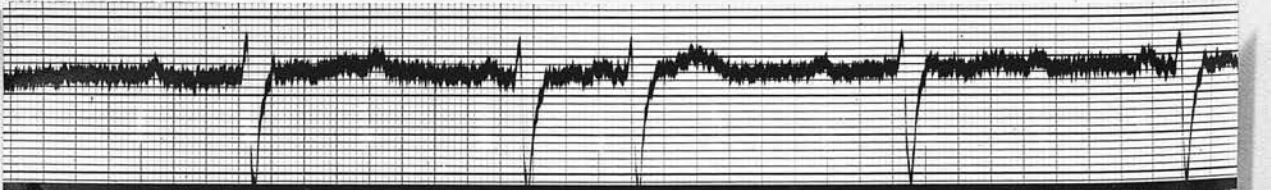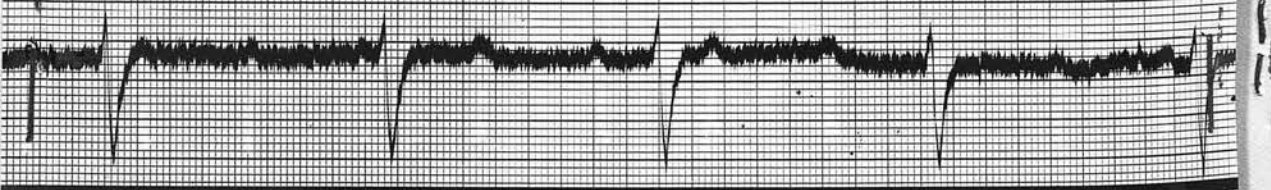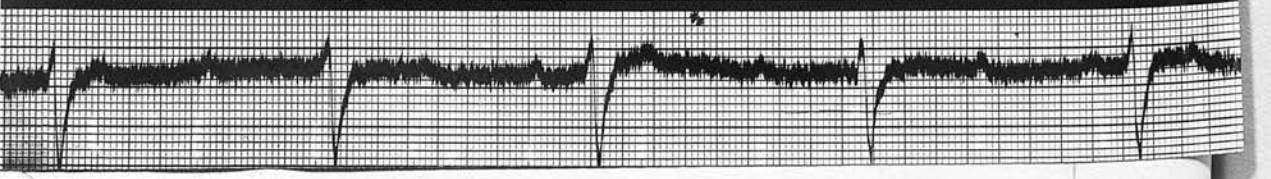


29 min after
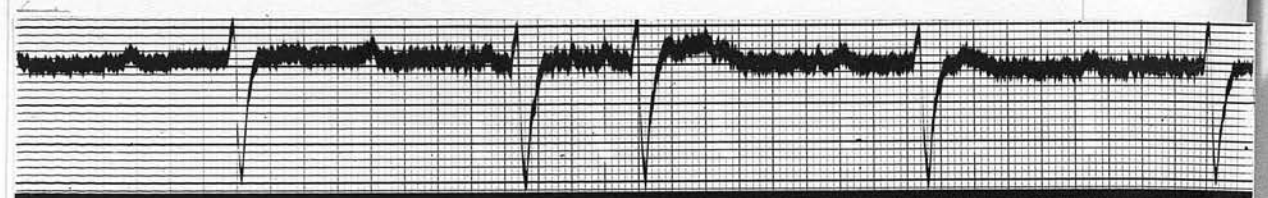
31 " "

33 " "

35 " "

37 " "

39 " "

44 " "

49 " "

54 " "

162.
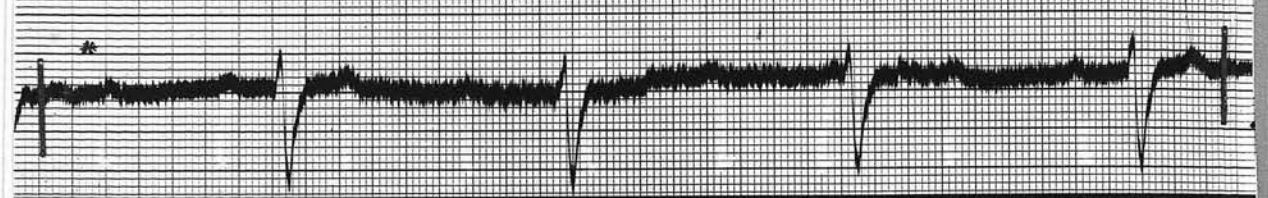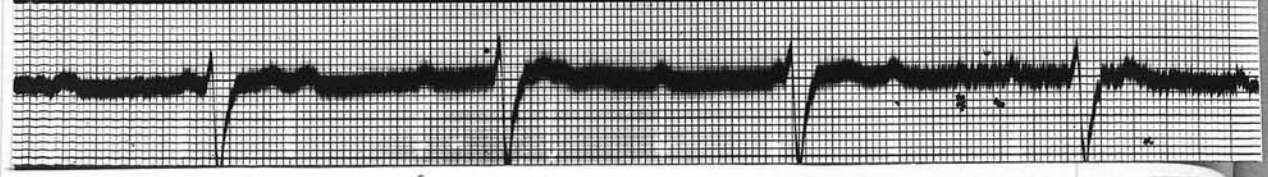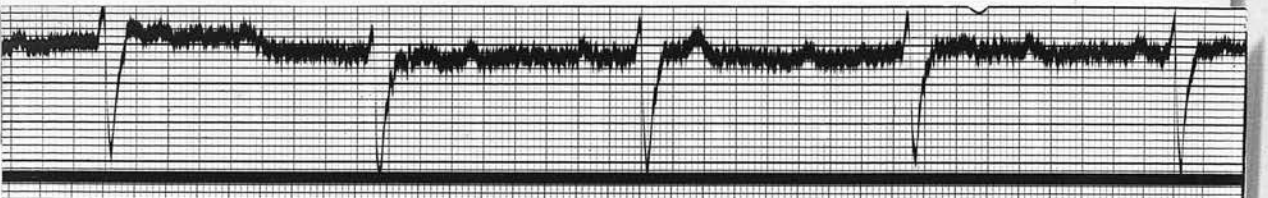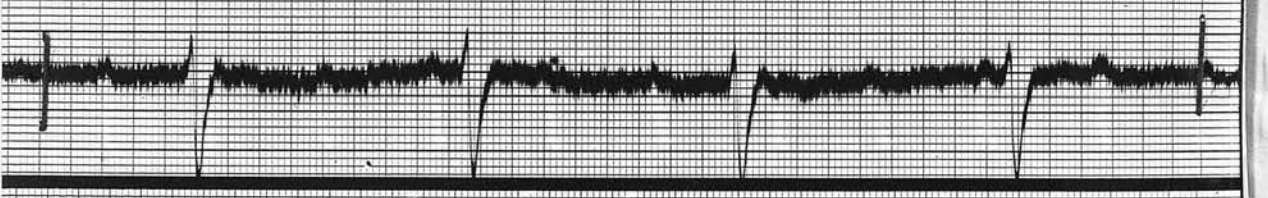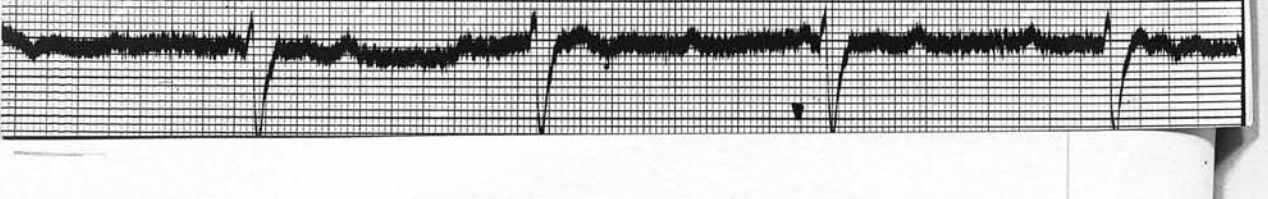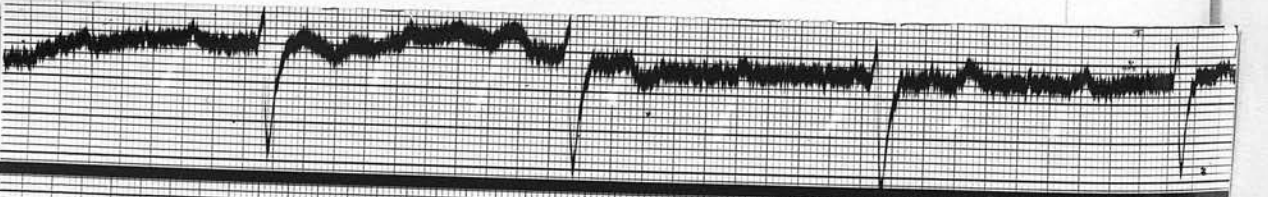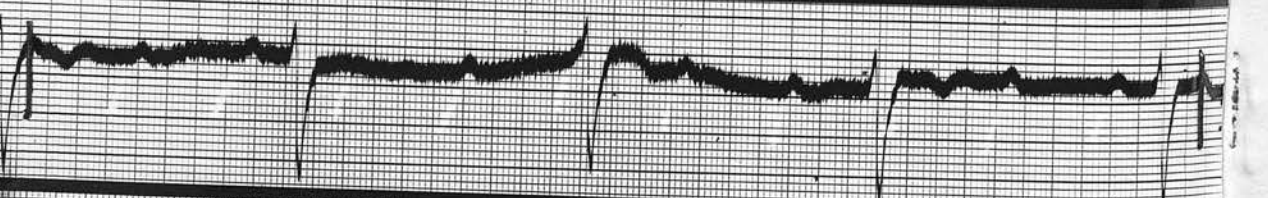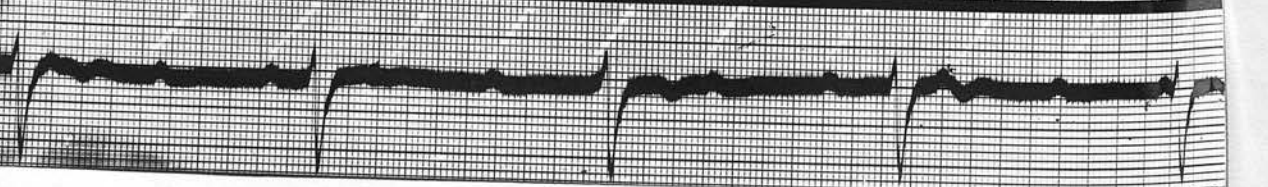
general the maximum acceleration occurred synchro-
nously in auricles and ventricles and by the end of
an hour the ventricles had returned to their origi-
nal rate, the auricles being a few beats quicker
than at the commencement of the observations. That
the response should be of such relatively short
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 general-
ly 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. Extra-
systole 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 ampli-
tude. The P waves were occasionally larger immedia-
tely 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 ad-
ministration.

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, demonstrat-
ed 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 mini-
mum 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 re-
corded/

Fig. 2 FIGURE 2.

Before Atropine :-

5½ min. before
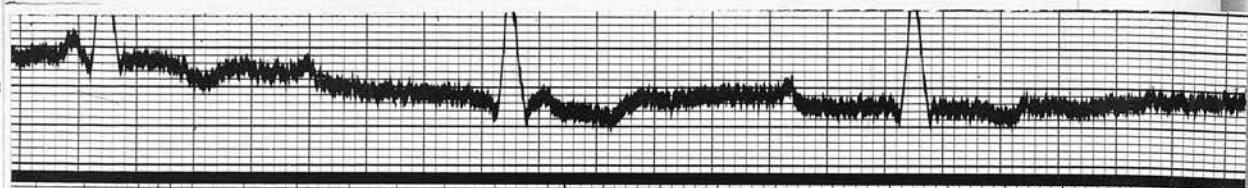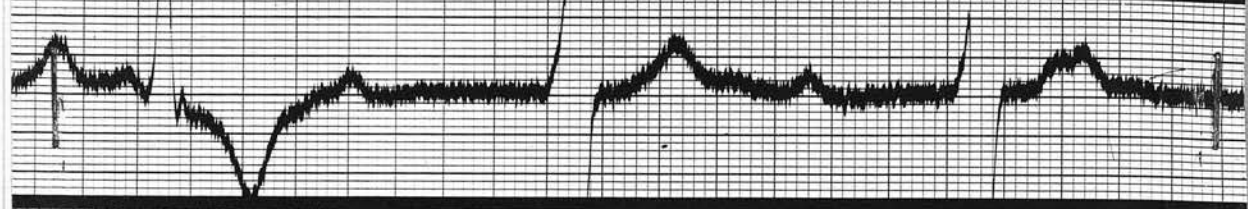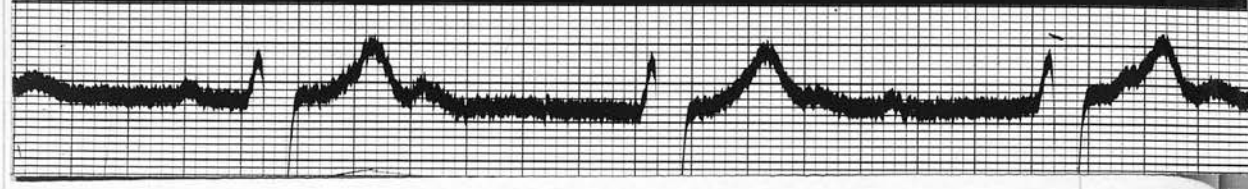
3½ min. "

2½ " "

After Atropine :-

½ min after

1½ min "

2½ min. "

4½ " "

6½ " "

8½ " "

164a
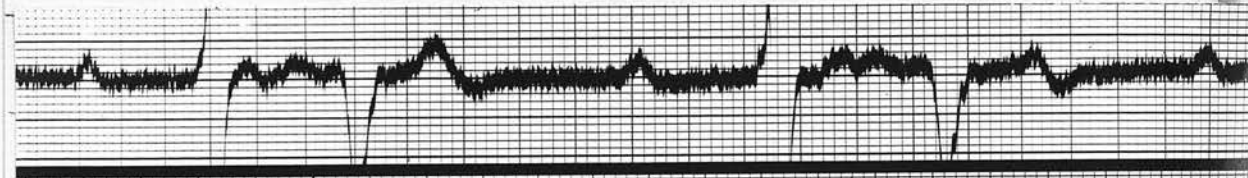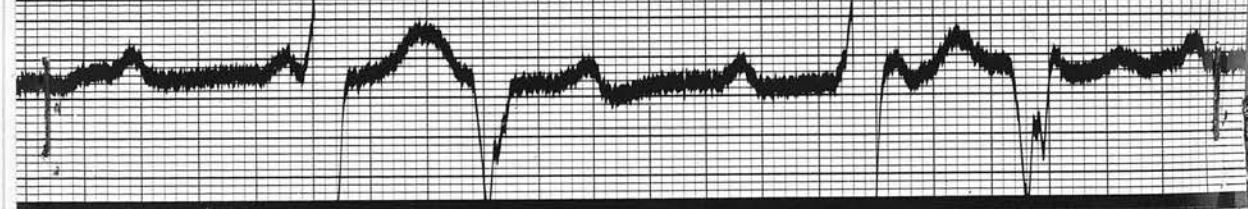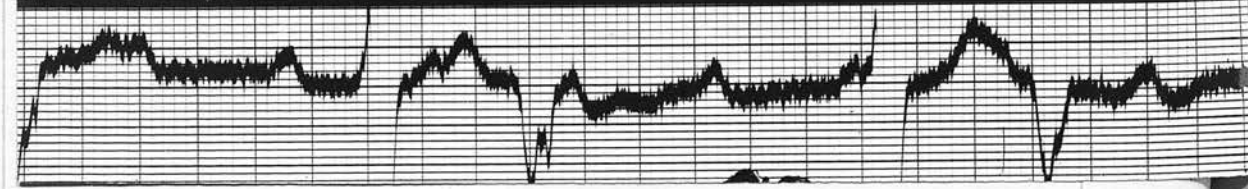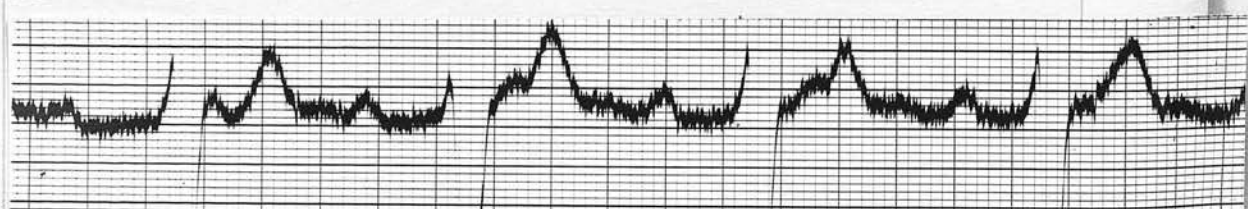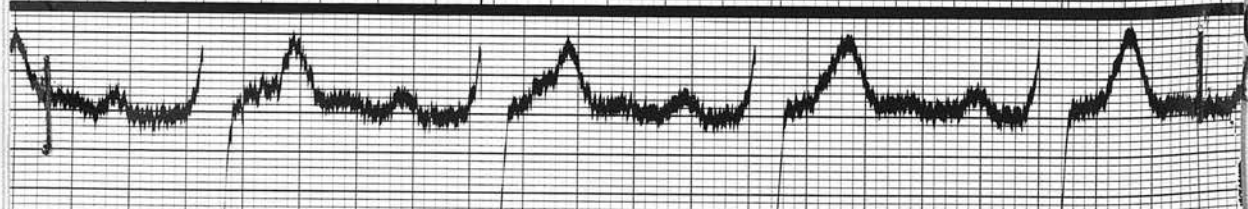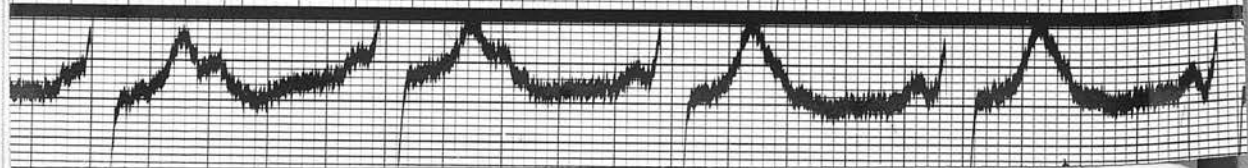
FIGURE 2 (Continued).
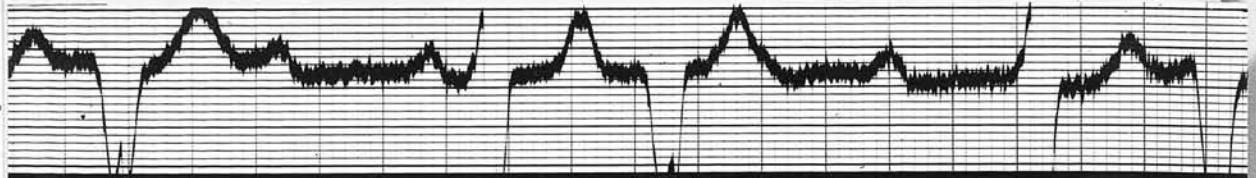
10½ min. after

12½ "   "
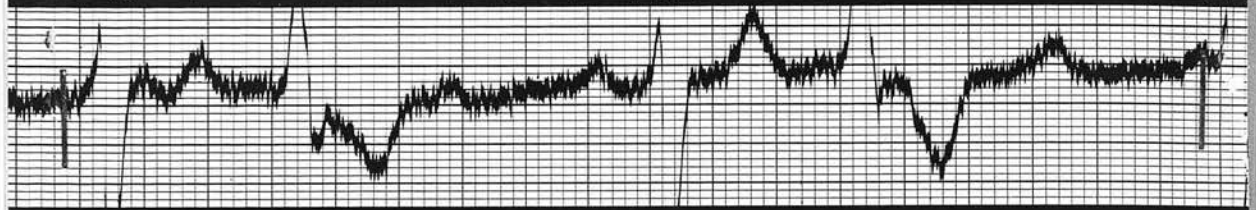
14½ "   "
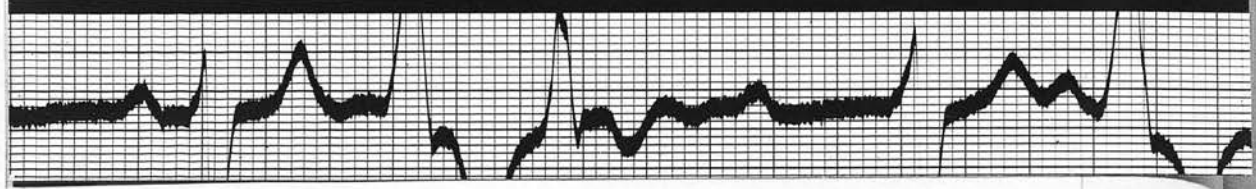
16½ "   "

18 "   "

21½ "   "

23½ "   "

25½ "   "

27½ "   "

164 b
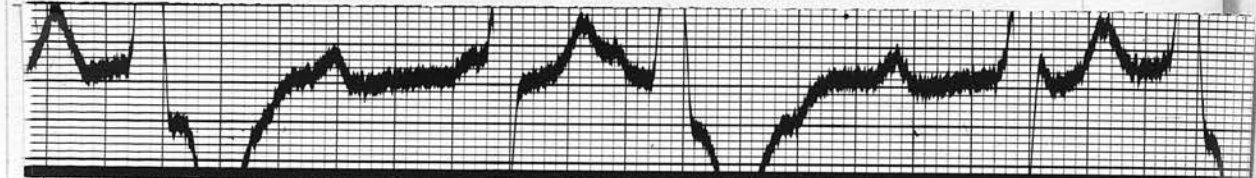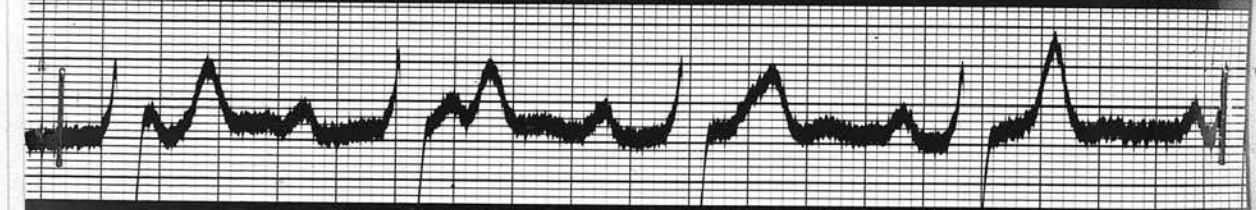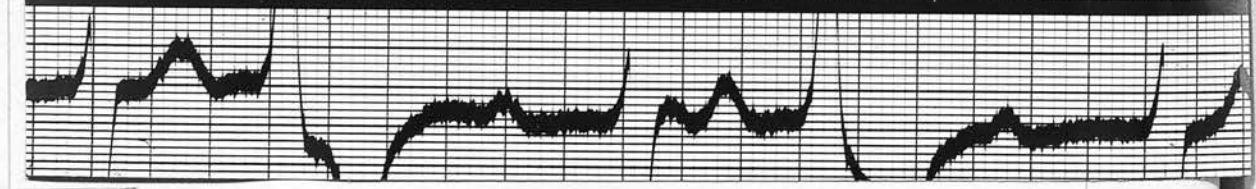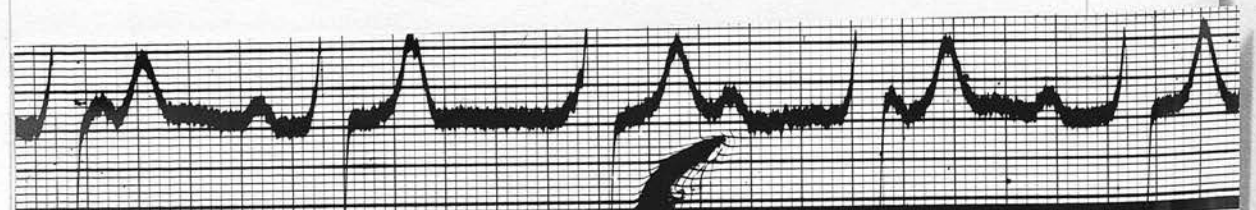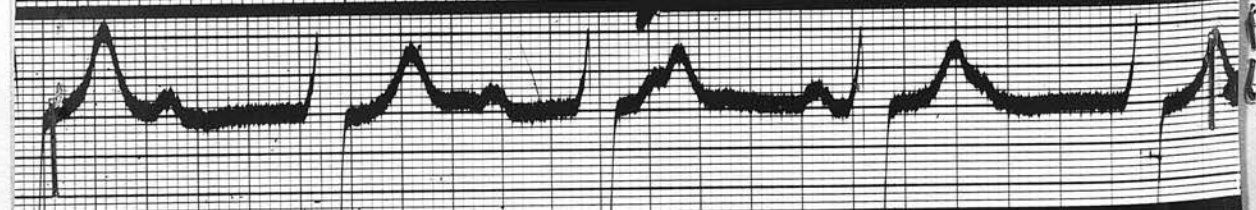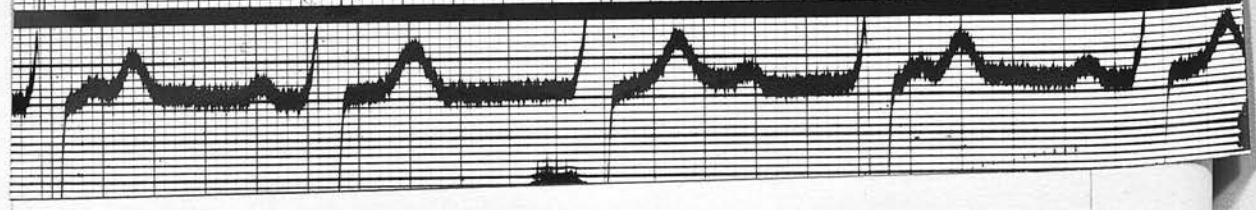
FIGURE 2 (Continued).

164c

29½ min after
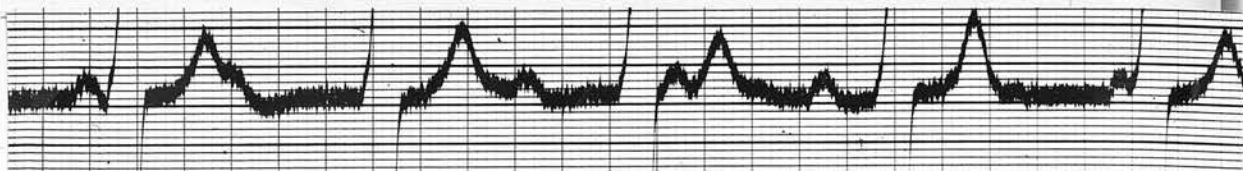
31½ " "
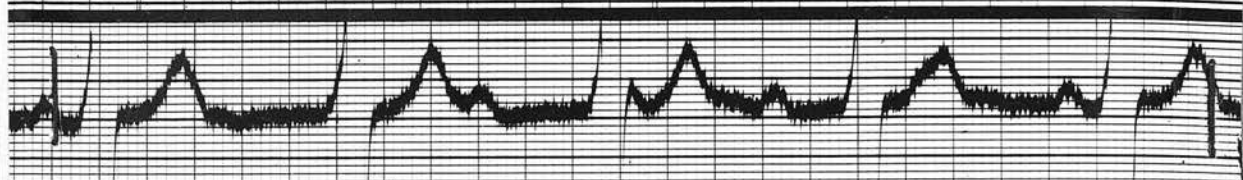
33½ " "
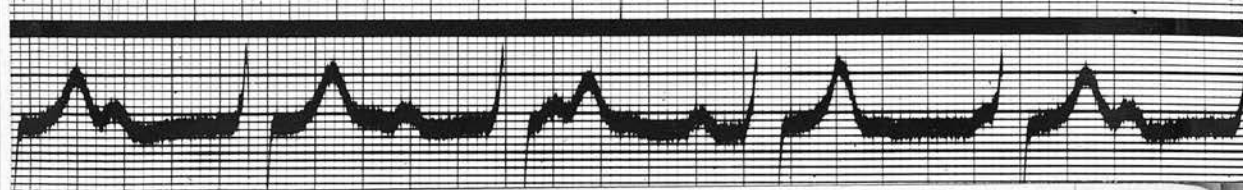
35½ " "
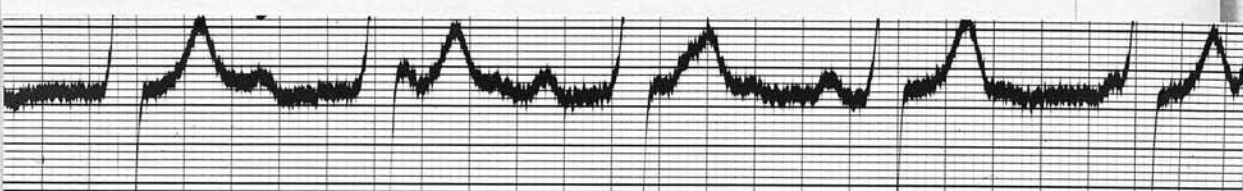
37½ " "
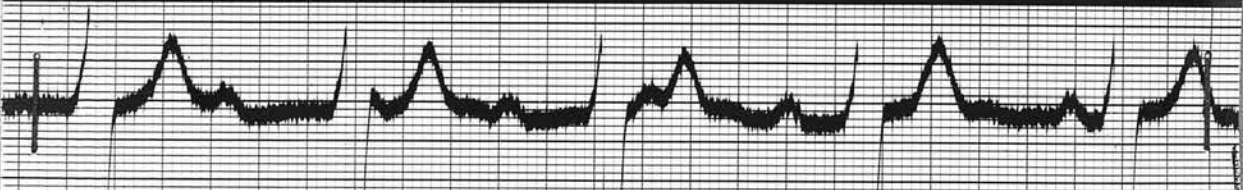
45½ " "
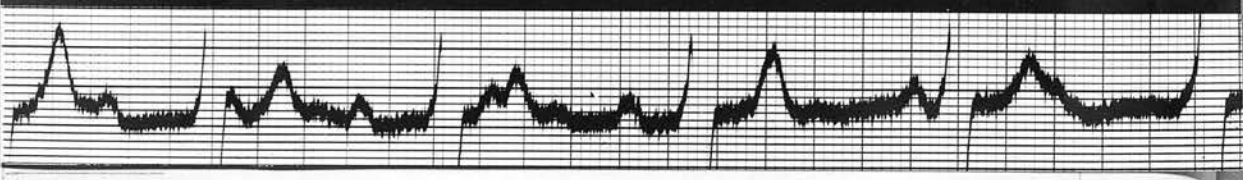
41½ " "
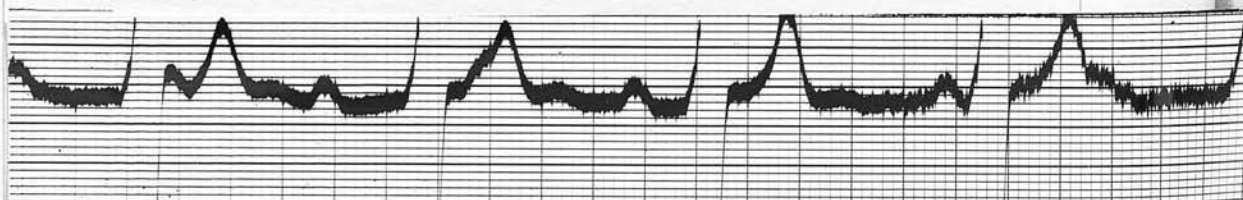
43½ " "
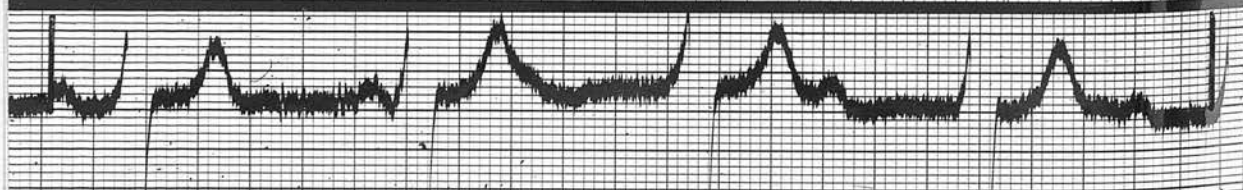
46 " "
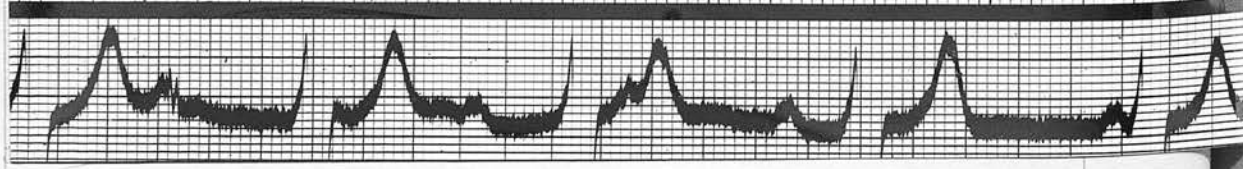
FIGURE 2 (Concluded).

1624

50½

54½

58½

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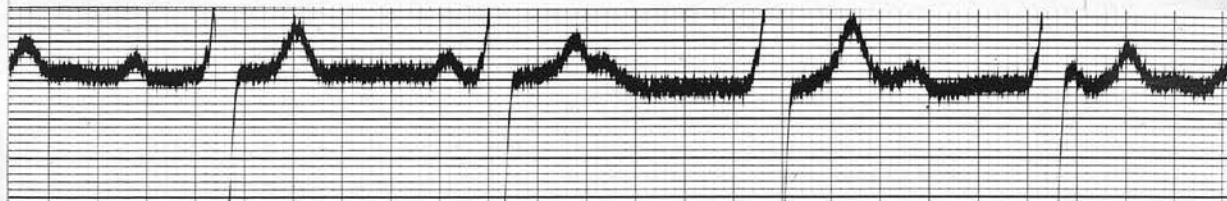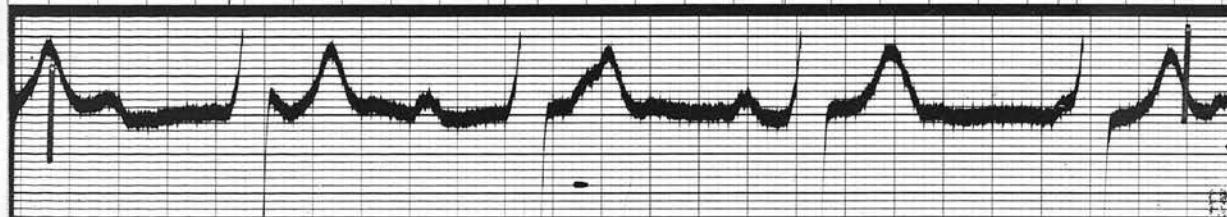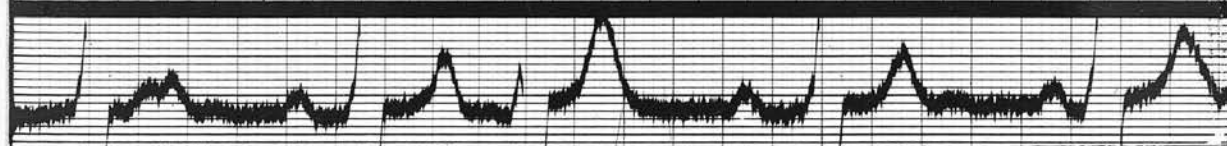
recorded under similar resting conditions.

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 + ·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 avail-
able 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)/

(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 com-
plete block in animals, which had survived for sev-
eral months the operative interference with the con-
ducting 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, "al-
though the strongest stimulation reduces slightly
the/

the rate of the ventricles". The ventricular re-
sponse to vagal inhibition occurred after 2 or 3
beats, when the auricles had already begun to quick-
en. 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 in-
crease of vagal tone may produce at least a slight,
though perhaps transient slowing. CRAWFORD (42)
has shown that the tone of the vagus centre de-
creases in later life, particularly after the age
of fifty years, that hearts the site of chronic de-
generative processes respond less than healthy ones,
and that as age advances the heart loses much of
its youthful rhythmicity. From this it would ap-
pear that a given degree of vagus stimulation is
likely to be followed by less conspicuous effects
in later life, particularly in the presence of or-
ganic heart disease.

There are several isolated instances re-
ported in the literature where vago-carotid pres-
sure 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/

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 experi-
ment was repeated on different days, bilateral pres-
sure was employed in several individuals, and oc-
casionally double ocular pressure was also recorded.
No attempt was made to measure the amount of pres-
sure 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 pres-
sure, 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-ef-
fects or recovery period.   In order to show that
vagus stimulation produces an effect on the ventri-
cular/

ventricular rate, it is not enough to demonstrate
slowing merely during the period of pressure.   If
the stimulation be the cause of the decreased fre-
quency, then the rate after pressure is released, sh
should approximate to that which existed before the
pressure was applied.   A natural decrease in the
frequency of the ventricular rate should not be con-
fused 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 com-
plexes.   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 preced-
ing 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 pre-
ceding the pressure was taken as the control ventri-
cular 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 re-
corded were disregarded and the rate after pressure
calculated for the second or third group of ventri-
cular/

TABLE XVIII.

RATES.

CASE NO. & INITS.	VAGAL PRESSURE	AURICULAR RATE RIGHT P.	LEFT P.	VENTRICULAR RATE RIGHT P.	LEFT P.	DECLINE IN RATE RIGHT PRESSURE AUR.	VEN.	DECLINE IN RATE LEFT PRESSURE AUR.	VEN.
1. Mrs T.	Before pressure / During " / After "	69.8 / 61.0 / 66.8	Ineffective	24.4 / 23.0 / 26.5	Ineffective	8.8	1.4	Ineffective	
2. W.W.	Before pressure / During " / After "	75.5 / 60.7 / 70.8	Ineffective	39.4 / 39.0 / 39.2	Ineffective	14.8	0.4	Ineffective	
4. W.T.	Before pressure / During " / After "	57.2 / 56.6 / 58.7	Inconclusive	23.6 / 23.3 / 23.4	Inconclusive	0.6	0.3	Inconclusive	
5. A.H.	Before pressure / During " / After "	Ineffective	Inconclusive	30.9 / 30.4 / 30.6	Inconclusive	+2.3	0.5	Inconclusive	
8. J.B.	Before pressure / During " / After "	Auricular Fibrillation		Ineffective 34.0 / 33.7 / 34.1		Aur.Fib.Ineff.		A.Fib. 0.3	

No.	Name		Auricular Fibrillation		Inef-fective		Aur.Fib. 0.7		A.Fib. Ineff.	
10.	Mrs C.	Before pressure	Auricular		27.4					
		During "	Fibrillation		26.7		0.7			
		After "			27.3					
11.	Mrs D.	Before pressure	86.2	86.0	44.0	43.6				
		During "	71.1	75.1	43.7	43.3	? 15.1	0.3	10.9	0.3
		After "	70.3	80.8	43.7	43.7				
		A minute later	86.0							
12.	J.D.	Before pressure	82.7	79.0	58.7	52.6				
		During "	52.0	57.3	45.7	44.3	30.7	13.0	21.7	8.3
		After "	81.2	86.3	53.8	61.2				
13.	Mrs H.	Before pressure	Inef-	63.5	Inef-	40.0				
		During pressure	fective	63.3	fective	39.7	Ineffective		0.2	0.3
		After "		64.8		38.8				
14.	Mrs Dev.	Before pressure	63.1	61.7 In-	30.8	29.6				
		During "	59.2	60.4 con-	26.9	29.0	3.9	3.9	1.3	0.6
		After "	61.5	59.6 clus-ive	30.1	29.6				

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 pres-
sure.　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 suf-
fered 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/

Plate I

1.51-1

— RIGHT VAGUS PRESSURE. —
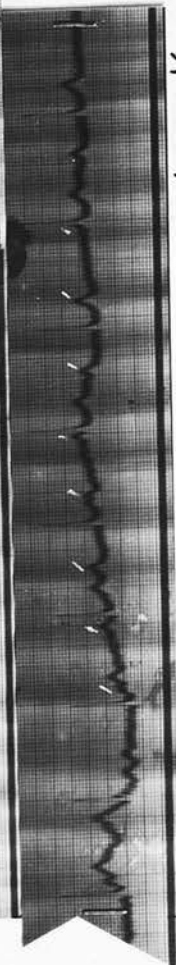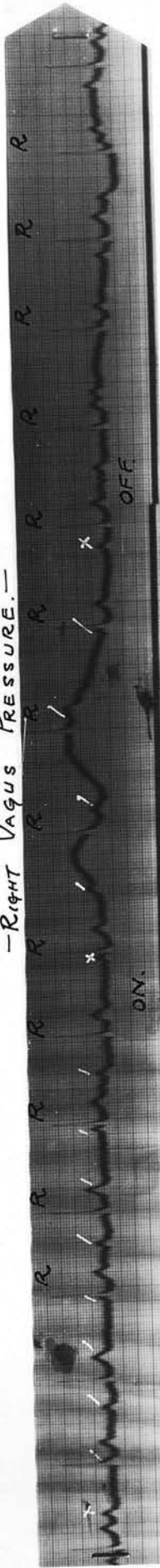
— LEFT VAGUS PRESSURE —

PLATE. 1.

Plate I here.

175.
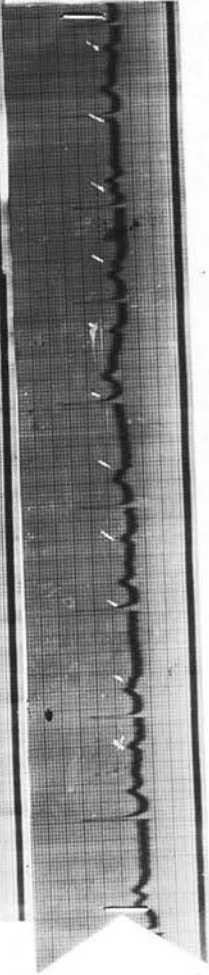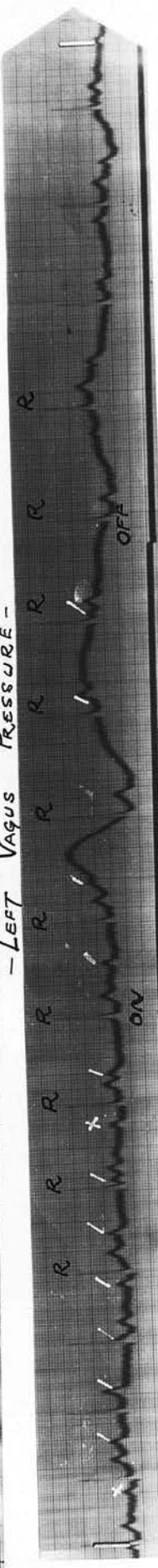
released, the result of vagus pressure was regarded
as inconclusive, even if the rate during pressure
was less than the minimum recorded during the con-
trol period.   In three of the ten individuals (Cases
1, 12 and 14) definite slowing of both auricular and
ventricular rates was observed during the 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 ob-
tained in Case 12.   This man's auricular rate de-
creased 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 auri-
cular rate declining by 21·7 beats and the ventri-
cular 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 in-
stance 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 in-
hibition after the bundle had been divided.   Phy-
sostigmine slows the heart and raises the blood pres-
sure in mammals, but in man, serious dizziness and
faintness occur before the heart is affected
(SOLLMAN (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 fre-
quently 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 parasym-
pathetic 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/

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 ex-
ceptions have been noted in the course of experi-
mental work, strong stimulation occasionally causing
a slight decrease in the ventricular rate.

The effect of right and left vagal stimu-
lation 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 in-
duced.

In the remaining seven cases the results
are not sufficiently decisive to permit of definite
conclusions.   The difficulties encountered in in-
terpreting the results are discussed.   As the re-
lease 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 parasym-
pathetic 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 mini-
mal 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 stimu-
lation 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 adrena-
line [SCHERF and ZDANSKY (192)], for beside para-
sympathetic release and peripheral vaso-dilatation,
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 pres-
sure comparable to that yielded by the polygraph
or electrocardiograph whereby changes in the rate
of the heart may be observed with accuracy through-
out 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 fif-
teenth 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 se-
conds, and it is not uncommon to find that at the
height of the reaction, within one minute of com-
mencement, 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 physio-
logical cause.

THE RESPONSE IN CASES OF COMPLETE HEART-BLOCK
_____

Although amyl nitrite was introduced by
JOSUÉ 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 syste-
matic 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 XIX.

CASE NO. & INITS.	AURICULAR RATE		GAIN		VENTRICULAR RATE		GAIN		BLOOD PRESSURE SYSTOLIC MINIMUM.	
	BEFORE	AFTER	ACTUAL	GAIN%	BEFORE	AFTER	ACTUAL	GAIN %	BEFORE	AFTER
1. Mrs T.	66.8	88.4	21.6	32.3	27.6	30.1	2.5	9.1	-	-
3. D.C.	76.6	138.1	71.5	93.4	43.1	44.4	1.3	2.9	246	180
4. W.T.	66.3	76.0	9.7	14.6	33.6	39.8	6.2	18.5	180	130
5. A.H.	67.9	78.4	10.5	15.5	32.6	33.1	0.5	1.5	165	104
8. J.B.	Auricular Fibrillation				33.0	34.9	1.9	5.8	200	188
12. J.D.	105.4	137.8	32.4	30.5	60.0	109.8	49.8	83.0	-	-
13. Mrs H.	72.2	94.1	21.9	30.3	44.4	85.8	41.4	93.3	156	103

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 in-
crease of 83.   In case 13, the initial rate was
44.4 and at the height of the reaction the ven-
tricles 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 remain-
ed 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 quantititative 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.

191a.

CASE NO. & INITS.	VENTRICULAR RATE		BLOOD PRESSURE		REMARKS
	PERCENTAGE GAIN	TIME ELAPSING	PERCENTAGE FALL	TIME ELAPSING	
1. Mrs T.	9·1	43 secs.	–	–	
3. D.C.	2·9	16 "	26·8	80 secs.	
4. W.T.	18·5	20 "	38·5	70 "	
5. A.H.	1·5	66 "	37·0	65 "	
8. J.B.	5·8	75 "	6·0	50 "	Nervous individual Only slight flush.
12. J.D.	83·0	46 "	–	–	
14. Mrs H.	93·3	40 "	34·0	65 "	

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 in-
stance 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 obser-
vation 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 caes exhibited a per-
centage fall of pressure ranging from 38.5 to 26.8.

The time elapsing from the start of in-
halation 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 corres-
ponding 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 circu-
lation rate after the administration of nitrites
in pathological cases, but some interesting ex-
periments in normal individuals have been reported
by LINDHARD (142) and by GAISBOCK and JARISCH
(75) .   It has been found that amyl nitrite in-
haled for two minutes produced a 100 per cent in-
crease 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-dilatation.
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 ventri-
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/

10.

1960

Systolic Blood Pressure.

Auricular Rate.

Ventricular Rate.

Time in Seconds.

Amyl nitrite inhaled

Calculated Rate. per Minute.

Systolic Blood Pressure.

Chart 11 here
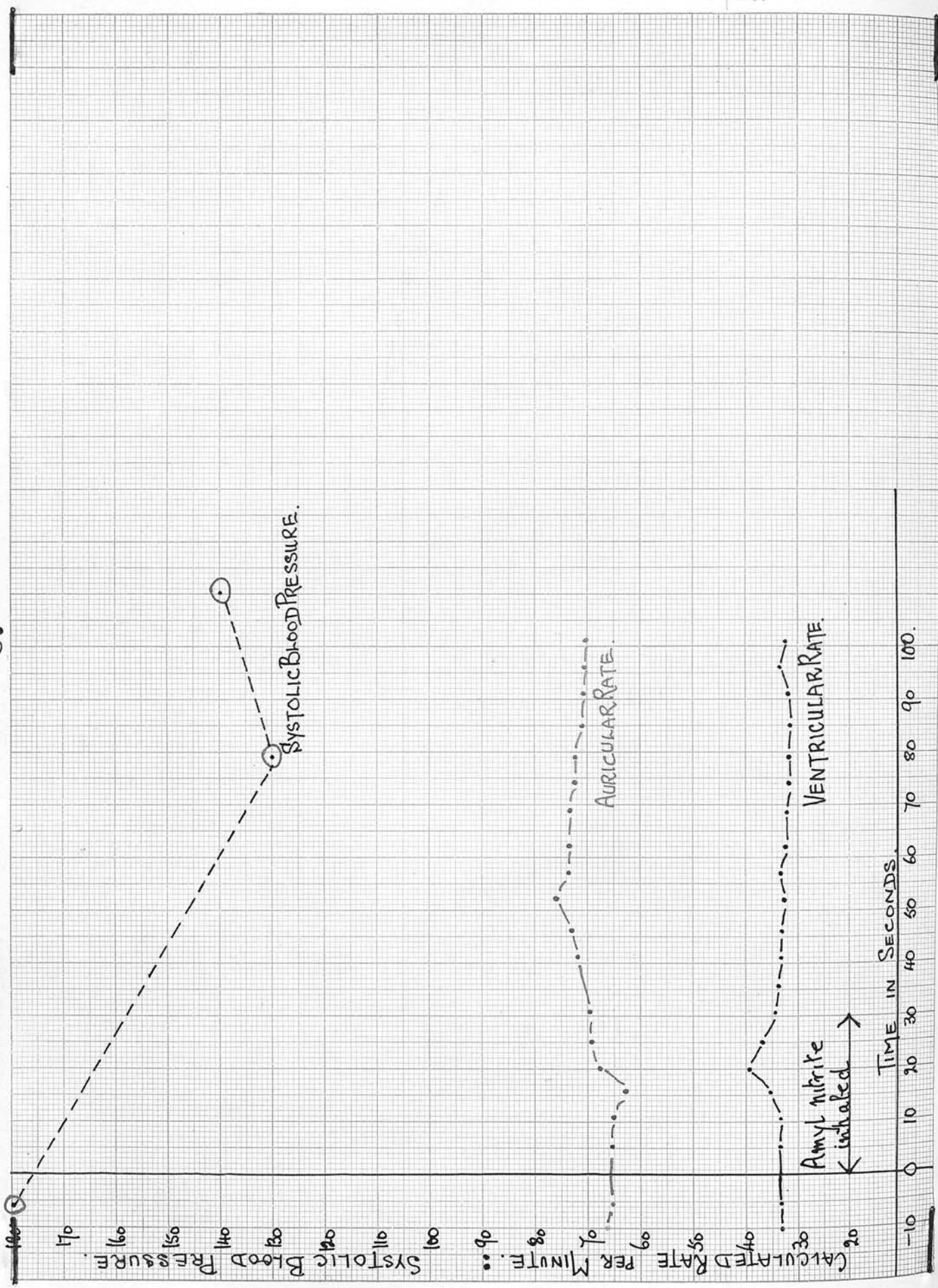
group composed of Cases 1, 3, 4 and 5.   Of the two
individuals (Cases 12 and 13) in whom amyl nitrite
produced a great acceleration of the idio ventri-
cular frequency, the reaction in the latter subject
has been selected as being suitable for comparison
with the first group.

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 ven-
tricular 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 ventri-
cular systolic discharge.

In chart No. 11, (Case 13) a totally
different type of reaction to amyl nitrite is de-
picted.   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/
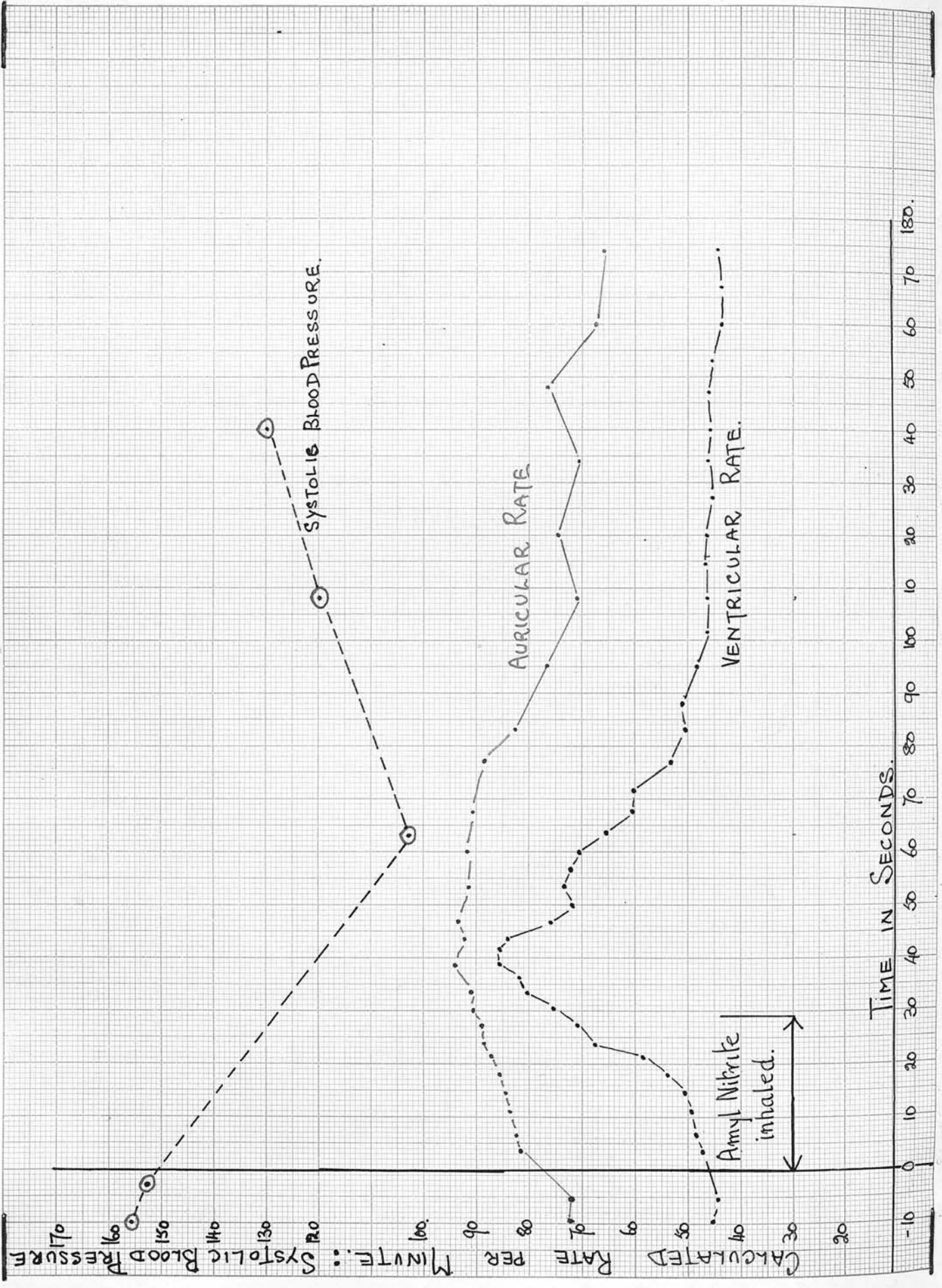
cut and mounted to show the immediate response to
the inhalation of amyl nitrite.   The start of in-
halation is marked by the signal in the lower part
of Strip 1 and the cessation in Strip 2.   Strip 4
which is the final portion of the film, ends at
174.0 seconds from the first inhalation of amyl
nitrite.   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 dis-
sociation 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 main-
tain 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/

Plate 2

198a

AMYL NITRITE INHALED:—

START

STOP

1.

2.

3.

4.

PLATE 2.
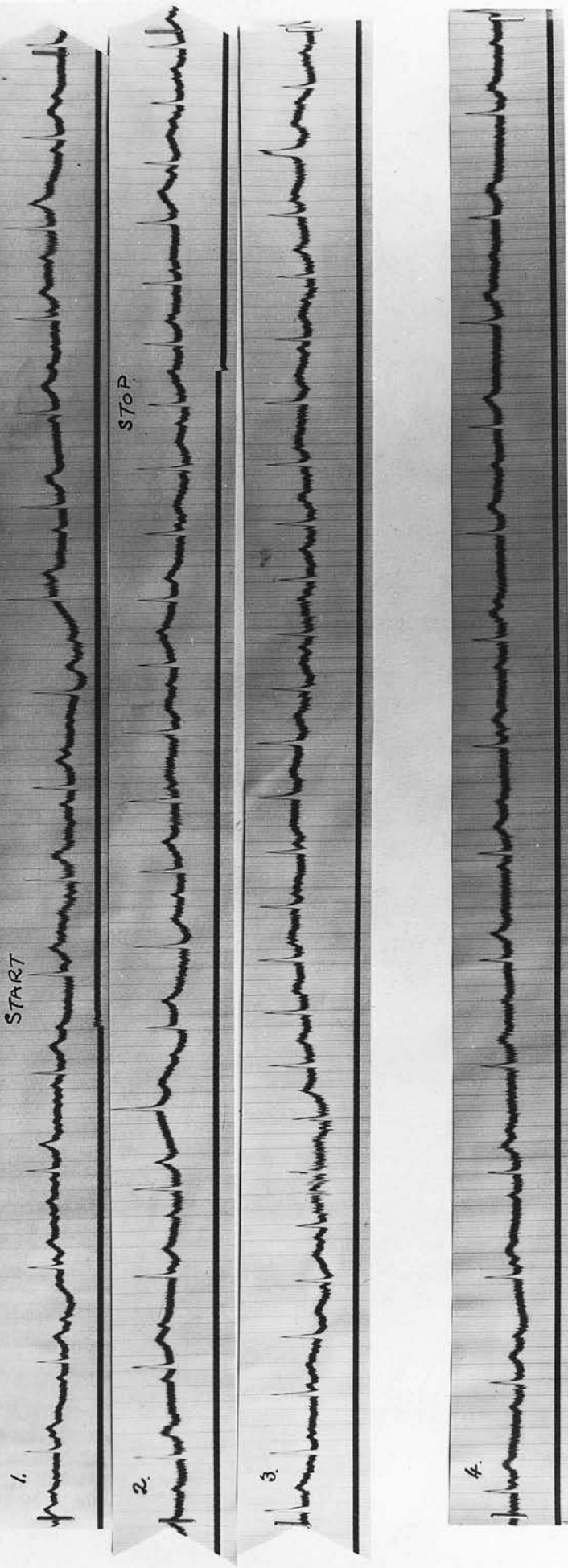
exertion, a minimal ventricular response is accompanied by a maximum auricular and vice versa.   It has already been suggested that this phenomenon is related to an increased venous return and that the excessive auricular rate results from an augmented Bainbridge reflex.   No such relationship is found 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 ven-
tricular gain was slight, ranging from 1.5 to 18.5
per cent.

As/

As the precise amount of amyl nitrite in-
haled must have varied in the different subjects the
results are not strictly comparable throughout this
series.   Nevertheless a decided effect on the vaso-
motor mechanism was invariably produced.   A defin-
ite facial blush was always observed and a throb-
bing headache commonly complained of.   The varia-
tion in dosage implies less consistency in these re-
sults 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 ventricu-
lar 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 ini-
tial 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 inhala-
tion 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 ven-
tricles showed a conspicuous acceleration, the
quickening occurred almost instantaneously and reach-
ed 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 in-
crease of blood pressure calls forth reflexes aris-
ing 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 sympa-
thetic origin on the one hand and reflex vagal in-
hibition on the other. It is believed that, at
least in certain instances, adrenalin also stimu-
lates 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 con-
sider the effect of direct sympathetic stimulation
in the presence of complete heart-block. The ear-
liest 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 accele-
ration of the ventricles.   ERLANGER (63)   ob-
tained similar results.   Having produced chronic
complete block in dogs, ERLANGER & BLACKMAN (64)
demonstrated an increase of 22 per cent in ventricu-
lar rate, and 15 per cent in auricular, on strong
sympathetic stimulation in these animals.   It is
therefore not surprising to find that adrenalin pro-
duces an augmentation of the rate and force of the
independent ventricular beat at least under experi-
mental conditions.   CULLIS & TRIBE (43), VAN
EGMOND (58), ROUTIER (190) HARDOY & HOUSSAY
.(95) and CLERC & PEZZI (33) are all agreed
that the administration of adrenalin after the pro-
duction 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 admini-
stration of adrenalin.

Three years elapsed before the results
obtained in the experimental laboratory were con-
firmed in cases of heart-block in man.   In 1916
DANIELOPOLU /

DANIELOPOLU & 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.
LUTEMBACHER (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 ris-
ing to 60 per minute.   This effect was followed by
some irregularity of the ventricular rhythm, with
pauses of sufficient duration to account for tran-
sient syncopal attacks.   For this reason, LUTEM-
BACHER 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 ven-
tricles 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 ventri-
cular rate was induced.   In one patient no rise
occurred in the auricular rate, and on three occa-
sions 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 re-
flex 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) & ARRILAGA (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 observa-
tion 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 com-
plete.   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 par-
tial, adrenalin facilitated conduction, but when
complete, the drug was without effect.   Just as
the underlying mechanism in the production of par-
tial 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 inhibi-
tion may then overcome the local tendency of adre-
nalin 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 adre-
nalin may be attributed to the nature of the dis-
sociation.   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 inter-
ference".

It is only necessary to mention brief-
ly the remarkable effect of adrenalin in the pre-
vention 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 in-
crease 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.   Electro-
cardiograms were recorded at intervals of two
minutes /

minutes for approximately one hour after the in-
jection, 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 adrena-
lin reaction.   Twenty-eight experiments were per-
formed on twelve patients, the dose of adrenalin
varying from 0.25 c.c. to 1.0 c.c. of 1/1000 solu-
tion (P.D. & Co.).   As the drug decomposes rapid-
ly on exposure to light and air, every care was
taken to insure the use of a preparation of full
potency.   The slightest discolouration 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 in-
jection 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 ob-
served 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 21

CASE NO. & INIT.	AURICULAR RATE				VENTRICULAR RATE			
	RATE before ADRENALIN	MAXIMUM RATE after ADRENALIN	GAIN in AURICULAR RATE	GAIN as PERCENTAGE of INITIAL RATE	RATE before ADRENALIN	MAXIMUM RATE after ADRENALIN	GAIN in VENTRICULAR RATE	GAIN as PERCENTAGE of INITIAL RATE.
1. Mrs T. (a)	70.4	105.0	34.6	49.1	29.2	42.3	13.1	44.9
" " (b)	75.3	92.6	17.3	23.0	25.0	39.1	14.1	56.4
3. D.C.	72.8	77.6	4.8	6.7	38.5	43.2	4.7	12.3
5. A.H.	58.0	69.8	11.8	20.3	30.6	41.6	11.0	35.9
6. J.W.	51.5	66.8	15.3	29.7	27.4	37.2	9.8	35.8
8. J.B.	Auricular fibrillation			—	32.9	39.7	6.8	20.7
10. Mrs C.	"	"		—	26.6	42.9	16.3	61.3
11. Mrs D. (a)	90.0	96.8	6.8	7.6	45.2	50.5	5.3	11.7
" " (b)	98.6	99.3	0.7	0.8	51.0	52.4	1.4	2.7
13. Mrs H.	76.1	82.9	6.8	8.9	41.7	45.6	3.9	9.4

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 consider-
ably in different cases and that the magnitude of
the reaction as it affects the auricles and ven-
tricles 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 ac-
celeration 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 maxi-
mum 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 /

12.
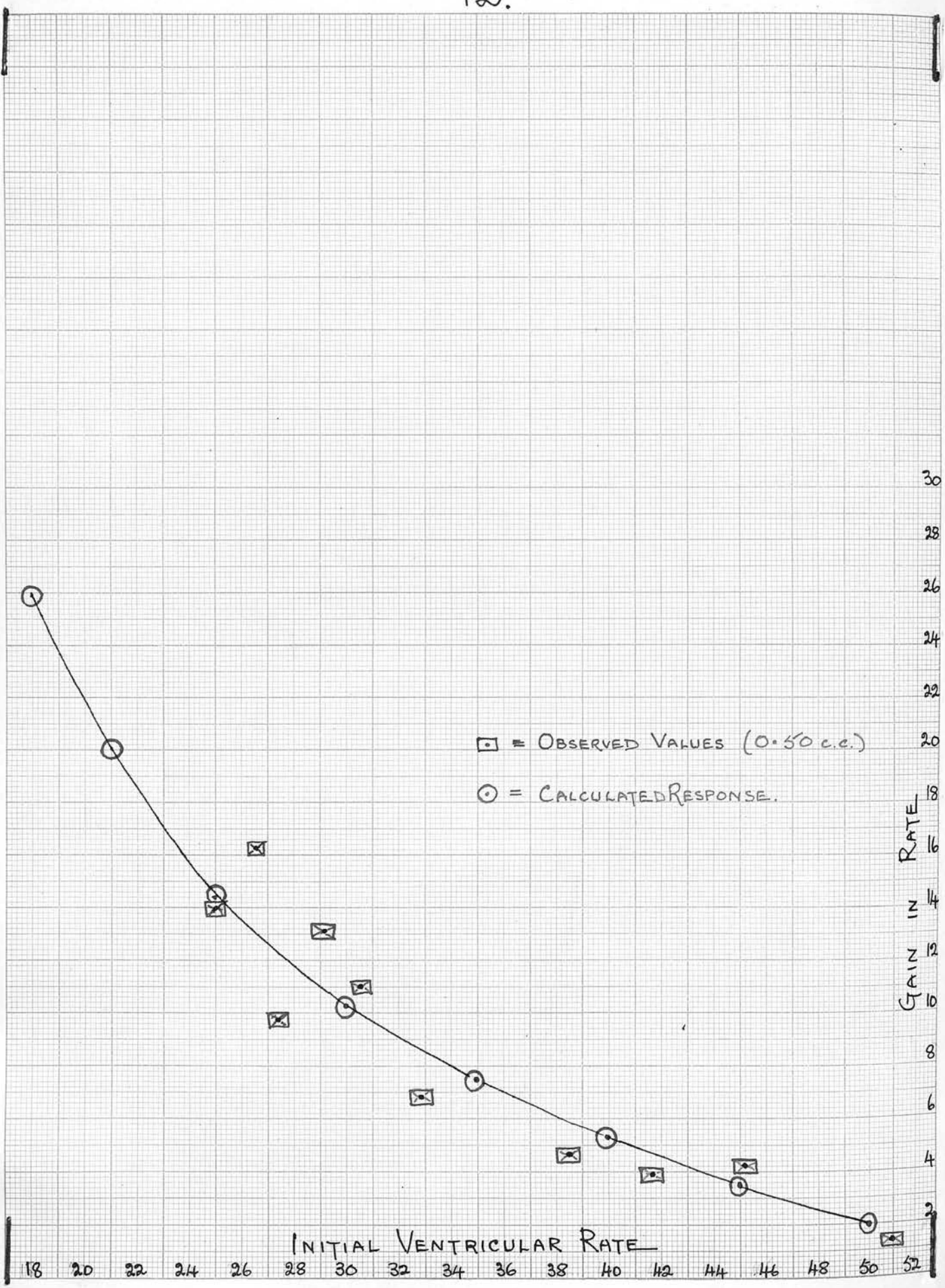
relationship becomes at once evident.   This is
shown in Chart 12 in which the results obtained in
ten experiments are inserted.

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 ex-
ponential 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 corres-
ponding exponential values against the initial rate,
the /

13.

$e^{-y} = 2.35x - 4.51.$

e^{-y} calculated

EXPONENTIAL OF OBSERVED INCREMENTS. (e^{-y})

INITIAL RATE (x)

18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52.
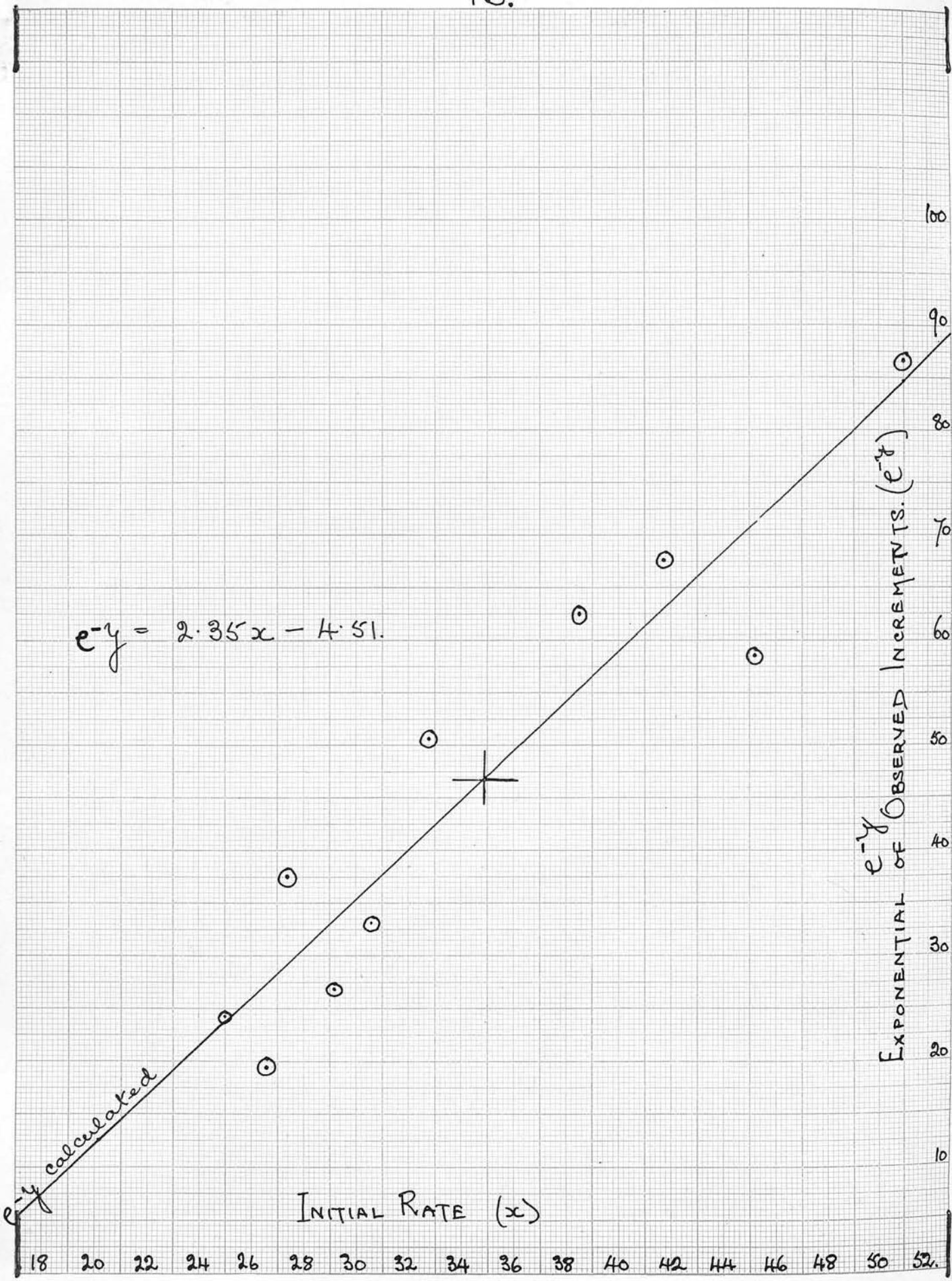
the points will fall along a straight line.   The

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).

<center>TABLE   XXII.</center>

x	y	e^{-y}
29.2	13.1	2698
25.0	14.1	2441
38.5	4.7	6250
30.6	11.0	3329
27.4	9.8	3753
32.9	6.8	5066
26.6	16.3	1959
45.2	5.3	5886
51.0	1.4	8693
41.7	3.9	6770

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.**

ADRENALIN DOSAGE CASE NO. & INITS.	0.25 c.c.			0.75 c.c.			1.0 c.c.		
	INITIAL VENTRIC. RATE.	GAIN in RATE	GAIN as PERCENTAGE of INITIAL RATE.	INITIAL VENTRIC. RATE.	GAIN in RATE.	GAIN as PERCENTAGE of INITIAL RATE.	INITIAL VENTRIC. RATE	GAIN in RATE	GAIN as PERCENTAGE of INITIAL RATE.
1. Mrs T.	26.6	14.9	56.0	23.8	20.2	86.7	21.0	19.4	92.4
3. D.C.	40.4	4.1	10.2	-	-	-	-	-	-
5. A.H.	-	-	-	36.0	7.4	20.6	-	-	-
6. J.W.	-	-	-	-	-	-	25.0	16.9	67.6
11. Mrs D.	43.0	2.1	4.9	-	-	-	-	-	-
13. Mrs H.	-	-	-	44.6	2.0	3.8	-	-	-

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 $e^{-y} = 2 \cdot 35x - 4 \cdot 51$, yields optimum values for e^{-y} 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.

TABLE/

14.

⊙————⊙ = Optimum Value for 0.5 c.c.
☒ = Observed   "   "   "   ".

⊙ = 1.0 cc.
⊗ = 0.75 cc.
☒ = 0.25 cc.
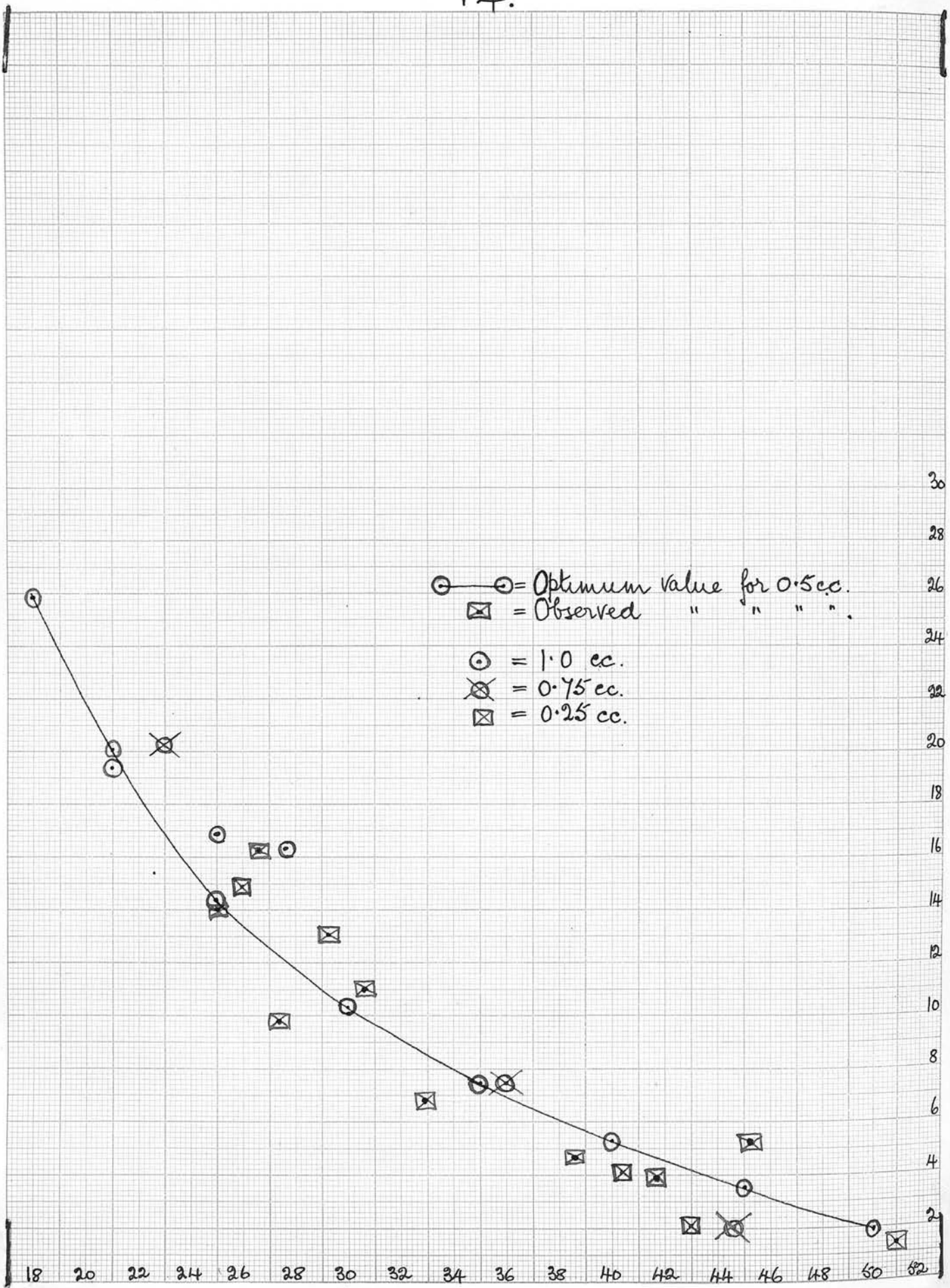
By again plotting the initial rate
against the observed gain for each dose, a remark-
able result becomes at once evident.   This is
shown in Graph   in which, by way of contrast,
the reactions to 0.5 c.c. adrenalin are also in-
cluded.   The continuous curve indicates the opti-
mum response to 0.5 c.c., 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 inter-
preted 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 govern-
ing 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 num-
ber 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 power-
ful chemical substance which induces the disintegra-
tion of the snails representing the substrate, which
is adsorbed on its surface.

"The exponential ratio of the concen-
tration 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 ap-
plies in some measure to the response of the idio-
ventricular 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 re-
lationship 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 indepen-
dence of the response to the size of the dose (with-
in 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 logarith-
mic 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 re-
action

$$E + S \longrightarrow ES$$

is governed by the law of mass action.   When, how-
ever, the sugar concentration is increased beyond
a certain limiting value, the surface is completely
covered /

covered, and the rate of hydrolysis becomes indepen-
dent 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 stimu-
lus".   This implies that in so far as blood-pres-
sure is concerned, a given dose of the drug does
not produce a uniform response under varying condi-
tions.   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)

The /

TABLE **XXIV.**

ADRENALIN DOSAGE	0.25 c.c.			0.75 c.c.			1.0 c.c.		
CASE NO. & INITIALS	INITIAL AURIC. RATE	GAIN in RATE	GAIN as PERCENTAGE of INITIAL RATE.	INITIAL AURIC. RATE	GAIN in RATE	GAIN as PERCENTAGE of INITIAL RATE	INITIAL AURIC. RATE	GAIN in RATE	GAIN as PERCENTAGE of INITIAL RATE
1. Mrs T. (a)	80.8	22.0	27.2	81.8	41.2	58.5	69.0	45.0	65.2
" " (b)	-	-	-	-	-	-	77.7	25.7	33.4
3. D.C.	78.1	9.7	12.4	-	-	-	-	-	-
5. A.H.	-	-	-	59.0	?41.0	? 69.5	-	-	-
6. J.W.	-	-	-	-	-	-	54.7	19.4	36.0
11. Mrs D.	89.8	3.7	4.1	-	-	-	-	-	-
13. Mrs H.	-	-	-	74.5	6.4	8.6	-	-	-

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 ven-
tricles increase in rate after an injection of
adrenalin and that the amount of acceleration in-
duced 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 ven-
tricular 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 /

15.

224a

PERCENTAGE VENTRICULAR ACCELERATION.

PERCENTAGE AURICULAR ACCELERATION.

⊙ = 0.5 cc. ADRENALIN
⊙ = DOSES OF 0.25, 0.75 & 1.0 cc.
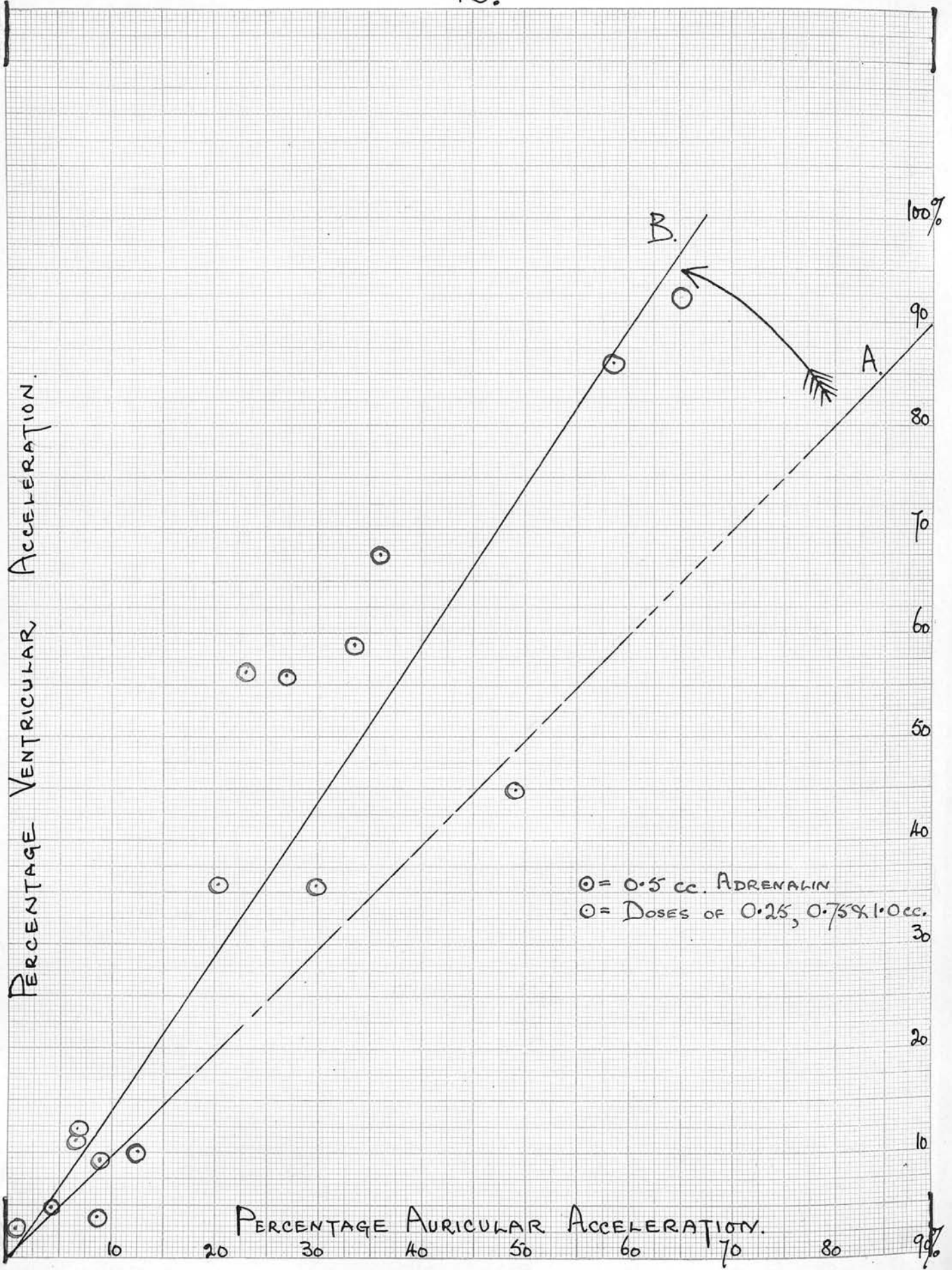
arch of the aorta are appreciably disorganised in
the presence of complete heart block, and it may
therefore be assumed that the rise of pressure, con-
sequent upon the injection of adrenalin, will call
forth inhibitory reflexes acting on the sino-auricu-
lar node.   The rhythmicity of the pace-maker 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 rela-
tion 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 pro-
portionate.   For instance, when the ventricles ac-
celerate 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 per-
centage ventricular acceleration increases, the
corresponding auricular gain lags more and more
behind.   It has already been shown that the great-
est 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 ap-
pear probable that the widening interval separating
the lines A and B, represents the effect of in-
creasing 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 /

16.
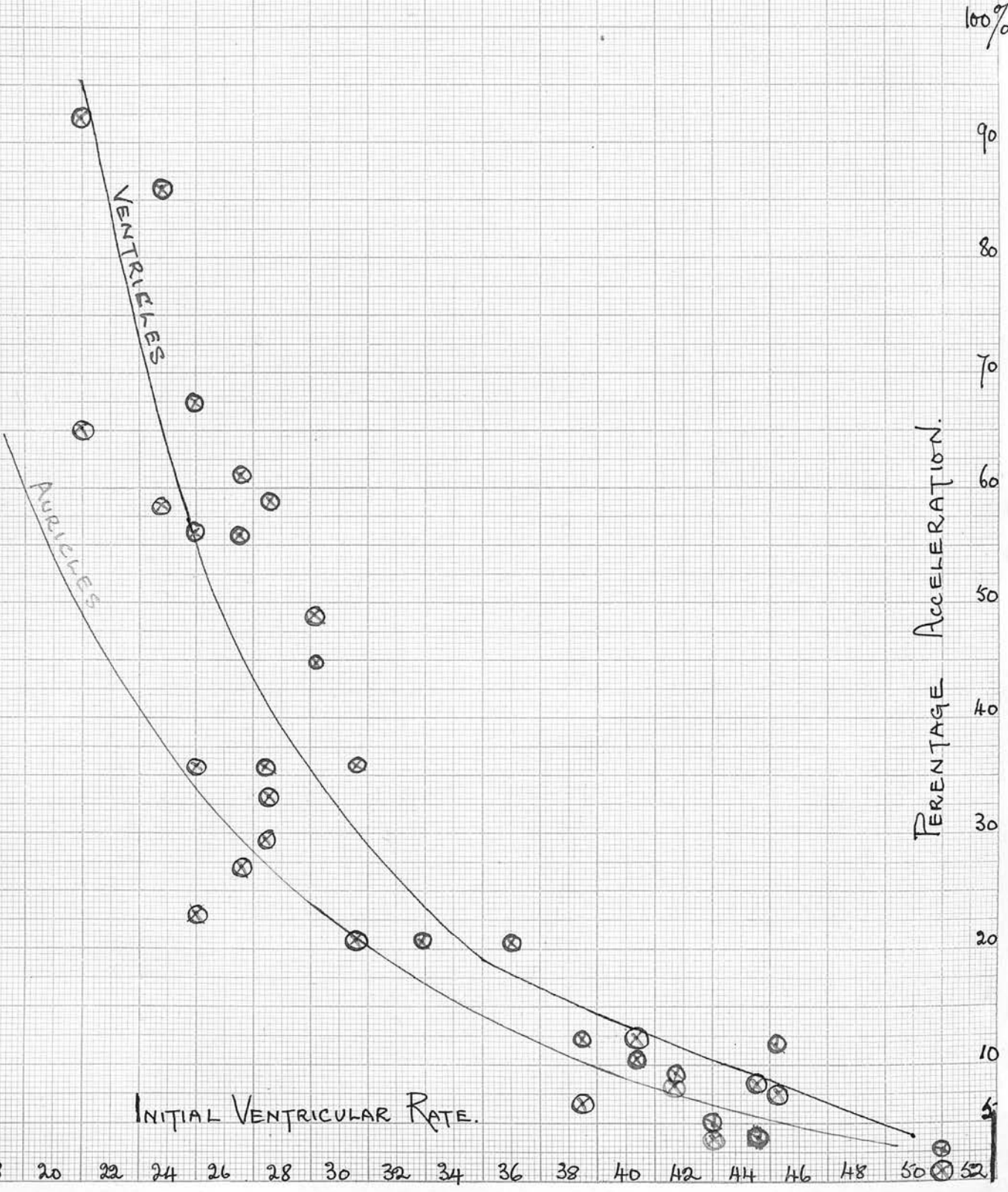
inhibitory vagal reflexes limit the auricular re-
sponse.   The more the ventricles gain in rate, the
greater is the lag in the auricular response.

The same phenomenon may also be demon-
strated 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 ini-
tial rates are approached the auricular curve dis-
plays a slight shift to the left indicating that
the auricular response tends to be restricted.
This is confirmed by again plotting the exponen-
tials of the percentage gains in rate for the two
chambers of the heart.   The ventricular exponen-
tials, 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 auricu-
lar response lag behind.   If the auricular inhibi-
tion be the result of increased blood pressure,
then it would seem correct to suppose that in com-
plete 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 sys-
tolic 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 in-
creased out of proportion to the oxygen require-
ments of the tissues.   This implies that adrenalin
acts as a whip to the heart, and that its main ef-
fects on, at least certain of the peripheral ves-
sels (e.g. the lung or elsewhere), must be dilator
rather /

FIGURE 3.

228 a

Before Adrenalin :-

11 min before
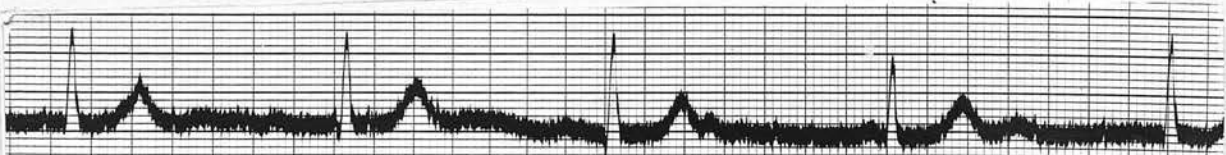
9 "   "
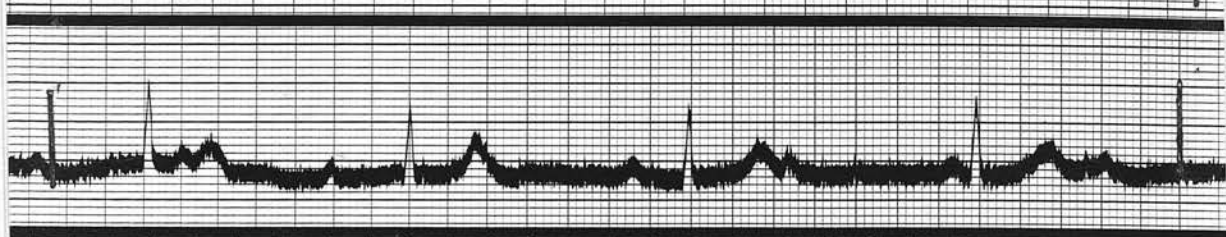
1 "   "
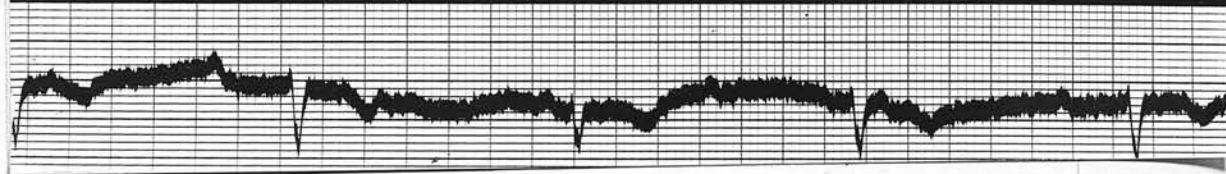
After Adrenalin :-

1 min after

2 "   "

4 "   "

6 "   "

8 "   "

10 "   "
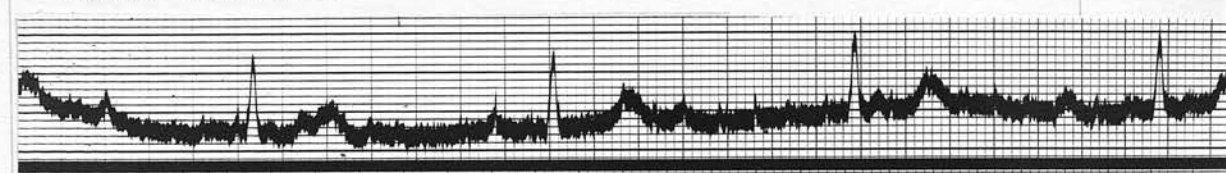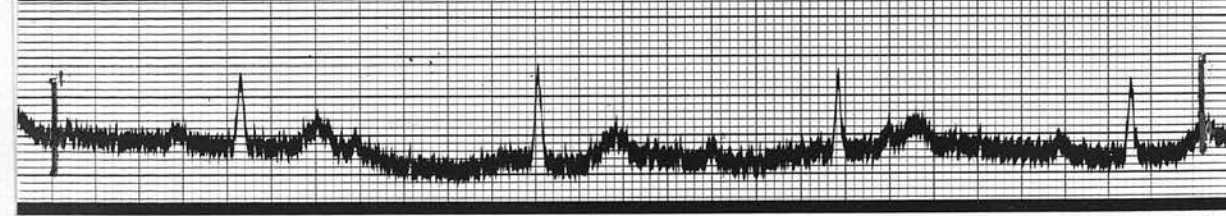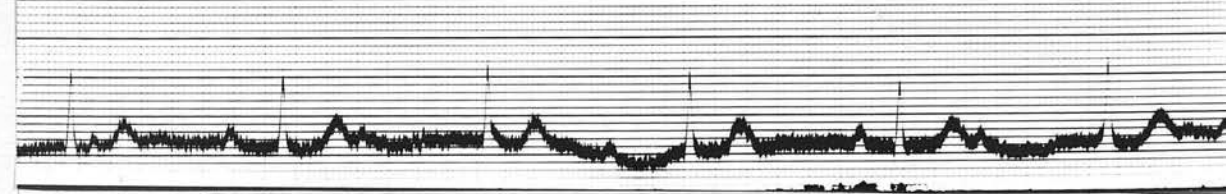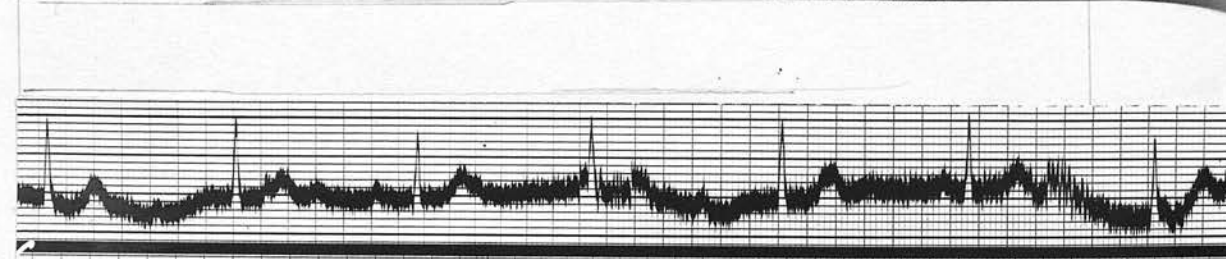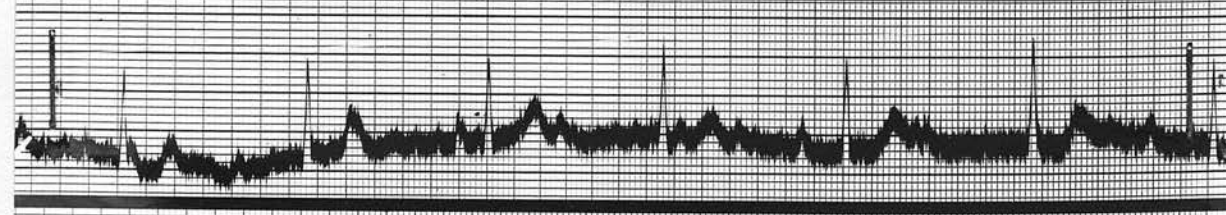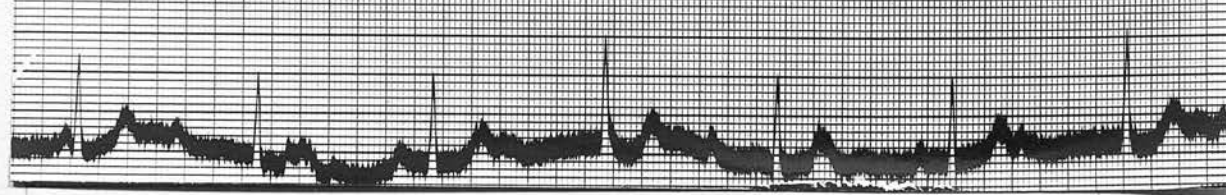
FIGURE 3 (continued).

12 min. after
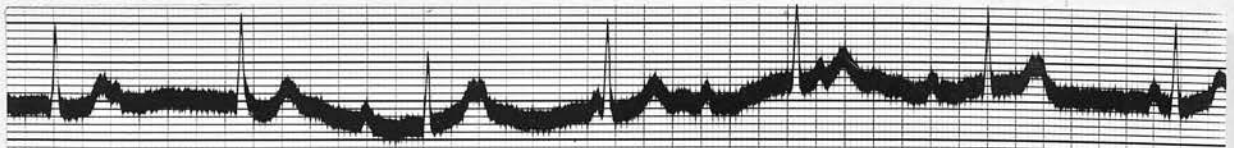
14 "   "
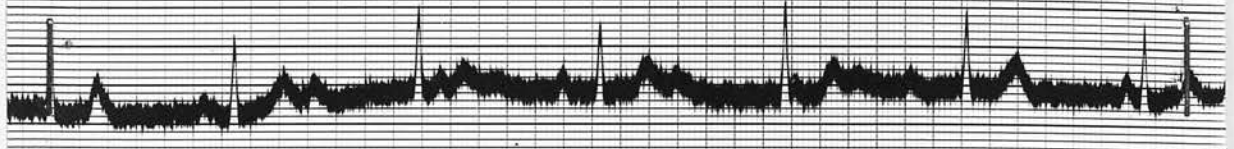
16 "   "
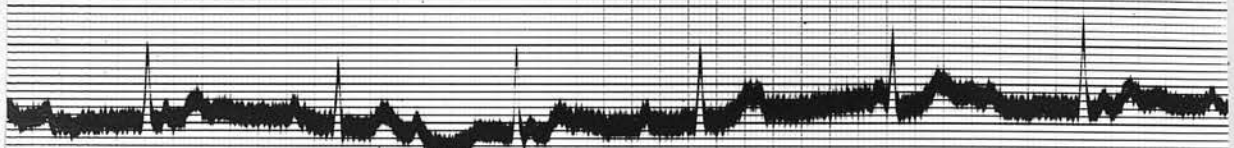
18 "   "
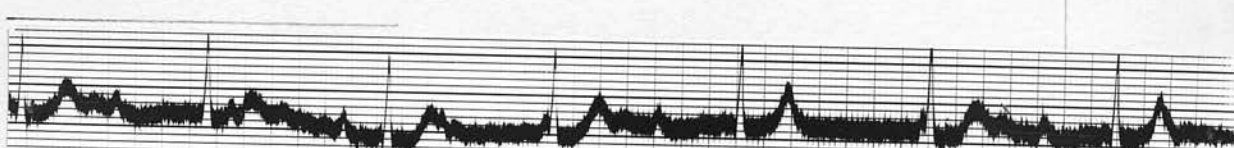
20 "   "
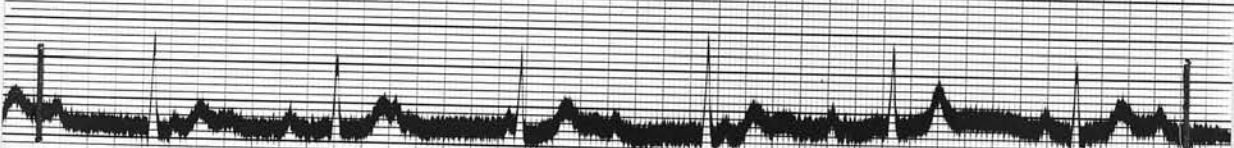
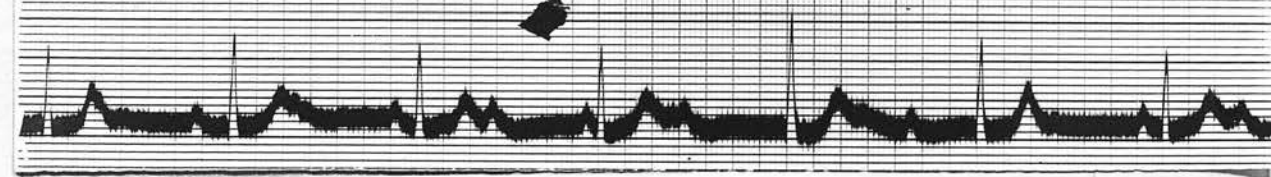22 "   "

24
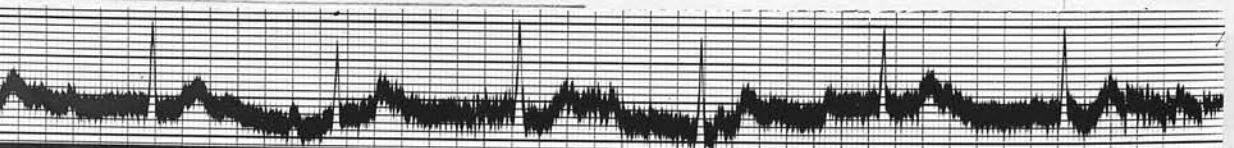
26
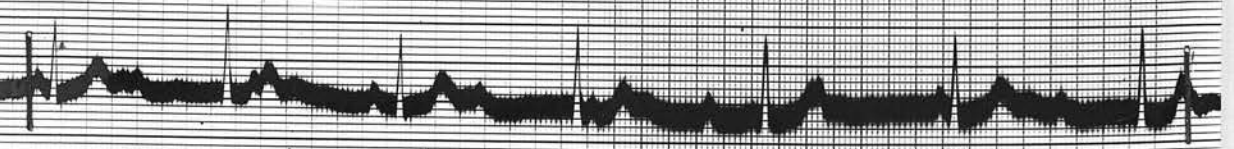
28
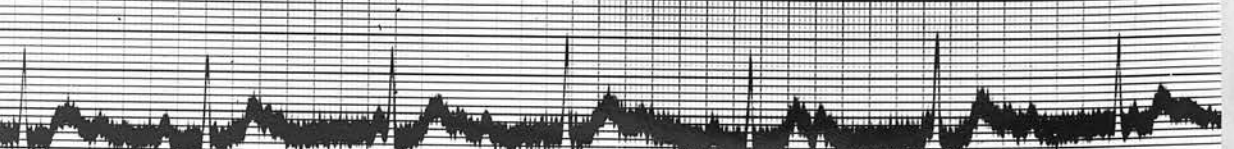
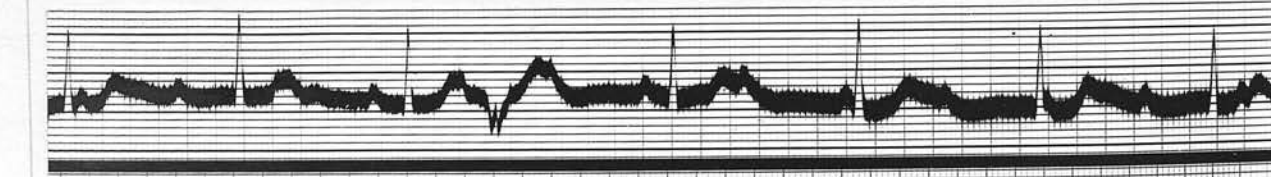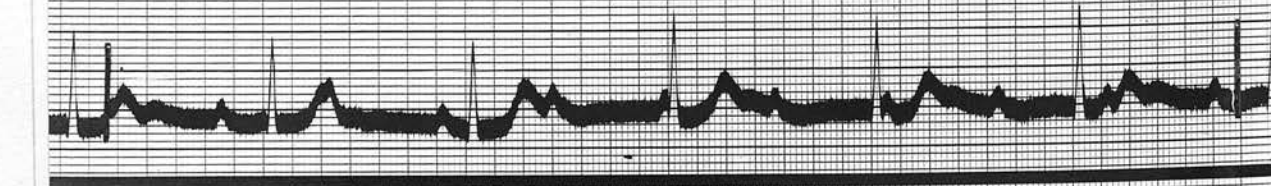FIGURE 3 (continued).

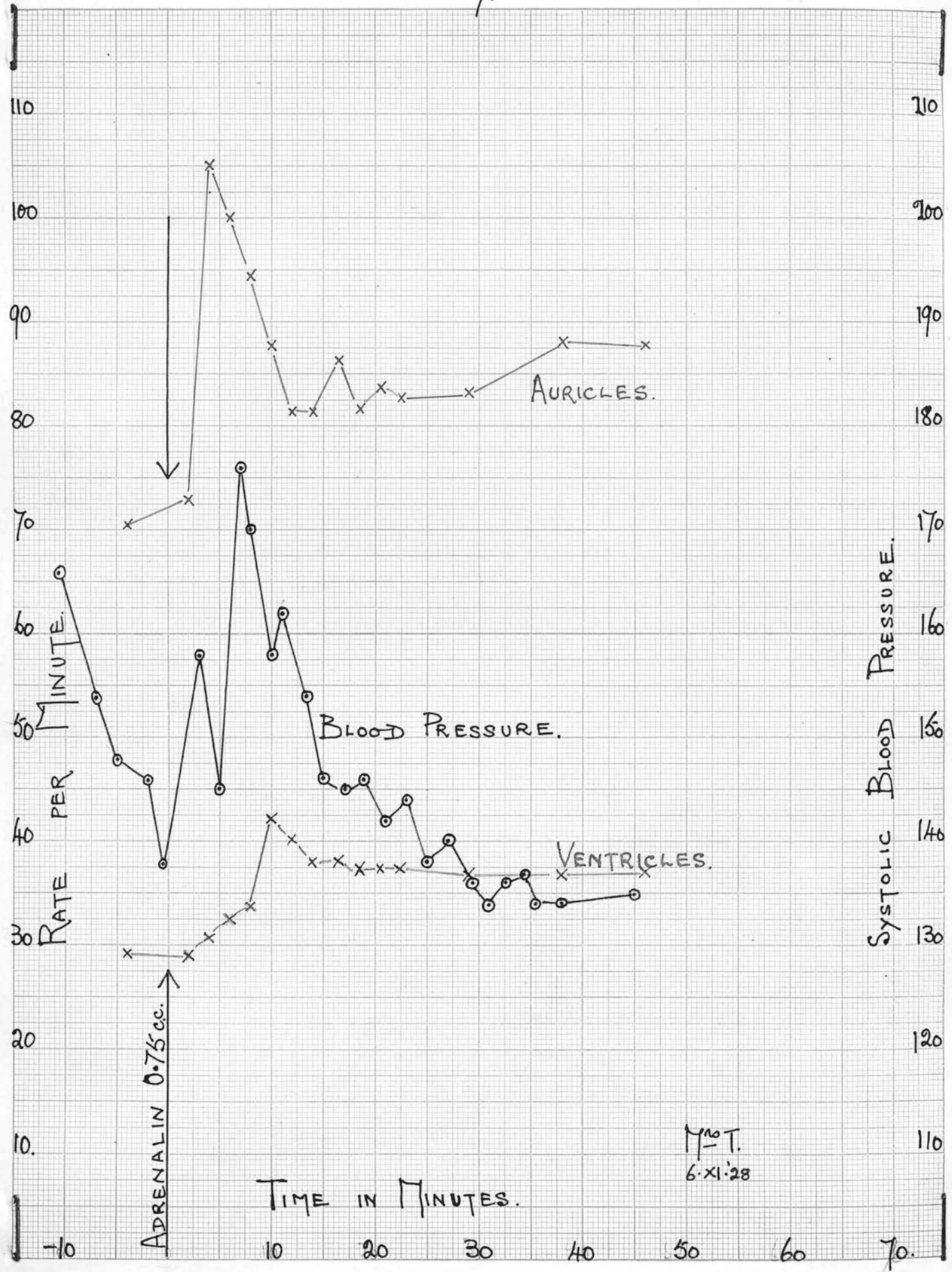FIGURE 3 (Continued).

32 mins after
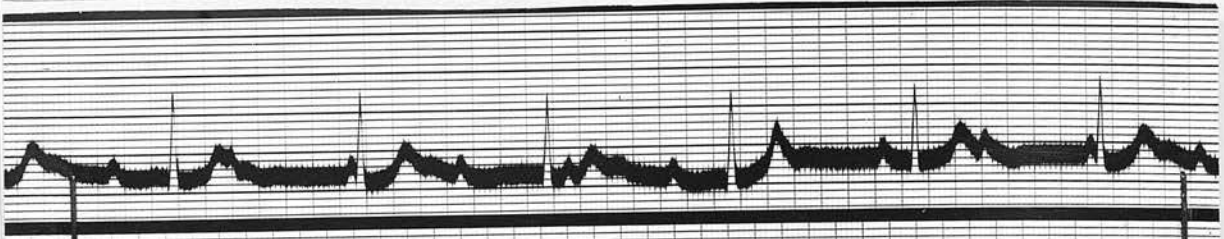
34 " "
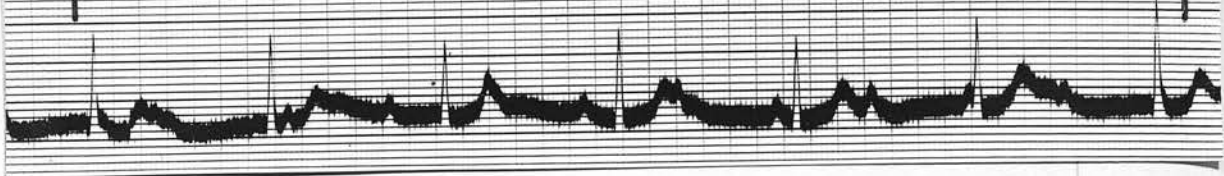
36 " "
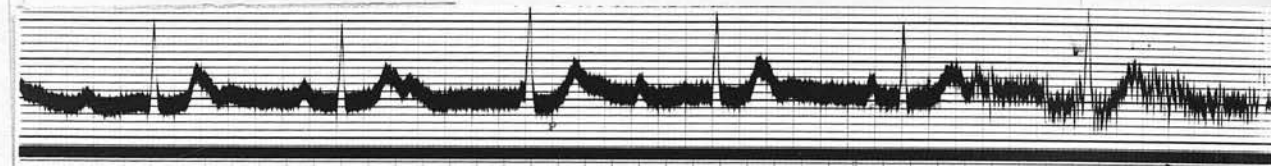
38 " "
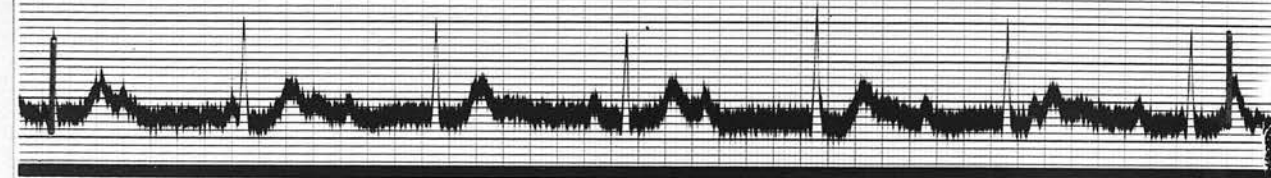
40 " "

44 " "

50 " "

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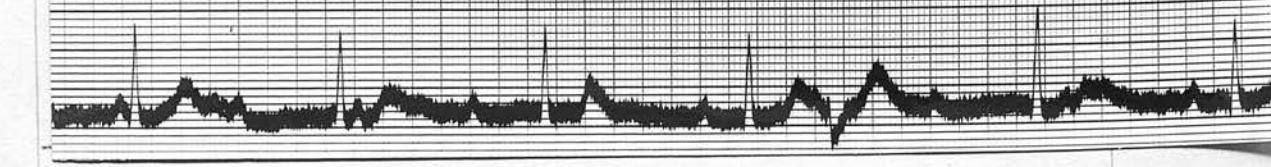
rather than constrictor.   The observations described
in these cases of heart-block support this view, for
the reason that the greater the ventricular response
the more do the auricles lag behind.   The ventricles
presumably have a large share in regulating the
blood pressure and consequently reflex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

The Course of the Reaction to Adrenalin.

An examination of the course of the re-
action to adrenalin in complete-block does not re-
veal 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 de-
tail 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
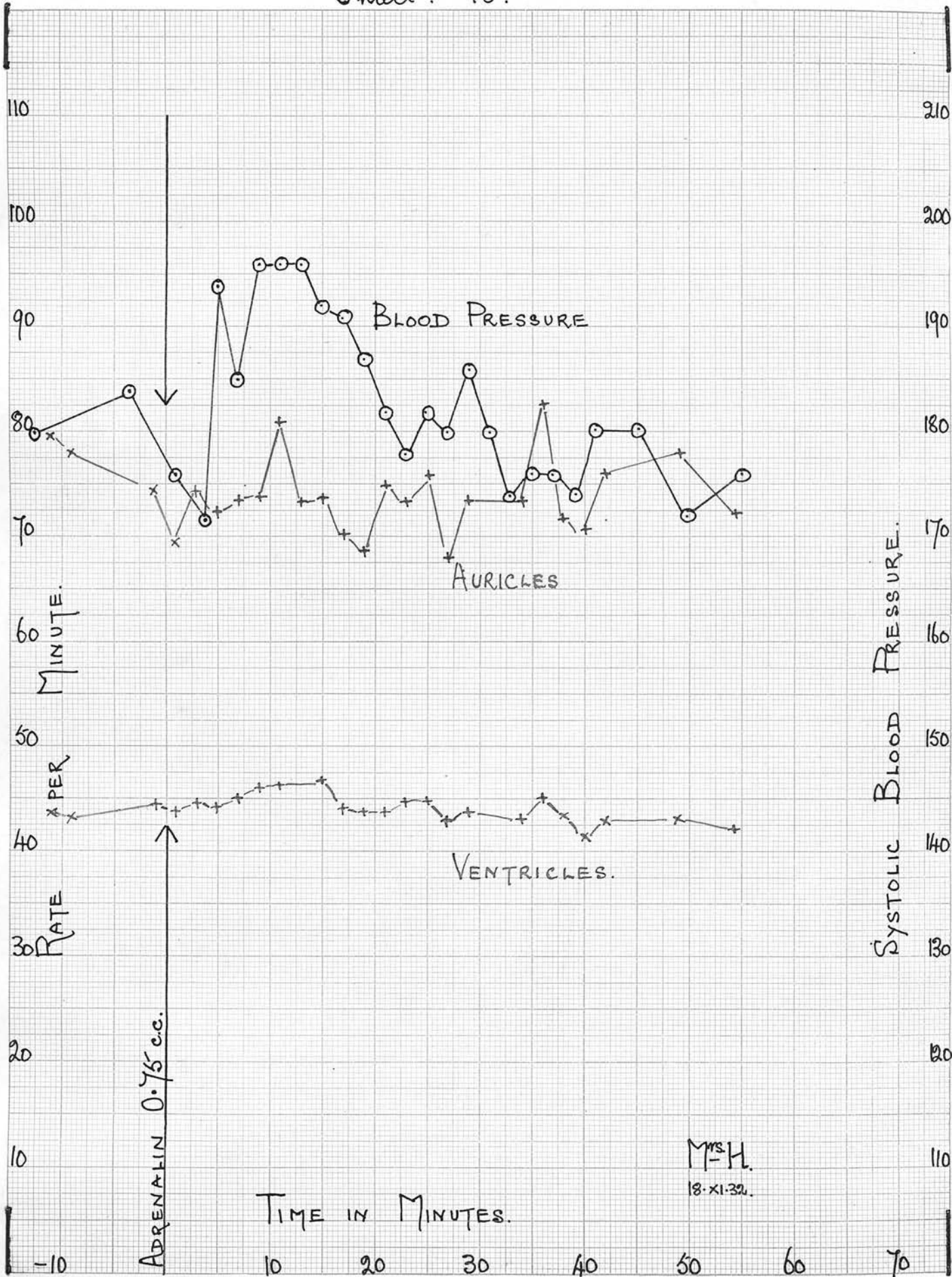have /

17.

229 a

AURICLES.

BLOOD PRESSURE.

VENTRICLES.

ADRENALIN 0.75 c.c.

RATE PER MINUTE.

TIME IN MINUTES.

SYSTOLIC BLOOD PRESSURE.

M^no T.
6·XI·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 fol-
lowed 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 accelera-
tion, 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.

MINUTE.

X PER

RATE

ADRENALIN 0.75 c.c.

TIME IN MINUTES.

SYSTOLIC BLOOD PRESSURE.

Mrs H.
18·XI·32.

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 in-
dividual, 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 fol-
lowed 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 sus-
picion of angina occurred in any of these cases of
block, although two suffered habitually from pre-
cordial 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 indivi-
duals.   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 re-
ceived two doses of respectively 0.25 c.c. and
0.5 c.c.   After each the amount of ventricular ac-
celeration exceeded that which would be expected for
the corresponding initial heart rate, and the reac-
tion was a trifle slower in onset, perhaps as a re-
sult 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
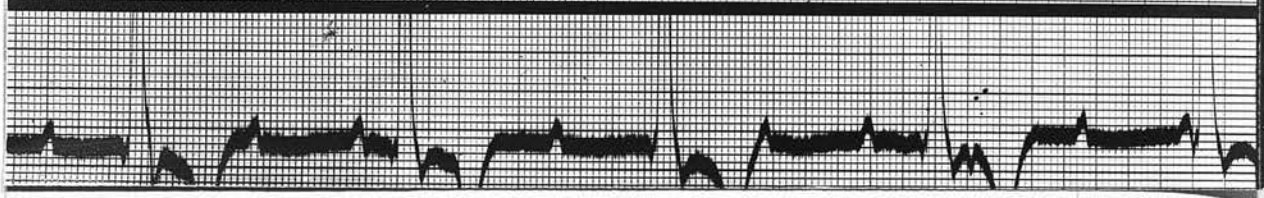defect in circulation should respond by an excessive
acceleration /

233a
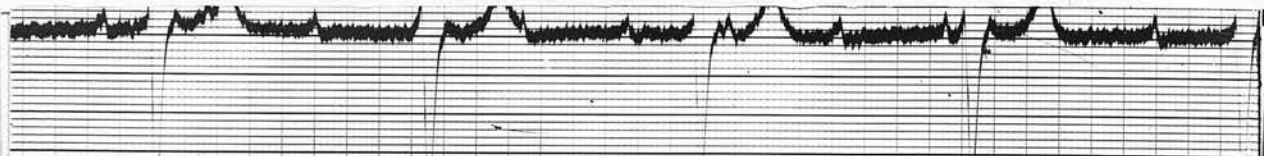
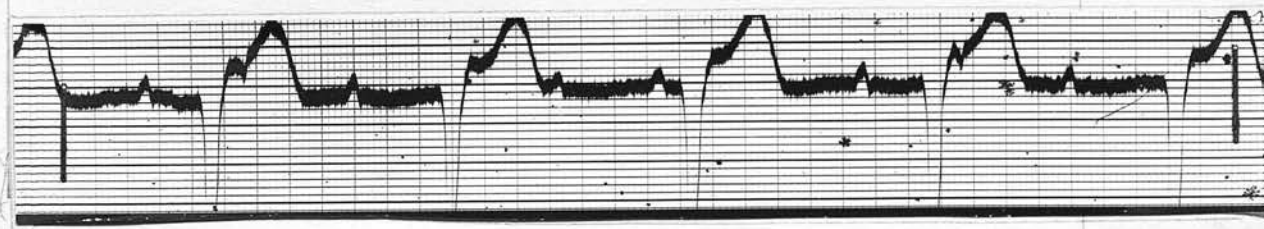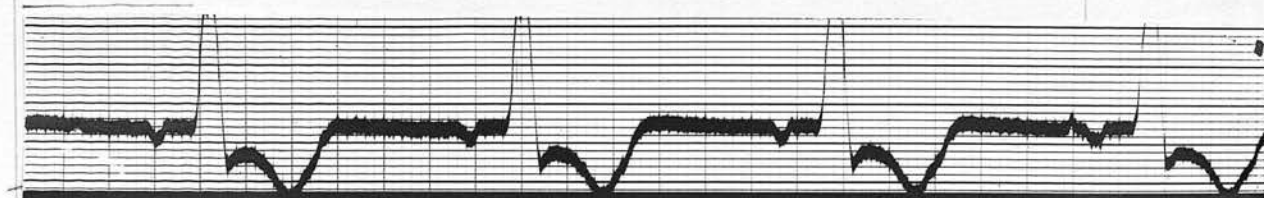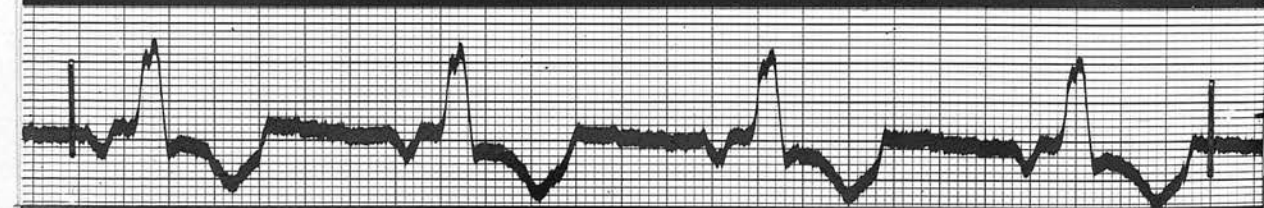FIGURE 4.

Lead 1
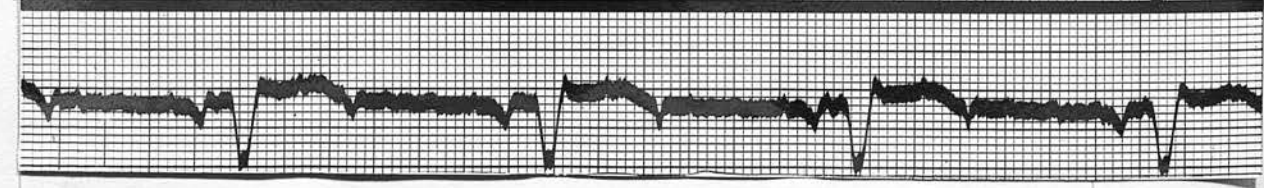
Lead 2
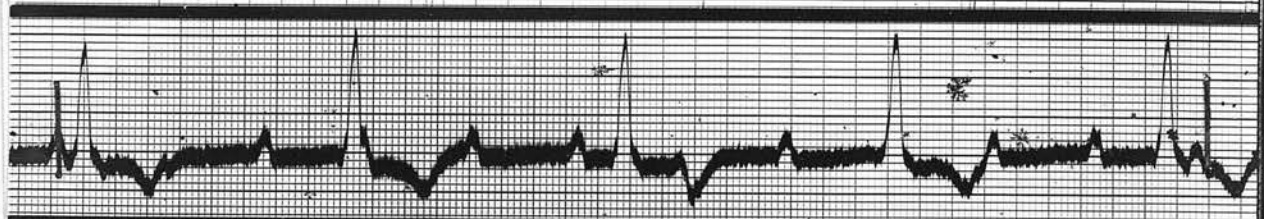
Lead 3.

FIGURE 5.

Lead 3

FIGURE 6.

Lead 1

Lead 2

Lead 3

acceleration, unless it be that, incapable of in-
creasing 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 to-
wards 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 deflec-
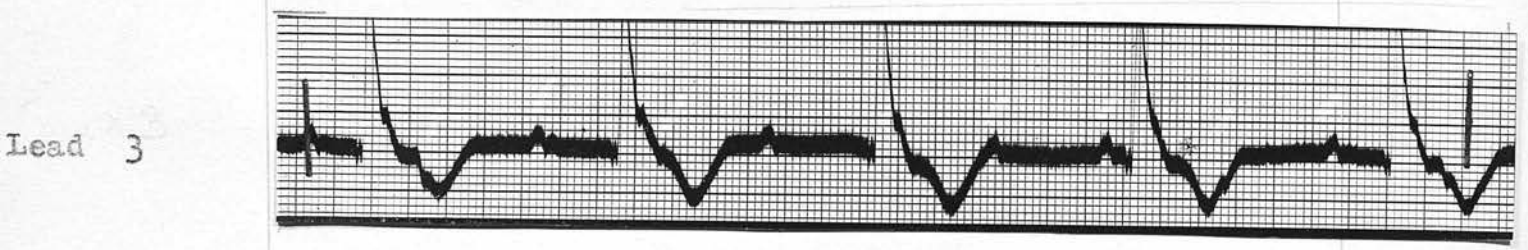tions downward in lead 1 and upward in lead 3.
Until /

FIGURE 7.

Lead 3

FIGURE 8.

Lead 1

Lead 2

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 collabora-
tors (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 com-
plete 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 per-
sisted throughout the experiment and the final re-
cords 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 com-
plexes 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 Q R S waves
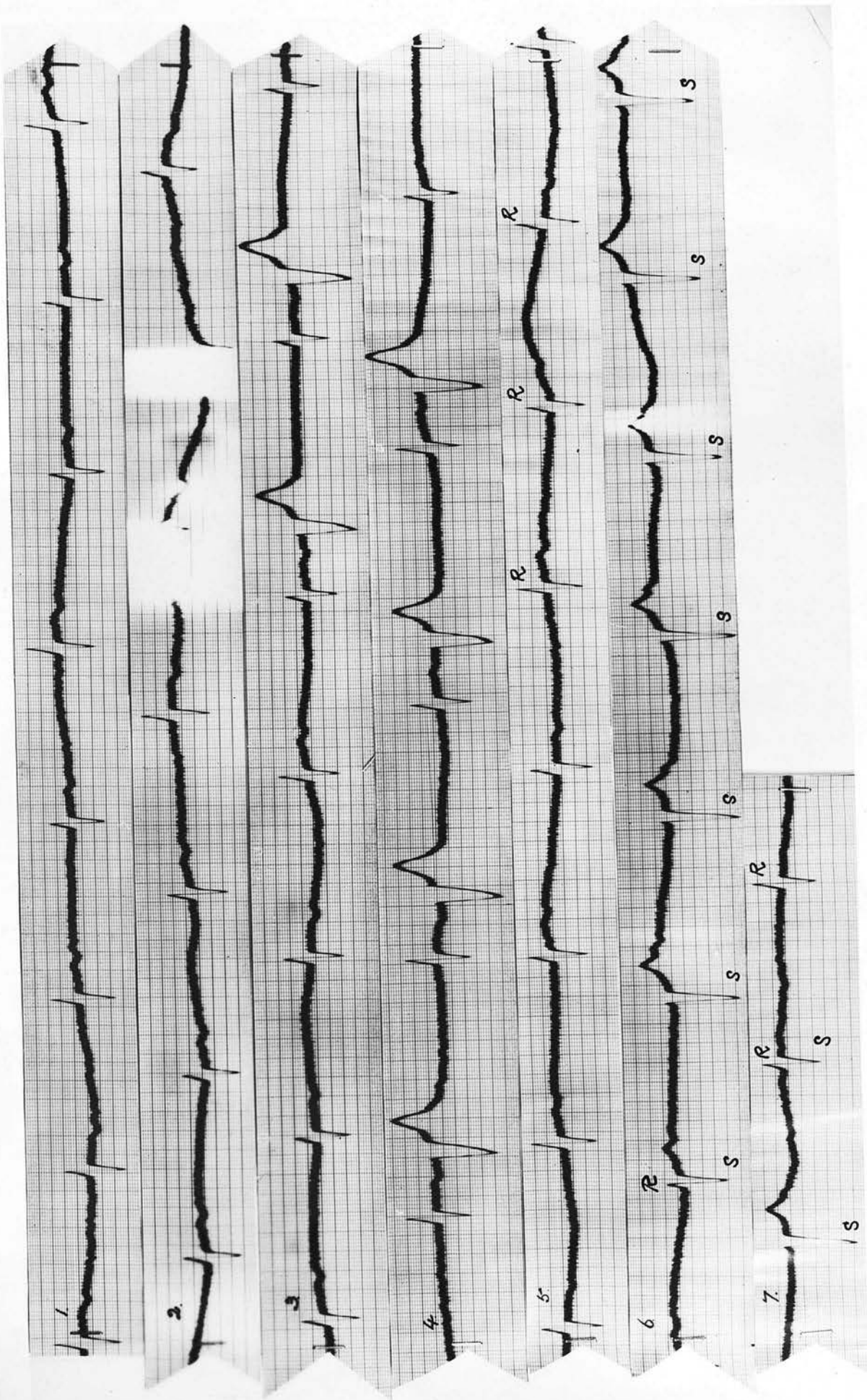in /

235'a.

Plate 3

1-451

PLATE 3.

Plate 3.

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 adrena-
lin 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 de-
monstrate 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 sub-
cutaneous dose of adrenalin varies as much in com-
plete 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 accele-
ration.   An increased frequency of both chambers
of /

of the heart persists after the blood pressure rise
has returned to its pre-existing level.   No un-
toward 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 ac-
celeration, 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 com-
plete 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 ab-
sence of conduction through the main stem of the
bundle.   During half-rhythm, the ventricular com-
plex 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 adeno-
sine.