OBSERVATIONS ON THE

EFFECTS OF SOME ENVIRONMENTALLY INDUCED

MENTAL STRESSES ON THE HEART

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ACKNOWLEDGEMENTS

DECLARATION

Some of the initial work done for this thesis has been presented

in Proceedings of a Symposium "New Perspectives in Beta-Blockade"

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Two papers have been submitted to the Lancet for publication; mention

has been made that they form part of this M.D. Thesis.

" My life is at the mercy of any scoundrel who choses to put me

in a passion".

JOHN HUNTER.

Hunter's death occurred during a dispute with the Governors

of St. George's Hospital regarding the exclusion of students whom

he considered to be the victims of a prejudice against the Scots.

SUMMARY

The cardiovascular effects of some environmentally induced mental stresses encountered in everyday life were studied in 33 normal healthy male subjects aged 23- 56 years and in 12 male patients with ischaemic heart disease aged 35 - 60 years. Two studies were designed; the first to examine the effects of beta-adrenoreceptor suppression on the tachycardia induced by the mental stress of driving, by catecholamine infusion, and by treadmill exercise; the second study was designed to investigate the magnitude of the effects of some normal everyday environmental stresses on the heart rate and the degree of modulation of these responses induced by blockade of the heart rate beta-receptors. The heart rate was measured from a radiotelemetered electro-cardiograph. The method of study included double-blind assessment and single-blind analysis with placebo control and 40 mg oral oxprenolol given in randomized order. The results in Study I indicated that relatively small doses of beta-receptor antagonists (40 mg oral oxprenolol) were capable of suppressing the heart rate increase induced by mental stress and catecholamines with much smaller effects on the response to physical exertion. The results in Study II showed that a number of everyday environmental situations were associated with substantial tachycardia and that these increases in heart rate were conspicuously reduced for up to 12 hours by 40 mg

oral oxprenolol. The association of everyday psychological or emotional stress with precocious coronary heart disease and the clinical implications of these observations in the treatment of emotionally induced anginal pain and the possible role of a relatively small dose of beta-receptor antagonist in suppressing the tachycardia associated with psychological stress is discussed.

INTRODUCTION

The possible patho-physiological effects of environmentally-induced psychological stress have recently attracted increasing attention. The interest has been stimulated by the assumption that the effects of such frequent stress may aggravate pre-existing athero-sclerotic heart disease and may even be an important factor in its pathogenesis. The evidence on which such important speculations are based require close examination. In the past the stimuli used to excite such cardiovascular reactions have often been unusual and frequently of such intensity as to bear little relationship to the emotional and mental stresses normally met in normal everyday life. There is little doubt that life in a Western urban society is associated with mental stress, but the frequency and magnitude of cardiovascular reactions to such stress are largely unknown. Furthermore, it is possible that the effects of such stresses may aggravate established coronary heart disease. It was the purpose of this study therefore to examine the effects on the heart of some of the psychological stresses usually met in everyday life in normal subjects and in patients with ischaemic heart disease.

HISTORICAL REVIEW

Emotionally induced tachycardia is a common personal experience and the cardiovascular responses to fear, sorrow, sexual arousal and other personal emotions have been the subject of extensive writings by many authors. A number of reports have documented the specific

circulatory changes occurring in a variety of mentally stressful situations.

Conspicuous changes in a number of circulatory variables have been observed in a variety of situations designed to cause mental stress.

1. In patients during provocative discussions of personal problems

    (Wolff, 1950).   In 35 patients who complained of "praecordial symptoms" the author found that the "majority" showed "significant" changes in heart rate when discussing personal problems which aroused "anxiety" and "resentment".   The tachycardia measured by electrocardiography, was "moderately severe" and "prolonged" in many of the subjects.

    However, the author omitted to define "praecordial symptoms" or to state the exact number of subjects who showed changes in heart rate and the magnitude of these changes.   In 18 of these patients, whom the author did not categorise clinically, he stated that the configuration of the electrocardiogram would have been interpreted as "abnormal" had they occurred during or after "standard exercise tests". The author also failed to define the abnormality, except to say that there were "T wave changes".

2. In normal individuals during heated arguments and electric shock stimuli

    (Bogdonoff et al 1959).   Twenty male volunteer University students were studied during cardiac catheterisation.   Two types of stimuli were used, "role enactment" and "electric shock".   The role enactment procedure consisted of experiments either creating an atmosphere of concern about the subject's welfare or accusing the subject of failing

to co-operate properly, e.g. his inability to remain absolutely quiet.
The electric shock stimulus consisted of the application of an
electrocardiographic lead plate to the lower extremity with the connection
made to a small rheostat giving a 5-volt 3 ampere stimulus. The results
were grouped according to the "quality" and "quantity" of "affect" change.
The affect "quality"and "intensity" were measured by

      i) the subjects ability to recall the experience

      ii) his ability to describe his feelings

      iii) the interpretation of the subjects statements by

          the interviewer.

The results indicated that the "intensity of affect" was directly
correlated with the change in cardiac output and heart rate, the increase
being most marked in the subjects in whom anxiety was greatest. The
authors did not remark upon the obvious difficulty of defining alterations
in or differences between affect changes in different subjects.

3. In medical students undergoing "particularly difficult and challenging"
    oral examinations.

(Bogdonoff et al, 1960). The situation chosen was a fifteen minute
oral examination of sixteen 4th year medical students. An electrocardiogram
using the limb leads was recorded throughout the examination. "Several"
subjects showed a tachycardia ranging from 120 to 166 beats per minute.
The degree of "affect arousal" (minimal, moderate or marked) was found
to broadly correlated with the increase in heart rate. All students
described some degree of tenseness, anxiety or fright.

However, the authors exact criteria of definition of "affect arousal"
was not given, precluding such studies being repeated.

4. In house-officers presenting clinical problems at physicians'
grand rounds

(Moss and Wyner, 1970).   The heart rate of ten house officers
was measured by electrocardiography whilst they were presenting cases
at grand rounds.   The heart rate increased from an average control
rate of 73 beats per minute up to an average of 154 beats per minute
immediately before or during case presentation.

5. In lecturers speaking before a critical audience

(Somerville et al, 1971).   The authors stated that the heart rate
increased to 100 to 120 beats per minute immediately before speaking;
reached 150-170 beats per minute whilst speaking and decreased to 120
beats per minute during question time.

This paper was presented at a meeting of the British Cardiac
Society.   The authors did not mention the number of subjects studied,
whether or not they were experienced speakers, the size and character
of the audiences addressed, or whether the peaks in heart rate were
associated with physical activity, such as moving across the lecture
rostrum, gesticulations etc.

6. In subjects during aggressively monitored mental arithmetic

(Brod et al 1959).   A timed arithmetic exercise was used as the
stressful stimulus in eight normotensive and ten hypertensive patients
during cardiac catheterisation.   After a period of control observations
the subject was asked to subtract a two-figure number from the previous
result every two seconds to a metronome.   This stimulus was maintained
for four minutes and the subjects were continuously and provocatively
urged to keep the given pace.   The authors stated that there was a "rise

in the heart rate", and documented the increase blood pressure and cardiac output in all subjects.

Despite the comprehensive nature of these studies, an increase in heart rate, from 60 to 90 beats per minute, is shown in only one patient in a diagram.

7.   In test pilots

(Roman 1965; Roman et al 1965).   This author and his colleagues reported two studies.   Two-seater high altitude Mach 2F-104b fighter aircraft were used in the first study.   The average control heart rates in six experienced pilots was 110 beats per minute when they were in actual control of the aircraft and 96 beats per minute when they were passengers in the same aircraft under similar conditions.   In the second study Roman and his colleagues demonstrated in a single test pilot an increase in heart rate from a control value of 80 beats per minute to 120 beats per minute during take-off and 105 beats per minute during landing an F-100 aircraft.   Heart rate measurements in these studies were made from electrocardiographic recordings on magnetic tape.

8.   In commercial air-line pilots during take-off and landing

(Flying Personnel Research Committee Reports, 1965 and 1966;

Ruffel Smith 1967;   Bateman et al 1970;   Thomson 1971).   In all instances there was a conspicuous elevation of the heart rate during take-off and landing.   The heart rate was also increased by unexpected difficulties and hazards during the remainder of the flying task, e.g. manoeuvres requiring a high degree of skill, or when there was some

element of danger.

The pilots heart rate was measured on electrocardiographic magnetic tape recorders and analysed by computer.

9.   Pilots training on a flight simulator

(Eliasch et al 1967; Bateman et al 1970).   Eliasch and his colleagues studied the response of the heart rate, cardiac output, systemic blood pressure and plasma catecholamines to mental stress in 16 pilots performing simulated flights on a ground-based cockpit simulator.   The average control heart rate was 73 beats per minute (range 55-86).   During flight simulation the average heart rate increased to 92 beats per minute (range 71-120) ($p<0.001$).   The blood pressure and cardiac output also increased by an average of 20 mm Hg. ($p<0.001$) and 2.6 l/min/sq.m. respectively ($p<0.001$).

Bateman and his colleagues studied the heart rate response of 12 volunteer training captains flying four different types of aircraft (Trident and Comet Jets, Vanguard and Viscount turbopropeller aircraft) in the following situations:

   i)   simulator training involving all phases of flight

   ii)   base training involving aircraft landing and

   iii)   line training that was a continuation of the work done during simulator and base training.

The average control heart rate was 66 beats per minute (range 59-75). During simulator training the average heart rate increased to 87 beats per minute (range 70-119);   during base training the average heart rate increased to 91 beats per minute (range 76-112);   during the line

training the average heart rate increased to 82 beats per minute

(range 74-94); and during line flying the average heart rate increased

to 85 beats per minute (range 73-107).

10. In ski-jumpers immediately before take-off

(Hanson and Tabaken 1964; Imhoff et al 1969). Hanson and

Tabaken studied the heart rate in four experienced subjects by

electrocardiography before the start of a 50 m. ski-jump. The

control heart rates of 56 to 80 beats per minute increased to 87 to

118 beats per minute just before the jump. Imhoff and his colleagues

measured the heart rate by radiotelemetry in nine experienced ski-jumpers.

Two minutes before the start of the jump, during the jump and one minute

after landing the average heart rates were 142, 145 and 128 beats per

minute respectively.

11. In motor-racing drivers immediately before and during a race

(Collins 1966; Taggart et al 1969). Collins demonstrated that

the heart rate increased immediately before the start of a motor race

up to 170 to 200 beats per minute or more. This tachycardia was

maintained or decreased only slightly during the race. The studies

by Taggart and his colleagues involved ten racing drivers; the results

were similar to those reported by Collins.

12. In motor-car drivers in heavy traffic

(Suenaga et al 1964; 1965a,1965b; Hoffman 1965; Dupius 1965;

Collins et al 1965; Simonson et al 1968; Bellet et al 1968; Taggart

and Gibbons 1969). Suenaga and his colleagues studied two healthy

drivers in city traffic and found "large fluctuations" of pulse rate with

increases of 40 beats per minute or more depending on road events and

speed.   The average level of the pulse rate was 15 beats per minute higher at fast than at slow speeds.

Hoffman noted an increase in heart rate of 40 per cent or more of the control value in 8 per cent of 600 healthy drivers during city driving.   Twenty six drivers with coronary artery disease showed similar changes.

Absolute values for heart rate were not given.   The heart rate was measured from the E.C.G. telemetered to the laboratory. This limited the driving distance to within 30 Km.

Low density highway driving was associated with an increase in heart rate of up to 20 per cent.   The heart rate increase was in excess of 20 per cent of the control value during urban driving in 28 per cent of drivers, rising to 42 per cent of healthy drivers during overtaking, sudden stops and other hazardous conditions.

The number of subjects and absolute values for heart rate were not given.

Dupius showed increases of pulse rate in healthy subjects in heavy traffic from 15 to 30 beats per minute and in overtaking up to 45 beats per minute.   There was a sharp initial increase of the pulse rate at the start of driving (20 to 30 beats).   The author does not state the number of subjects studied.

Collins and his associates in a study of three drivers also showed "high heart rates" with "large fluctuations" depending on road events in their published figures.

Simonson and his associates recorded the heart rate of the

driver and the passenger during the same ride on two consecutive
periods of 30 minutes of city driving.   The response of the driver
and the passenger was nearly identical from a resting value of 75 to 95
beats per minute and the increase in heart rate correlated closely to
critical road events.

Bellet and his colleagues studied 65 normal young men between 25-39
years and 66 subjects with proven coronary heart disease between 38-
72 years, in city driving lasting two and a half hours, avoiding areas
of heavy traffic.   The electrocardiogram was recorded on magnetic
tape.   In the normal subjects the heart rate increased up to 145 beats
per minute during driving and in subjects with ischaemic heart disease
the heart rate increased to 155 beats per minute.

The central heart rates were not given in this study.

Seventeen per cent of the subjects with coronary artery disease
developed ischaemic electrocardiographic changes consisting of
S-T depression and multifocal ventricular ectopic beats.

Taggart and Gibbons studied 32 normal drivers and 24 drivers with
ischaemic heart disease during drives of 20 minutes in central London.
These drivers were experienced, driving their own cars along familiar
but crowded traffic routes.   Brief periods of tachycardia in excess
of 140 beats per minute were recorded in both groups.   Electrocardiographic
"ischaemic S-T and T wave changes" occurred in 13, with "gross changes"
in 6 subjects with ischaemic heart disease.

13.   In train drivers during operation of high-speed trains

(Yoshio Noda 1965).   The Japanese National Railways' New
Tokaido Line was opened to traffic in October, 1964.   This railway

line was specially built for high speed travel and drivers were specially trained for these high speeds. Heart rate measurements were conducted on a test section. At 150 km/hour the increase in heart rate was 106% of the control value. At a speed of 200 km/hour, the driver's heart rate increased to 111% of the control value. The author did not mention his method of heart rate measurement.

14. In male volunteers sorting ball-bearings to the accompaniment of distracting noise and lights

(Carlson et al 1967). In this study 33 male volunteers were divided into three groups of 11, matched for age, blood pressure and blood lipid content. One group acted as a control only listening to light music; the second group ingested 3 grams of nicotinic acid in six divided doses during the first 3 hours of the 6 hour experiment. This group and the third group sorted ball-bearings to the accompaniment of distracting noise and lights.

The heart rate was measured from an electrocardiograph and the blood pressure was measured from a direct left brachial artery catheter. The average resting heart rate of the control group was 65 beats per minute. The average heart rate in the group that ingested nicotinic acid rose to 79 beats per minute from a control value of 69 beats per minute; and the third group showed an average increase to 77 beats per minute from a resting heart rate of 63 beats per minute.

The control group showed no changes in blood pressure. In the "nicotinic acid group" the systolic blood pressure rose by 14 mm Hg and the diastolic blood pressure rose by 9 mm Hg. The remaining group showed a rise of 12 mm Hg in the systolic blood pressure and 9 mm Hg in diastolic blood pressure.

CONCLUSIONS

It is apparent that the majority of these studies were concerned with the circulatory response to intensely exciting or even unnatural psychological stresses. Many of the stimuli used are rarely met in normal everyday life. However, they do indicate the possible magnitude of the response of the heart and other circulatory variables to non-exertional stress. It is of some importance therefore to determine the range of cardiovascular responses to situations commonly occurring in everyday life. Many people drive motor-cars, but few undertake to subtract 17 from 1194 every two seconds to a metronome, watched by aggressive medical staff. It is these considerations that prompted the following studies.

The following programme of investigation was therefore designed to measure the cardiovascular effects of some of the more stressful environmental situations normally encountered in everyday life in normal healthy subjects and in patients with ischaemic heart disease and to examine the role of sympathetic stimulation of the heart in these responses.

Two studies were therefore undertaken.

The first study was undertaken to determine the relative contribution of sympathetic stimulation of the heart to the tachycardias associated with the mental stress of motor-car driving, catecholamine infusion and walking. This study was also designed to give information regarding the magnitude and duration of the suppression of these tachycardias achieved

by the oral beta-receptor antagonist oxprenolol.

The second study was designed to investigate the magnitude of
the effects of some normal everyday environmental stresses on the
heart rate and the degree of modulation of these responses induced by
a similar degree of blockade of the heart rate beta-receptors as achieved
in the first study.

ETHICAL CONSIDERATIONS

The ethical aspects of these studies were given careful consideration
(Medical Research Council Annual Report, 1964; Ormrod, 1968). It
was inherent in the design of these studies that the majority were
carried out with inconspicuous electrocardiographic recordings
during each patient's normal everyday activities; invasive techniques
were not employed. A large number of clinical reports and general
clinical experience has shown the relative freedom from side effects
of the small doses of the beta-receptor antagonist oxprenolol used in
these studies. In Study 1 invasive techniques were used for the
isoprenaline infusion. In these studies the subjects were myself
or my hospital colleagues, all of whom fully understood the aims and
nature of the investigations and procedures involved.

STUDY 1

THE DIFFERENT EFFECTS OF ADRENERGIC BETA-RECEPTOR BLOCKADE ON THE HEART RATE RESPONSE TO MENTAL STRESS CATECHOLAMINES AND EXERCISE

INTRODUCTION

Emotional stress, catecholamines and physical exertion all induce an increase in heart rate. During recent studies of the effects of environmentally-induced psychological stress on the heart I noticed that small doses of the beta-receptor antagonist oxprenolol had a conspicuously greater effect on the tachycardia associated with mental stress than on the heart rate increase during walking. In view of the possible therapeutic implications of this observation the following study was designed to define more closely the quantitative relationship between the tachycardias due to these three stimuli in terms of their inhibition by beta-receptor antagonists.

METHOD

Subjects

Studies were made on six normal males aged 26 - 47 years. None had any symptoms of systemic disease and in all the blood pressure was within normal limits. I was one of the subjects; the remainder were professional colleagues who fully understood the aims and nature of the investigation.

Design of Study

Each subject was studied in three different test situations.

1. Driving a motor-car for 15 - 20 minutes in heavy city traffic.

2. In the supine position during a two-minute intravenous isoprenaline infusion sufficient to raise the heart rate to the levels observed during driving.

3. During treadmill walking of two minutes duration sufficient to raise the heart rate to similar levels.

Preliminary studies were carried out to familiarize each subject with the programme of investigation and determine the peak heart rate response regularly achieved by motor-car driving; the dose of intravenous isoprenaline and level of treadmill walking necessary to give a similar heart rate increase was then determined. Motor-car driving, carried out over a random route through Leeds city centre for 15 - 20 minutes repeatedly resulted in heart rate increments of 30 beats/min. or more in all subjects. The intravenous isoprenaline infusion rate necessary to induce a similar tachycardia varied between 3 - 7 ug/min. for two minutes in different subjects. A similar increase in heart rate was induced by treadmill walking at 3 m.p.h. on 10 - 15° incline for two minutes.

The definitive double-blind studies were commenced at 8.00. a.m. two hours after a light breakfast and one hour after a single oral tablet of 40 mg oxprenolol or matched placebo tablet. A control electrocardiogram was done with each subject sitting quietly at the wheel of his car. A 15 - 20 minute period of city driving was then

undertaken on a random route selected on an ongoing basis by an observer travelling as passenger. The subject than returned to the laboratory, and, after ten minutes rest, a two minute intravenous infusion of isoprenaline was given in a dose that had been determined beforehand would raise the heart rate in that subject by approximately 30 beats per minute. After a further ten minutes rest by which time the heart rate had returned to pre-isoprenaline infusion levels the treadmill exercise test was performed. Similar studies were repeated at 2, 4, 6, 8 and 12 hours. The programme was repeated three or four days later after placebo or oxprenolol.

Between the test periods each subject returned to his normal professional duties. No restriction was placed on their activities except that they were asked not to eat large meals or smoke within an hour of the subsequent test, as both have been shown to result in considerable increases in heart rate

Active and placebo tablets were coded in pairs for each subject. The heart rate was measured from an electrocardiographic record taken blind into a closed container during the final 10 seconds of every minute of the study, and counted and checked by two uninvolved colleagues.

Techniques, Measurements and Statistics

The heart rate was measured from the record made on a portable electrocardiograph (Cambridge Transrite Model 111). Values were averaged from the 15 - 20 one minute records taken during each driving period, averaged over the final ten seconds of the isoprenaline

infusion and during the final ten seconds of the second minute of treadmill exercise.

During the isoprenaline infusion and treadmill walking test the electrocardiogram was also displayed on an oscilloscope (S.E. Laboratories SEM 121).

Isoprenaline (Evans Medical Ltd) was given as a continuous intravenous infusion into a hand or arm vein via a subcutaneous needle by an electromechanical pump (Harvard Model 901) with a variation in rate of less than 2 per cent. The concentrations were arranged so that the volume of fluid infused was between 2 - 5 ml/min. Walking was carried out on a treadmill (Quinton Instruments Model 18-54) with which the subjects were familiar. Subjects drove their own motor-cars, with manual gearboxes. Speed limits were obeyed.

The variability of the response to the test situation was calculated in each subject from the placebo results as a percentage (SEM/Mean) and averaged for the group.

RESULTS

The effects of 40 mg oral oxprenolol compared to placebo on the heart rate response to motor-car driving, isoprenaline infusion and treadmill walking in six normal subjects is presented in the accompanying figure I and tables I, 2 and 3.

From the placebo results, the average variability about the mean increase in heart rate to driving, isoprenaline and exercise was 10 per cent (range 3.8 - 13.8), 3 per cent (range 3.1 - 3.9) and 3 per cent (range 3.0 - 3.4) respectively, Table 4. Compared to the

results with placebo, the tachycardia associated with motor-car driving and isoprenaline infusion was conspicuously reduced for up to 12 hours after 40 mg oral oxprenolol. In the same subjects, the drug had much less effect on the heart rate response to exercise.

DISCUSSION

These results clearly demonstrate the different effects of a similar degree of beta-receptor blockade on the increase in heart rate associated with mental stress and catecholamine infusion compared with the effect on a similar tachycardia induced by exercise. Although the mechanism by which mental stress induces an increase in heart rate is unknown, the similar suppression of the tachycardia associated with motor-car driving and that due to infused catechblamines by the same degree of beta-receptor blockade suggests that both tachycardias are probably induced by a similar increase in concentration of catecholamines at the cardiac beta-receptor sites controlling the heart rate. Although it does not necessarily follow that there is a similar increase in level of circulating catecholamines an increase in the concentration of plasma catecholamines has been observed in racing-car drivers in parallel with an increase in heart rate (Taggart et al, 1969). At extreme levels of exertion the increase in heart rate is predominantly due to direct sympathetic stimulation of the cardiac heart rate receptors; the adrenomedullary catecholamines appear to play little part in this response. But at the levels of exercise used in the present studies, with heart rates of 100 - 120 beats per minute, the tachycardia is due both to sympathetic stimulation and

vagal withdrawal (Donald and Shepherd, 1963; Robinson, 1966). In fact the results of the present studies indicate that the degree of direct sympathetic activity involved in the heart rate increase at this level of normal everyday exertion is probably small compared with the vagal withdrawal component. This is probably the most likely explanation for the different effects of small doses of beta-receptor antagonists on the heart rate response to the three stimuli observed in the present studies.

These findings have important clinical implications in the treatment of angina pectoris. One of the ideals of medical treatment is the establishment of a dose-response relationship, namely the administration of only sufficient drug as is necessary to achieve the desired effect. Although the mechanisms responsible for precipitating anginal pain in susceptible subjects are unknown (Robinson, 1971; Taylor, 1973), the onset of pain is closely correlated with an increase in heart rate (Robinson, 1971; Epstein et al, 1971; Taylor, 1973), whether this be induced by exercise or by the mentally stressful activities of everyday life. These results suggest that the dose of beta-receptor antagonist necessary to suppress the tachycardia in these different situations may differ widely. The single dose of propranolol oroxprenolol necessary to produce a near-maximum suppression of exercise tachycardia is 160 mg (Taylor et al, 1973). However, the maximum effectiveness of this dose in this respect is relatively short-lived and the majority of angina patients experience relief from exercise induced symptoms only with repeated daily doses of this order (Prichard and Gillam, 1971).

The present results suggest that anginal pain associated with anxiety or emotion may be controlled by much smaller doses of drug than those necessary to afford relief in exercise situation.

These studies were undertaken as an essential preliminary to the investigation of the cardiac response to everyday mental stress and its modulation by beta-receptor antagonists (Study II). The results indicate that the increase in the heart rate response to psychological stress may be largely suppressed throughout the waking hours by a dose of beta-receptor antagonist that has no detectable mental effects (Turner, 1972) and only small relatively short-lasting effects on the heart rate response to exercise.

SUMMARY

The magnitude and duration of effect of a single 40 mg oral tablet of oxprenolol on the tachycardias associated with motor-car driving, isoprenaline infusion and walking was measured in six normal subjects by a double-blind technique. The heart rate increase due to driving and isoprenaline was conspicuously reduced for more than 8 hours; the reduction in exercise tachycardia was substantially less. These results indicate that relatively small doses of beta-receptor antagonists will suppress the heart rate increase induced by mental stress and catecholamines with relatively little effect on the response to exercise. The clinical implications of these observations in the treatment of emotionally-induced anginal pain and their possible role in suppressing the tachycardia associated with psychological stress is discussed.
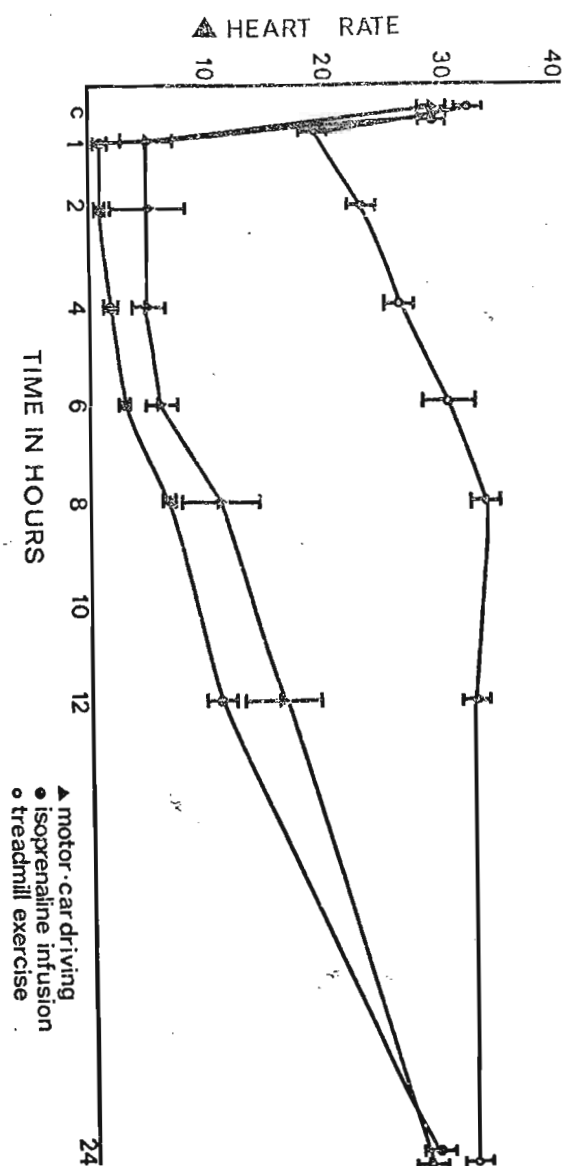
FIGURE 1

The effect of oral oxprenolol on the heart rate response to motor-car driving (▲); isoprenaline infusion (●) and treadmill walking (O) in six normal subjects.
40 mg oral oxprenolol was given immediately after the control study (C).
Data expressed as mean ± standard error of mean.

TABLE 1   INCREASE IN HEART RATE IN NORMAL SUBJECTS DURING MOTOR-CAR DRIVING IN CITY TRAFFIC

AND ITS MODULATION BY BETA-ADRENORECEPTOR BLOCKADE

SUBJECT	TEST	CONTROL [1]	TIME IN HOURS AFTER PLACEBO OR 40 mg OXPRENOLOL [2]						INCREMENT [3]
			1	2	4	6	8	12	
1	PLACEBO	69	24	24	20	28	30	28	26 ± 1
	OXPRENOLOL	60	9	7	7	3	6	10	–
2	PLACEBO	65	37	35	27	35	23	27	30 ± 4
	OXPRENOLOL	56	6	4	4	6	9	21	–
3	PLACEBO	71	29	23	29	41	26	39	31 ± 3
	OXPRENOLOL	66	3	4	4	5	16	24	–
4	PLACEBO	76	26	21	26	22	26	24	24 ± 1
	OXPRENOLOL	68	4	7	7	6	8	10	–
5	PLACEBO	70	36	38	20	31	23	28	29 ± 4
	OXPRENOLOL	66	7	5	5	6	14	20	–
6	PLACEBO	73	24	30	26	20	31	20	25 ± 3
	OXPRENOLOL	62	3	4	4	7	10	12	–
MEAN ± SEM	PLACEBO	71 ± 2	34 ± 3	29 ± 3	25 ± 2	30 ± 3	27 ± 2	28 ± 3	29 ± 1
	OXPRENOLOL	* 63 ± 2	5 ± 2	5 ± 3	5 ± 1	6 ± 1	11 ± 3	* 16 ± 3	–

[1] Heart rate during sitting period before test.

[2] Values relate to increases in heart rate over control values

[3] Average heart rate increment over control value (Mean ± SEM)

* p < 0.001 Significance of differences relate to comparison with placebo value.

TABLE 2 INCREASE IN HEART RATE IN NORMAL SUBJECTS DURING ISOPRENALINE INFUSION AND ITS MODULATION BY BETA-ADRENORECEPTOR BLOCKADE

SUBJECT	TEST	CONTROL[1]	TIME IN HOURS AFTER PLACEBO or 40 mg OXPRENOLOL[2]						INCREMENT[3]
			1	2	4	6	8	12	
1	PLACEBO	67	27	29	32	26	27	31	29 ± 1
	OXPRENOLOL	62	2	0	3	4	10	12	–
2	PLACEBO	64	34	34	30	31	29	33	32 ± 1
	OXPRENOLOL	58	0	0	2	1	6	8	–
3	PLACEBO	69	29	35	27	29	32	30	30 ± –
	OXPRENOLOL	61	0	1	0	2	8	11	–
4	PLACEBO	67	28	24	27	24	29	32	27 ± 1
	OXPRENOLOL	62	0	3	2	3	5	9	–
5	PLACEBO	71	32	35	30	28	27	30	30 ± 1
	OXPRENOLOL	65	1	1	2	3	3	10	–
6	PLACEBO	68	26	29	33	24	28	30	28 ± 1
	OXPRENOLOL	60	0	2	1	4	9	14	–
MEAN ± SEM	PLACEBO	68 ± 1	29 ± 1	31 ± 2	30 ± 1	27 ± 1	29 ± 1	32 ± 1	29 ± –
	OXPRENOLOL	* 61 ± 1	1 ± 0	1 ± 0	2 ± 0	3 ± 0	7 ± 1	* 11 ± 1	–

[1] Heart rate during control period lying supine before test

[2] Values relate to increases in heart rate over control values

[3] Heart rate increment over control value (Mean ± SEM)

* $p < 0.001$ Significance of differences relate to comparison with placebo value.

TABLE 3 INCREASE IN HEART RATE IN NORMAL SUBJECTS DURING TREADMILL WALKING AND ITS

MODULATION BY BETA-ADRENORECEPTOR BLOCKADE

SUBJECT	TEST	CONTROL[1]	TIME IN HOURS AFTER PLACEBO OR 40 mg OXPRENOLOL[2]						INCREMENT
			1	2	4	6	8	12	
1	PLACEBO	94	30	35	32	31	27	33	31 ± 1
	OXPRENOLOL	71	20	26	26	27	28	35	–
2	PLACEBO	92	29	28	32	34	35	31	32 ± 1
	OXPRENOLOL	72	15	22	30	36	33	32	–
3	PLACEBO	76	32	28	27	31	34	33	31 ± 1
	OXPRENOLOL	63	17	23	23	26	34	32	–
4	PLACEBO	88	34	31	33	30	35	29	32 ± 1
	OXPRENOLOL	76	23	22	26	31	37	31	–
5	PLACEBO	84	30	33	31	27	31	33	31 ± 1
	OXPRENOLOL	70	20	24	25	26	33	30	–
6	PLACEBO	87	34	31	30	35	28	32	32 ± 1
	OXPRENOLOL	74	21	23	25	31	34	30	–
MEAN ± SEM	PLACEBO	* 87 ± 3	32 ± 1	31 ± 1	* 31 ± 1	31 ± 1	32 ± 1	32 ± 1	32 ± 1
	OXPRENOLOL	71 ± 2	19 ± 1	23 ± 1	26 ± 1	30 ± 2	33 ± 1	32 ± 1	–

[1] Heart rate during control period standing still for two minutes before test

[2] Values relate to increases in heart rate over control values

[3] Heart rate increment over control value (Mean ± SEM)   * p < 0.001 Significance of differences relate to comparison with placebo value.

TABLE 4   VARIABILITY IN HEART RATE INCREMENT DURING MOTOR CAR DRIVING

ISOPRENALINE INFUSION AND TREADMILL WALKING

SUBJECT	Motor Car Driving	Isoprenaline Infusion	Treadmill Walking
1	3.8	3.4	3.2
2	13.3	3.1	3.4
3	9.7	3.3	3.2
4	4.2	3.9	3.1
5	13.8	3.3	3.2
6	12.0	3.6	3.0
Average	9.5	3.4	3.2

Variability calculated as $\dfrac{SEM}{Mean}$ x 100 of heart rate increments at 1, 2, 4, 6, 8, and 12

hours during placebo studies.

INTRODUCTION

Reports concerned with the measurement of some of the effects of emotional and environmental stress on the heart have already been reviewed. However, as pointed out in the introduction, the majority of these studies were concerned with the responses to stress that were often extreme and frequently unnatural in the context of everyday life. The present study was therefore designed with a different attitude, namely to examine the magnitude and duration of the effects of normal everyday stimuli on the heart.

METHODS

Subjects: The following groups of subjects were studied:

1. Normal Subjects:

These consisted of a group of eight healthy male subjects who were either business acquaintances and professional staff of the hospital. Their ages ranged between 26 - 56 years. None were obese or diabetic, systemic arterial blood pressure was normal in all, and none had any symptoms or signs of systemic disease.

2. Patients with Ischaemic Heart Disease

Studies were also made on twelve company directors and business executives suffering from proven ischaemic heart disease.

A) Six were suffering from exercise-induced angina pectoris.

Their ages ranged from 35 - 60 years. None of them were obese, hypertensive, diabetic or suffering from signs and symptoms of systemic disease.

The diagnosis of angina pectoris was based on the following criteria:

i) no electrocardiographic S-T segment depression at rest
but a depression of the J point of more than 0.1 mV during
exercise induced pain with a prompt return of the S-T
segment to the isoelectric line on stopping exercise (Fig 2)

ii) a left ventricular end-diastolic pressure of less than 12 mm
Hg at rest increasing to more than 25 mm Hg at the onset
of exercise.

B) Six had suffered a definite myocardial infarction between 6 and
12 months previously for which they had been admitted to the
Coronary Care Unit of Leeds General Infirmary. None of them
were obese, hypertensive, diabetic or suffering from signs of
systemic disease. Their ages ranged between 36 - 60 years.

The diagnosis of myocardial infarction was based on the following criteria:

i) electrocardiographic changes consisting of Q waves greater than
1 mm, S-T segment elevation and T wave inversion with
reciprocal changes in the opposite leads. The evolution
of the infarct followed the normal pattern of regression of
the S-T segment elevation with residual Q waves and T wave
inversion in these.

ii) Serum enzymes done serially over days 1, 2 and 3 showed
a raised level of at least two of them on the second day.
The serum glutamic oxalacetic transaminase, serum glutamic
pyruvic acid transaminase, creatinine phosphokinase and lactic
acid dehydrogenase were measured in the hospital chemical
pathology laboratory by autoanalyser methods. The normal

range of values for this laboratory is:

8 - 22 IU/L,

4 - 203 IU/L

less than 60 IU/L and

150 - 480 IU/L respectively.

3. Bus Drivers

Following the demonstration that motor-car driving induced substantial increases in the heart rate both during city and motorway driving, the study was extended to include observations on bus drivers. Two groups of experienced bus-drivers were studied:

A) Thirteen during long-distance travel. Their ages ranged between 30 - 58 years. They were of normal height and weight and none had signs or symptoms of any systemic disease.

B) Six during city bus-driving. Their ages ranged between 26 - 40 years and they were or normal height and weight. None of them had any signs or symptoms of systemic disease.

4. Two B.B.C. radio and television commentators and performers were studied; one during professional soccer matches and the other during variety programmes.

The radio and television commentator was a male aged 36 years, of normal height and weight and had no symptoms of systemic disease. He belonged to a regular sports programme and gave live commentaries frequently during the soccer season.

The radio and television performer was a male aged 48 years, of

normal height and weight with no symptoms or signs of systemic

disease. He has a regular "pop" music programme which is recorded

the day before the live transmission. The audience comprises of about

150 teenagers.

5. Four normal subjects who claimed that they were particularly

excited by watching horror, mystery, thriller and live boxing television

programmes were studied. Their ages ranged between 23 - 50 years.

None had any symptoms or signs of systemic disease and none were

obese, diabetic or suffering from systemic hypertension.

DESIGN OF INVESTIGATION

The measurement of cardiovascular responses to everyday stress imposes considerable technical restrictions and it is mandatory that they fulfil certain limiting criteria:

1. The measurements should be capable of detecting changes in those variables which directly reflect alterations in sympathetic influence on the circulation.

2. They should be capable of continuous, extended and repeated use.

3. They should be so unappreciated by the subject that they in no way interfere with his normal activities.

Furthermore, in order to describe the cardiac response to as full a spectrum of environmental and psychological stress as is usually met in everyday life it was considered that more valuable information would be obtained by studying the effects of stress on the heart serially in a group of subjects than the effects of different stresses in separate larger groups.

Normal subjects and patients with ischaemic heart disease were therefore studied serially under the following situations:

1. Motor-car driving on a motorway.

2. Motor-car driving in city traffic.

3. Motor-car passenger.

4. Rail passenger

5. Aircraft passenger

6. Spectator at football matches

7. Television viewing of comedy, drama and documentary film.

8.   Radio and Television commentators and performers.

9.   Bus drivers during long-distance journeys and during

      city driving.

The reasons for the choice of these situations were that the
psychological stress involved formed part of the subject's normal
everyday life-pattern and was unlikely to be accompanied by physical
exertion.   The studies were extended to include bus drivers, rail
and aircraft travel and radio commentators after the early results
had shown the conspicuous effects on heart rate of motor-car drivers
and passengers and radio and television viewing.

It was decided to study the effects of blockade of the heart rate
beta-receptors for two reasons:-

1) to assess how much of the tachycardia was due to a

     sympathetic stimulation;

2) to explore the possible therapeutic usefulness of these drugs

     in these situations.

The technical difficulties involved in measuring variables other
than the heart rate reliably and continuously in normal subjects and patients
with ischaemic heart disease have already been mentioned.   Similarly
there was considerable difficulty for logistic reasons in carrying out
a double-blind assessment in every instance.

Double-blind measurements would require continuous electro-
cardiographic recording over extended periods of time which was
impractical as there was no apparatus available capable of such recording
when the study commenced.   Therefore, the majority of this study
was of necessity single-blind as the observer recording the results

could detect the heart rate response of the subject. In order to eliminate the influence of suggestion one of the studies was carried out after the ingestion of an oxprenolol matched placebo tablet containing Sucrose, 192 mgs, Tricalcium Phosphate 14 mgs, Wheat Starch, 70.59 mgs, Bitrex perfume 0.01 mg, Magnesium Stearate 1.40 mg, Kallidon 25.8 mgs and Talc 14 mgs. The other study was carried out one hour after taking 40 mg oral oxprenolol. The order of administration of the tablets was randomised in pairs. However, a short double-blind study was initially carried out to examine any differences that may have been introduced by subject suggestion or observer bias.

In order to determine the circulatory response to environmental and psychological stresses during normal everyday activities, frequently over many hours, and serially on a number of occasions (e.g. during different modes of travel before and after beta-receptor antagonists) non-invasive extravascular methods were mandatory. Extravascular monitoring of the heart rate was the only method which would fulfil these criteria in intact man. The extravascular measurement of heart rate by radiotelemetry offers perhaps the optimum method in that the heart rate directly reflects the degree of sympathetic stimulation of the heart and by this method it can be measured continuously, repeatedly and for extended periods of time without physical appreciation by the subject under study. It has the added advantage that in these circumstances the heart rate is linearly related to the level of exogenously infused catecholamines

in individuals at rest (Wexler et al 1971; Majid et al 1973; Taylor et al 1973) and it also appears to be the predominant variable aggravating the symptoms of ischaemic heart disease (Robinson 1971; Taylor 1973). Repetative measurement of the blood pressure by sphygmomanometer was found to be impractical under many conditions and distracting to the subject under study; continuous measurement from indwelling arterial cannulae was similarly impractical for extended periods in the real-life situations envisaged. For these reasons heart rate alone was chosen to monitor the degree of cardiac sympathetic activity. This in no way detracts from the criticism that the measurement of changes in a single variable can do little more than indicate the direction of changes in sympathetic influence, that such measurements cannot be used to indicate either quantitative changes in sympathetic drive or to indicate the overall influence of such changes on the heart and vascular system. But the gain in the facility with which the measurements of heart rate can be made far outweigh the disadvantages of using more cumbersome and distracting methods.

TECHNIQUES

Heart rate was measured electrocardiographically by a radiotelemeter (Parks Electronics Laboratory, Beverton, Oregon, U.S.A.), (Figs 3 and 4).

The apparatus consisted of:-

1. Receiver (Model RD-27) - a small battery operated unit (26 x 16.5 x 10 cm) with a frequency matched to the transmitter and an output voltage of 1 to 5 millivolts, suitable for the input to a variety of E.C.G. recorders.

2. Transmitter (Model 27) - a frequency modulated transmitter

(16 x 9.4 x 4 cm) powered by two 9 volt transistor radio batteries.

The transmitter was attached to the subjects belt with two leads

to the chest electrodes; strapped in the vicinity of the right shoulder

so that its end was free and inconspicuous..

3. Ratemeter (Model 503 - E) - this was battery powered and was able

to operate either directly from the subject or from the telemetry

receiver.   The ratemeter and electrocardiograph could be used

on the receiver at the same time.   It has a 250 beats per minute

scale with an alarm signal and cumulative counter.

The telemetry system was able to operate satisfactorily with an outside

range of 100 to 200 yards but in buildings with steel mesh under the plaster

the range was severely restricted.   The battery life was about 16 hours.

The condition of the batteries was checked by the meter on the telemetry

receiver and the ratemeter.

The radiotelemeter system picked up potentials from the electrodes

and sent them by radio to the receiver for recording on the electro-

cardiograph or ratemeter.

Two bipolar silver chloride electrodes were used (Becton Dickinson

U.K. Limited) with the following specifications:-

Electrode-to-skin offset voltage as low as 300 microvolts with

an electrode to skin impedance as low as 100 ohms where

the epidermis was pricked.

The electrode lead cables were plugged into the transmitter.   The

electrodes consisted of a reservoir for the electrode paste;

Industrial Medical Instruments adhesive washers securely held electrodes to the skin. To make a firm contact the electrodes were applied to skin which had been shaved. One electrode was placed on top of the sternum and the second electrode below the left nipple, usually about 2 inches from the nipple both below and towards the anterior axillary line. The electrical resistance (measured by an ohmmeter) between two electrodes on the chest was ideally around 3000 ohms or lower. The resistance was lowered by abraiding the skin and rubbing a small amount of electrode paste into the skin at the contact point with a cotton-tipped applicator. Industrial Medical Instruments skin cleaner swabs were most efficient for preparing the skin for electrode sites. The swab was a combination of ingredients including isopropyl alcohol and skin emulsifiers absorbed into a mildly abrasive unit. The swabs had been specially formulated to:

1. remove all the insulating elements from the skin surface and

2. actually deposit a conductive film on the skin.

The heart rate was monitored continuously and plotted at 30 or 60 second intervals depending on the variation of the monitored changes observed. The fidelity of the apparatus was measured by recording directly from the transmitter and separately from an electrocardiograph machine. The fidelity was found to be absolute (Fig. 5).

A Philips School's 24" Television Receiver (Model No 8692) suitably modified to show video-taped programmes was used for the viewing of the comedy, drama and documentary films.

The Philips Type LDL 1000/00 video-machine used a $\frac{1}{2}$ inch video-tape (Philips VER 6 8945 002 06002) on a 6 inches diameter spool, which ran over one and a half hours.

REST
NO PAIN

J POINT

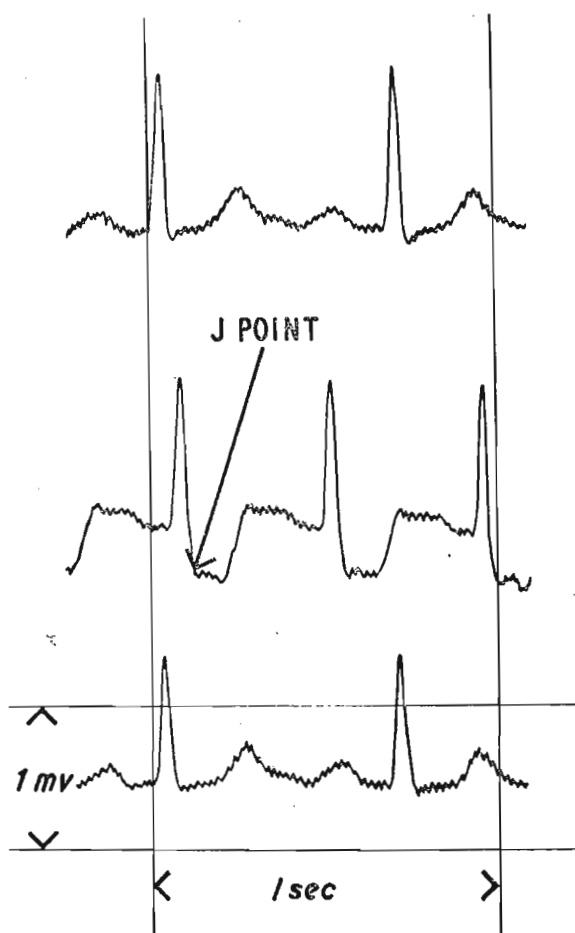WALKING
PAIN

RECOVERY
NO PAIN

1 mv

1 sec

FIGURE 2

Diagnostic changes in the exercise electrocardiogram in a patient with angina pectoris.

FIGURE 3

Photograph of the radiotelemeter apparatus. (Parks Electronics
Laboratory, Beverton, Oregon, U.S.A.)

1. Chest Electrodes 4. Receiver
2. Transmitter 5. Ratemeter
3. Antennae wire 6. Electrocardiograph Machine.
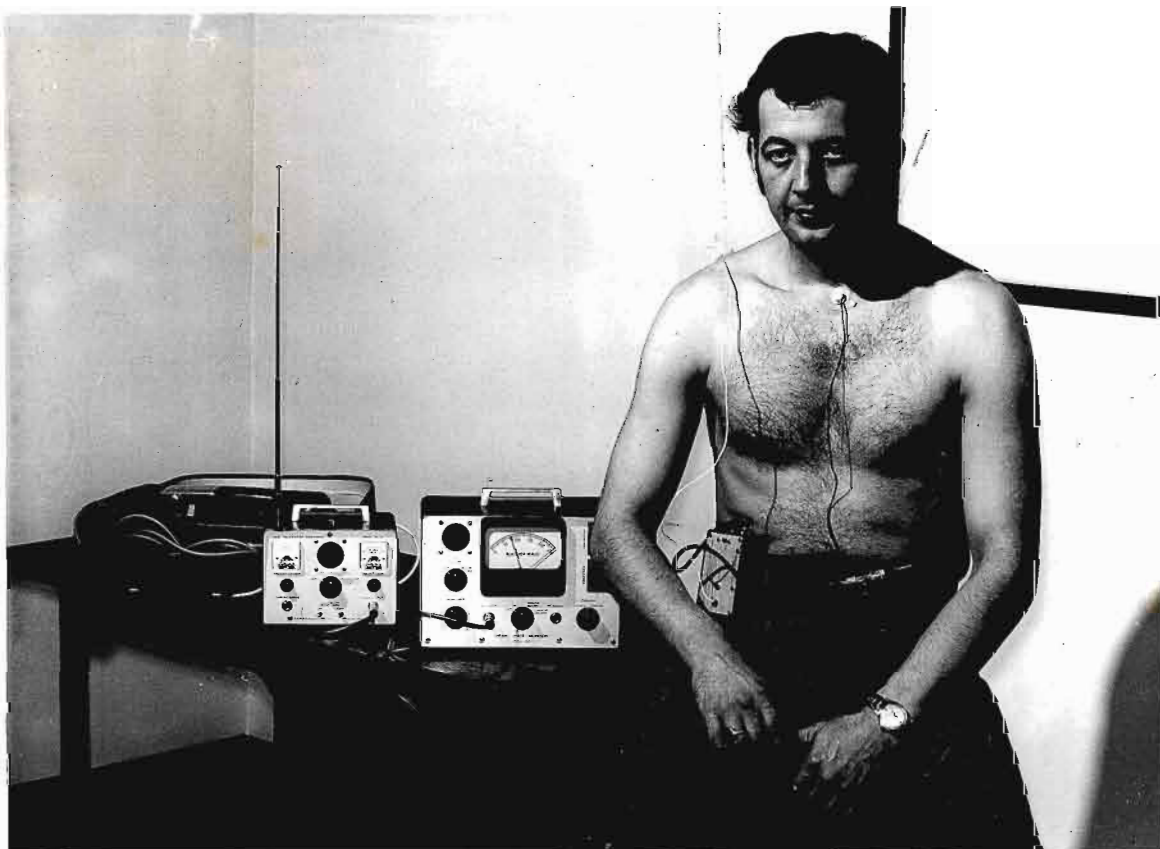
FIGURE 4

Photograph of one of the subjects connected to the radio–telemetry system.

1. Chest electrodes
2. Transmitter
3. Antennae wire.
4. Receiver
5. Ratemeter
6. Electrocardiograph machine.

MATCHED SEGMENTS OF ECG RECORDINGS TAKEN DIRECTLY
ON A MINGOGRAF 34 ECG MACHINE AND ECG SIGNALS
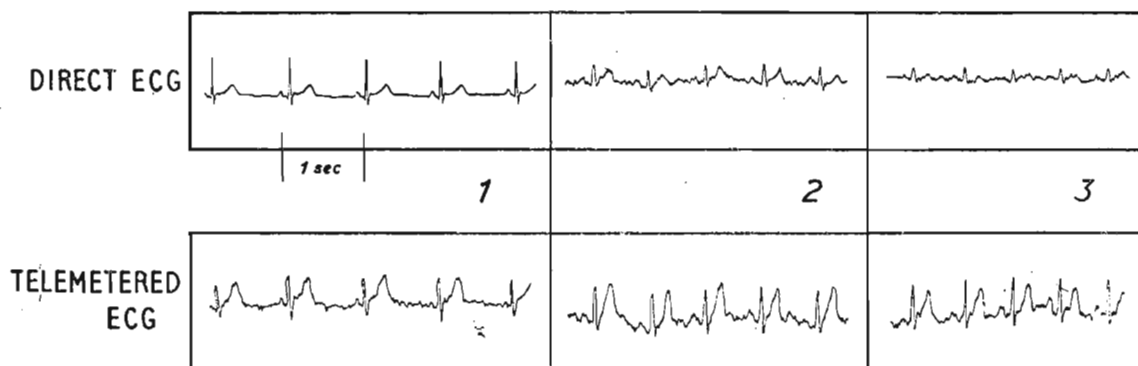FROM A TELEMETRY RECEIVER TO DEMONSTRATE FIDELITY.

FIGURE 5

Electrocardiographic record showing the ABSOLUTE fidelity
of the telemeter transmitter.

RESULTS

The results are discussed under the respective sections with a selection of illustrative figures and tables. The remainder of the individual figures of the results are included in the Appendix.

A summary of the results is included at the end of the chapter.

TRAVEL BY MOTOR-CAR

Motor-car journeys were made throughout the year under various weather conditions; these ranged from clear summer and spring days to dark, rainy, foggy days and with occasional winter snow and sleet. The majority of the studies were done between Leeds and London, a distance of approximately 200 miles on the M1 motorway. Other studies were carried out during driving on the A1 and A1/M1 trunk roads between Leeds and Newcastle (approximately 120 miles). All of these journeys were done as part of the normal everyday duties of the businessmen concerned. The journeys were done in normal saloon cars and one high powered coupe.

Studies of the effects on the heart rate of motor-car driving in city traffic were carried out in Leeds at times when traffic density was usually high, during the early morning (8 - 9. a.m.) and evening (5 - 6 p.m.) rush hours. Journeys lasted from 15 - 25 minutes.

In order to eliminate the influence of suggestion, the study was carried out in a single-blind fashion. One of the studies was carried out after the ingestion of an oxprenolol matched placebo tablet. The other study was carried out one hour after taking orally a 40 mg tablet of oxprenolol.

A) Motor-car drivers

1) Motorway driving

a) normal subjects - (Fig. 6 and 7; Table 5)

The heart rate was recorded during continuous driving in varied weather conditions from the centre of Leeds to the centre of London, (approximately 200 miles) or between Leeds and Newcastle (approximately

120 miles). Driving was commenced one hour after taking 40 mg

oxprenolol or a matched placebo tablet, the order of administration

being randomized in pairs. During control studies, i.e. after taking

the placebo tablet, the conspicuous peaks of heart rate were found to

be usually related to the usual motorway hazards, e.g.

    i) bunching of cars in the fast lane

    ii) overtaking or being overtaken without warning

    iii) sudden showers of rain

    iv) potentially hazardous moves by other drivers

    v) short bursts of high speed

    vi) driving through unexpected mist or fog patches

    vii) unexpected appearance of police vehicles

The ingestion of 40 mg oxprenolol taken one hour before a journey

carried out under similar conditions conspicuously reduced the peak

responses in heart rate observed in the placebo studies.

    b) <u>Patients with ischaemic heart disease</u> (Figs. 8 and 9; Table 6)

      A similar pattern of peaks of tachycardia was seen throughout

the journey undertaken after ingestion of placebo. The peaks of heart

rate observed in these patients were associated with similar travelling

events to those detailed for the normal subjects. Similarly these peaks

of tachycardia were completely suppressed after 40 mg oral oxprenolol

taken one hour after the start of the journey.

  2) <u>City Driving</u>

    a) <u>Normal Subjects</u> (Figs 10 and 11; Table 7)

      This commuter study was done in high density traffic in Leeds

city.   Significant peaks of tachycardia were seen with a high total
cumulative heart rate one hour after taking a placebo tablet.   The peaks
of tachycardia were related to the hazards that often occur during
driving in congested city traffic e.g.

i)   taking sudden avoidance action when pedestrians suddenly
step into the street.

ii)   trying to avoid the results of hazardous manoeuvres by other
drivers.

iii)   a potentially dangerous move by the driver himself

iv)   the frustration of driving behind a long queue especially
when late for an appointment

v)   the sudden changing of lights necessitating emergency
braking on the part of the driver.

The cumulative heart rate was reduced and the peaks of tachycardia
significantly reduced after 40 mg oral oxprenolol taken one hour before
the journey.

b)   Patients with ischaemic heart disease (Figs 12 and 13;   Table 8)

A similar pattern of peaks of tachycardia as were seen in
the normal subjects were observed in all patients after placebo.   These
peaks were associated with similar traffic events as were seen in
the normal subjects and were similarly suppressed after 40 mg oral
oxprenolol.

B)   Motor-car Passengers

a)   Normal Subjects   (Figs 14 and 15;   Table 9)

When the same normal subjects were travelling as motor-car

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passengers lesser levels of tachycardia and smaller peaks of heart rate responses were observed throughout the journey one hour after taking placebo. The basal level of heart rate was reduced and the peaks of tachycardia suppressed by 40 mg oral oxprenolol in all subjects.

b) <u>Patients with ischaemic heart disease</u>   (Figs 16 and 17; Table10):

The peaks of tachycardia in these patients were similar to those observed in the normal subjects after placebo.   Similarly 40 mg oral oxprenolol resulted in a significant reduction in these peaks of tachycardia.

TRAVEL BY TRAIN

These journeys were undertaken for routine business purposes to London by British Rail inter-city express. Journeys were undertaken throughout the year and the usual journey time was $2\frac{1}{2}$ - $3\frac{1}{2}$ hours. The heart rate response was recorded an hour after taking a 40 mg oxprenolol or a matched placebo tablet; the order of administration was randomized in pairs.

RAILWAY TRAIN PASSENGERS

a) Normal Subjects (Figs 18 and 19; Table 11)

The pattern of the heart rate response travelling by train was much more subdued with few peaks throughout the inter-city journey between Leeds and London as compared to that observed in the same normal subjects during motor-car travel on the motorway and commuter traffic. The basal heart rate was lowered by 40 mg oral oxprenolol taken one hour before the start of the journey, but the response to the drug was much less conspicuous than during motor-car travel.

b) Patients with ischaemic heart disease (Figs 20 and 21; Table 12)

The heart rate response during train travel after placebo was similar to that of the normal subjects. The heart rate response was subdued after 40 mg oral oxprenolol, taken one hour before commencement of the journey.

TRAVEL BY AIRCRAFT

Flights were made throughout the year and covered a wide range

of weather conditions. During the summer and spring, days were often

ideal for flying with a cloudless blue sky. But, during the autumn

and winter adverse conditions were often met with thick fog, low clouds

and the aircraft frequently had to fly entirely by instruments and make

blind landing approaches. Frequently the cloud base extended from

2000 ft to 12000 ft so that the whole journey involved blind flying in

turbulent conditions. Two types of aircraft were used for these journeys.

Vickers Viscount turbopropeller aircraft with 73 seats and Hawker-

Siddeley Trident jet aircraft with 123 seats both run by North-East

Airlines. The turbopropeller aircraft journey from Leeds to London,

an approximate distance of 200 miles, was usually flown in the routine

aircraft corridor at an altitude of 12000 feet and speed of 300 m.p.h. with

a flight time of approximately 55 minutes. The jet journey was from

Newcastle to London, a distance of approximately 330 miles and was

flown at an altitude of 29000 feet at 600 m.p.h. with a usual flight time

of 40 minutes.

It was not possible to use a double-blind method of study for two

reasons. The 12 hour duration of the anti-stress effects of oxprenolol

determined from the previous study precluded a study based on a single

return flight. And the costs involved ruled out two separate return flights

in each individual (with an observer). A single blind study was

used in preference to open trial to obviate the effects of subject

suggestion. However, one patient, who suffered a myocardial infarction

six months prior to the study, was given an oxprenolol matched

placebo tablet on both the outward and return journey on the turbo-propeller flight (Fig. 22).

The first study was carried out on the outward journey one hour after the ingestion of placebo.   The return flight was carried out one hour after taking a 40 mg tablet of oral oxprenolol.

1) Leeds - London by Viscount Turbopropellor aircraft

   a) Normal Subjects (Figs 23 and 24;   Table 13)

      Travel by these aircraft from Leeds to London after placebo was associated with conspicuous peaks of tachycardia throughout the flight but particularly during:

         i)   take-off and landing

         ii) during air turbulance

         iii) in response to unusual noises

         iv) attitude of the aircraft

         v)   hazard warnings by the captain or crew

         vi) captain's announcements of diversions of the aircraft to another airport.

   After 40 mg oral oxprenolol taken one hour before the return flight the peaks and cumulative heart rate were much reduced despite similar test conditions.

   b) Patients with ischaemic heart disease (Figs. 25 and 26;   Table 14)

      These subjects showed a similar response to that observed in normal subjects;   the peaks of tachycardia observed during the placebo test were conspicuously reduced after 40 mg oral oxprenolol, despite the very similar test situation.

2) Newcastle-London by Trident Jet aircraft

   a) Normal Subjects (Figs 27 and 28, Table 15);

   Travel by jet aircraft from Newcastle to London after placebo
showed conspicuous peaks of tachycardia throughout the flight and in
particular during take-off, landing and during adverse flying conditions
similar to those experienced during the flights by turbopropeller aircraft.

   40 mg oral oxprenolol taken one hour before the return flight
abolished the peaks of tachycardia and decreased the total cumulative
heart rate.

   b) Patients with ischaemic heart disease (Figs 29 and 30; Table 16);

   These subjects showed a similar response to the normal subjects
and the peaks of tachycardia were completely suppressed on the return
flight one hour after 40 mg oral oxprenolol.   The total cumulative
heart beats were also decreased.

SPECTATOR VIEWING

Live viewing at Football Matches

This was a study of the heart rate response of spectators during live football matches. These matches were played in different and varying weather conditions either on a Wednesday evening or a Saturday afternoon, and involved First Division matches with Leeds United's first team. The subjects studied were all interested in football and the local Leeds United team in particular. Some of the studies were done an hour after the ingestion of an oxprenolol matched placebo tablet and the other study an hour after the ingestion of 40 mg oral oxprenolol; the order of taking the tablets being reversed in pairs, in randomised order. In other studies 40 mg oral oxprenolol was ingested after the first 30 minutes of the match and the effects on the heart rate was monitored throughout the subsequent 60 minutes. The resting heart rates were taken over a 15 minute period before the start of the match with the subject sitting quietly reviewing the programme.

a) Normal subjects

Watching soccer matches one hour after the ingestion of an oxprenolol matched placebo tablet as spectators (Figs 31 and 32, Table 17) was often associated with conspicuous peaks of tachycardia. These were associated with:

   i) goal scoring

  ii) near misses

 iii) fouls on home-side players

or iv) misinterpreted decisions by the referee.

40 mg oxprenolol taken orally one hour before the start of a soccer match completely suppressed the peaks of tachycardia and the total cumulative

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heart beats. The action of onset of 40 mg oral oxprenolol taken 30 minutes after the commencement of the match can be seen in Fig. 35 during passive soccer viewing. The suppression of the peaks of tachycardia could be seen 30 minutes after ingestion of 40 mg oral oxprenolol.

b) Patients with ischaemic heart disease

The heart rate response during passive spectator viewing (Figs 37 and 38 Table 18) was similar to the normal subjects both after the ingestion of the placebo tablet and after 40 mg oral oxprenolol.

Television viewing of Football Matches

The television viewing soccer programme involved watching B.B.C.'s live transmission of national or international soccer matches. 40 mg oral oxprenolol was given after the first 30 minutes of the game.

a) Normal Subjects

Watching soccer matches during live television transmission was associated with conspicuous peaks of tachycardia (Figs 33 and 34). The suppression of the peaks of tachycardia could be seen 30 minutes after the ingestion of 40 mg oral oxprenolol (Fig. 36.)

Passive viewing of soccer matches was associated with a greater tachycardia than watching live television transmission.

b) Patients with ischaemic heart disease

The heart rate response during live television transmission was similar to the normal subjects before and after the ingestion of 40 mg oral oxprenolol (Figs 39 and 40).

These illustrations of the individual responses were consistent for all subjects studied whether normal or patients with known ischaemic heart disease. The response to 40 mg oral oxprenolol was equally consistent in all individuals in all situations.

TELEVISION VIEWING

Normal subjects and patients with ischaemic heart disease
were shown videotaped films of a Drama, Comedy or Documentary
on each of successive two evenings in randomized order during
the normal viewing hours after 6.00. p.m.   None of the subjects
had seen the programme before, neither were they aware that
these were videotaped series.   One of the programmes was
seen an hour after the ingestion of an oxprenolol matched placebo
tablet and a similar programme of the same series was seen an
hour after 40 mg oral oxprenolol;   the order being randomly
varied.

The Drama series consisted of an hour's viewing of the
tragic and suspense ridden "Scales of Justice".   The series
were re-enactments of true crimes;   of the trial that followed
and of the passing of the sentence which was suspect in a lot
of cases.   The subjects reported feelings of anger, agitation
and excitement throughout the performance.

The stimulus chosen for the Comedy series was the pleasant
and charming comedy of "Doctor in the House".   This was a series
of 30 minutes of hilarious comedy depicting the mischief and
the trials and tribulations of a group of hospital interns under a
dominating consultant.   There was much laughter and the subjects
reported being very amused.

The Documentary series was a programme of 25 minutes on the

war in Vietnam. During watching the subjects reported anger
and concern for the casualties of the war.

Resting heart rates were taken over 10 minutes prior to
the start of the programme with the subject sitting quietly in a
comfortable chair.

a) Normal Subjects (Figs 41, 42 and 43; Table 19).

Watching videotaped programmes of Drama, Comedy or
Documentary on television during the normal viewing hours at
6.00. p.m. produced conspicuous peaks of tachycardia one hour
after the ingestion of an oxprenolol matched placebo tablet.
The least degree of tachycardia occurred while watching documentary
programmes. 40 mg oral oxprenolol taken one hour before the
programme suppressed the peaks of tachycardia and substantially
lowered the cumulative heart rate.

Subjects sensitive to either thriller, horror or live boxing
films monitored in their own homes exhibited high peaks of
tachycardia one hour after the ingestion of placebo. Three of
the four subjects became very tense and anxious, complained of
palpitations and switched off their television sets. 40 mg oral
oxprenolol taken one hour before a similar programme by the
subjects suppressed the peaks of tachycardia and decreased the
total cumulative heart rate (Figs. 44, 45 and 46.)

b) Patients with ischaemic heart disease (Figs 47, 48 and 49; Table 20)

These subjects showed a similar heart rate response as the
normal subjects. Some of the patients with angina pectoris

complained of retrosternal discomfort during exciting moments in the televised programmes after taking the placebo tablet; this sensation did not occur after taking 40 mg oral oxprenolol one hour prior to the start of viewing.

RADIO AND TELEVISION COMMENTATORS
AND PERFORMERS

The emotional reactions of radio and television commentators reporting live sports events followed the natural swings in the excitement of the game.   A greater degree of "emotional stress" was involved in a radio and television personality involved in the popular "Top of the Pops" teenage "pop" music show, shown on B.B.C. television on Thursday nights.

The heart rate response was studied one hour after taking an oxprenolol matched placebo tablet, and one hour after taking 40 mg oral oxprenolol before the start of the programme on separate occasions.   The television personality study on the "pop" music show was repeated on another occasion without the ingestion of any tablets.   Resting hearts were taken over 15 minutes an hour prior to the start of the programme.

Conspicuous tachycardia with high peak heart rates occurred throughout the commentary and performance of the radio and television personalities after the placebo tablet and also without the ingestion of any tablets in the "pop" music artist.   This was accompanied with a high basal cumulative heart rate.   One hour following the ingestion of 40 mg oral oxprenolol the tachycardia and peak heart rates were significantly reduced with a low basal cumulative heart rate.   There was no apparent adverse effect on their individual performances. (Figs 50, 51 and 52;   Table 21).

BUS DRIVERS

<u>Long Distance Driving</u> (Figs 53, 54 and 55, Table 22).

Experienced long distance bus drivers were studied during

the summer when good weather conditions usually prevailed and

the roads were congested with holiday traffic.   These trips

involved journeys of between 130 - 480 miles and the buses

conveyed holiday makers to their respective destinations.

Driving was confined predominantly to the towns with short

motorway runs.

In order to obviate the effects of suggestion this study was done

one hour after the taking of a placebo tablet.   Oral oxprenolol

was not given to these drivers.

This is the record of almost continuous driving mainly

confined to towns with short motorway runs.   The pattern of

heart rate changes in these experienced bus drivers is similar

to that of motor car drivers in similar circumstances.

Significant peaks of tachycardia are seen throughout the journey;

especially through towns and during hazardous motorway and poor

weather conditions.

<u>City Driving</u>   (Figs 56, 57 and 58, Table 23).

This study was confined to drivers, experienced in driving in

London, on their own familiar bus routes.   The study was under-

taken during the summer;   traffic conditions in London are poor

with overcrowded roads and pedestrian hazards.   The heart

rate response is shown by continuous tachycardia and high peak

rates, entirely correlated to the hazards of city driving,

throughout the journey.
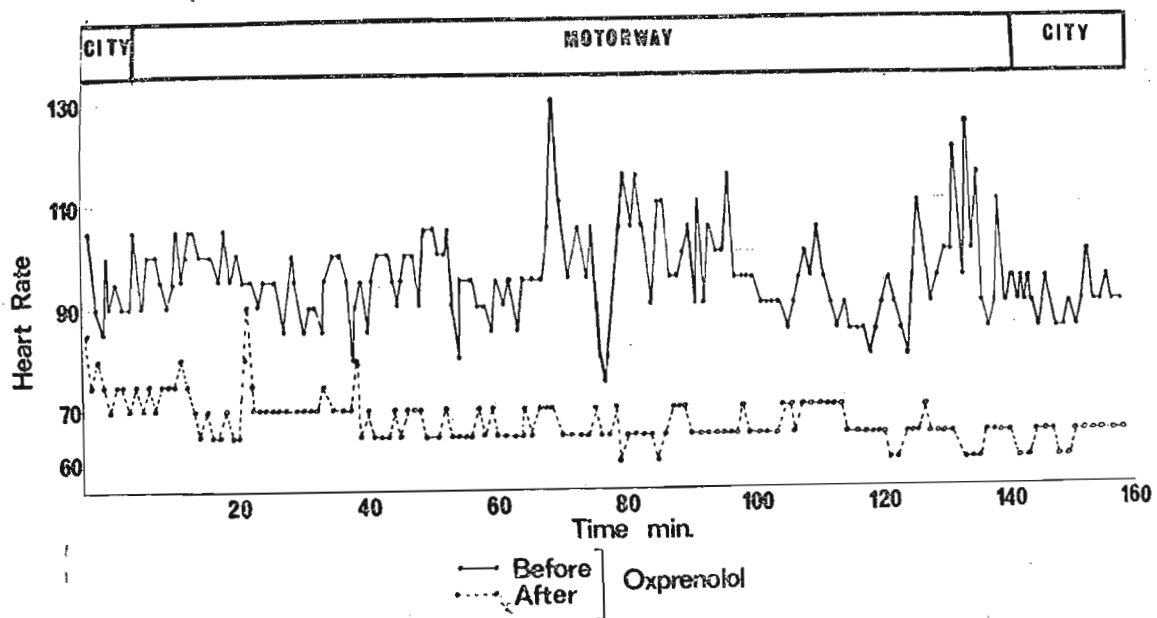
FIGURE 6

Records of the heart rate in a normal subject driving a motor-car between Leeds and London before and after 40 mg oral oxprenolol
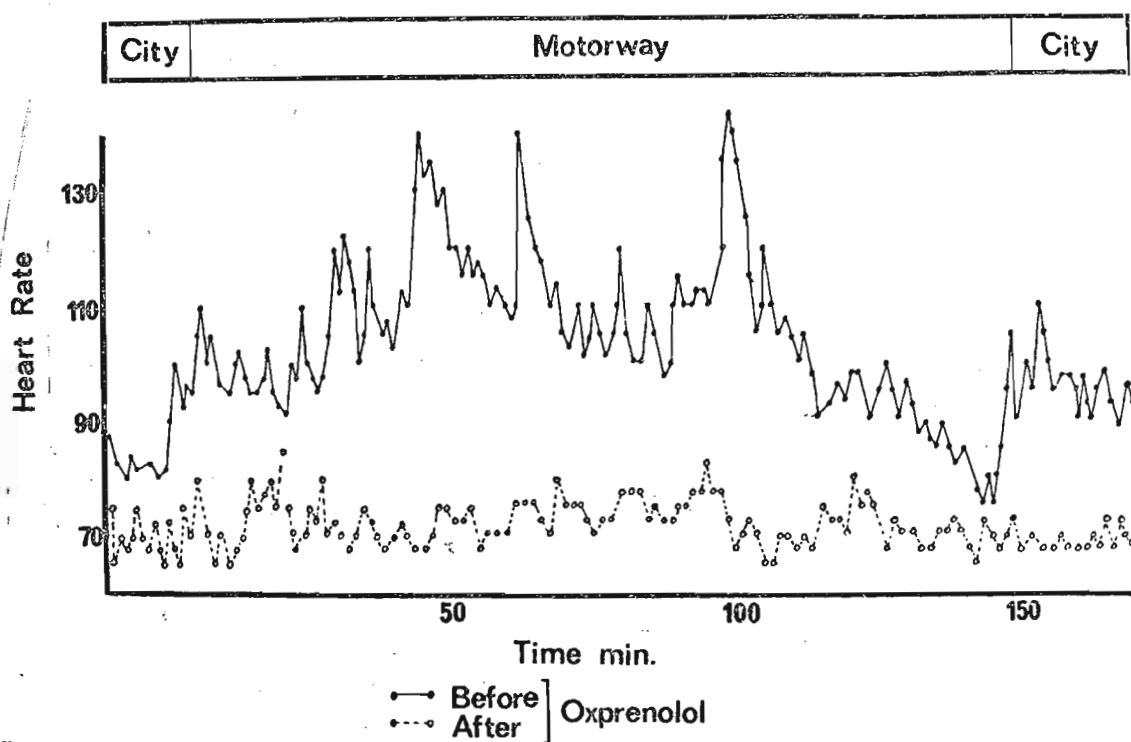
FIGURE 7

Record of the heart rate in a normal subject driving a motor-
car between Leeds and London before and after 40 mg oral oxprenolol.

TABLE 5 HEART RATE RESPONSE OF NORMAL MOTORWAY DRIVERS AND ITS MODIFICATION BY ORAL OXPRENOLOL

| Subjects | Control Heart Rate [1] per minute | | Peak Heart Rate [2] | | Cumulative Heart Rate [3] | | | |
| | | | | | Total Heart Rate | | Heart Rate per minute | |
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
SHT	70	65	130	80	18200	12281	83	59
MKM	70	65	130	85	17200	11624	108	73
MP	80	70	130	80	18380	15400	92	77
AF	70	60	100	75	14080	12100	69	59
PH	70	60	140	70	16630	11009	83	55
CNR	85	65	130	90	19510	13220	98	66
GAP	80	70	140	80	17384	14800	87	74
GHK	75	66	130	80	23760	15465	107	70
MEAN	75	66	129	80	18143	13237	91	67
SEM ±	± 2	± 1	± 4	± 2	± 980	± 625	± 5	± 3

1. Heart rate during control period sitting still before test

2. Values relate to the maximal heart rate during the trip

3. The total heart rate over the journey.
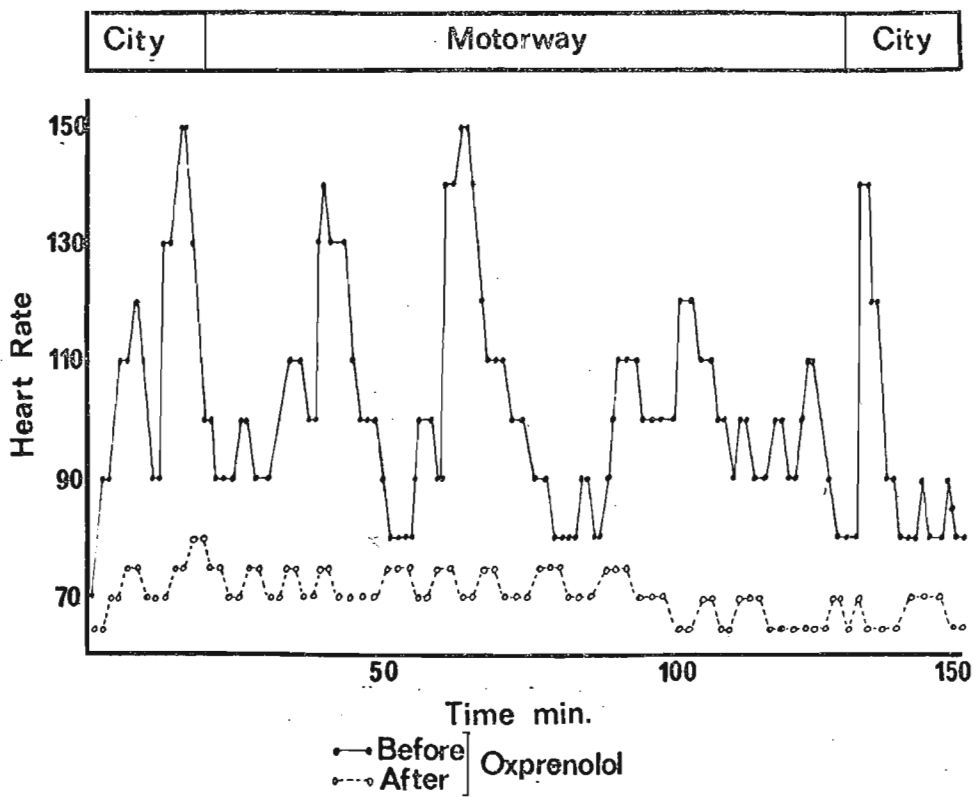
FIGURE 8

Record of the heart rate in a patient with ischaemic heart
disease driving a motor-car between Leeds and London before
and after 40 mg oral oxprenolol.
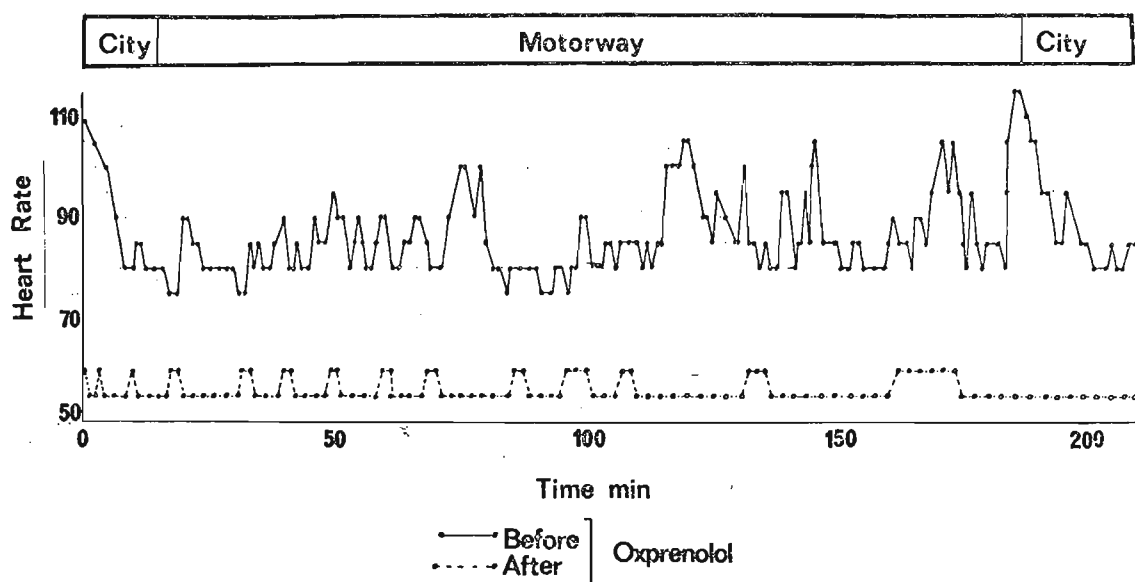
FIGURE   9

Record of the heart rate in a patient with ischaemic
heart disease driving a motor-car between Leeds and London
before and after 40 mg oral oxprenolol.

TABLE 6 HEART RATE RESPONSE OF DRIVERS WITH ISCHAEMIC HEART DISEASE AND ITS MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate[1]		Peak Heart Rate[2]		Cumulative Heart Rate[3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
JR	85	75	110	85	18981	15190	105	84
LG	80	60	145	85	17387	12887	102	76
AS	75	70	140	80	17200	12282	78	56
SB	70	65	150	80	14100	9975	94	67
JM	75	65	135	85	18648	13296	93	66
SDS	65	60	90	80	10948	9200	78	68
JB	75	55	115	60	16586	10694	83	53
DM	80	60	120	90	14675	10071	113	77
McCaa	75	60	105	70	21333	12933	85	54
GA	60	55	100	65	10625	7121	89	59
MEAN	74	63	121	78	16048	11365	92	66
SEM ±	± 2	± 2	± 6	± 3	± 1094	± 751	± 4	± 3

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.
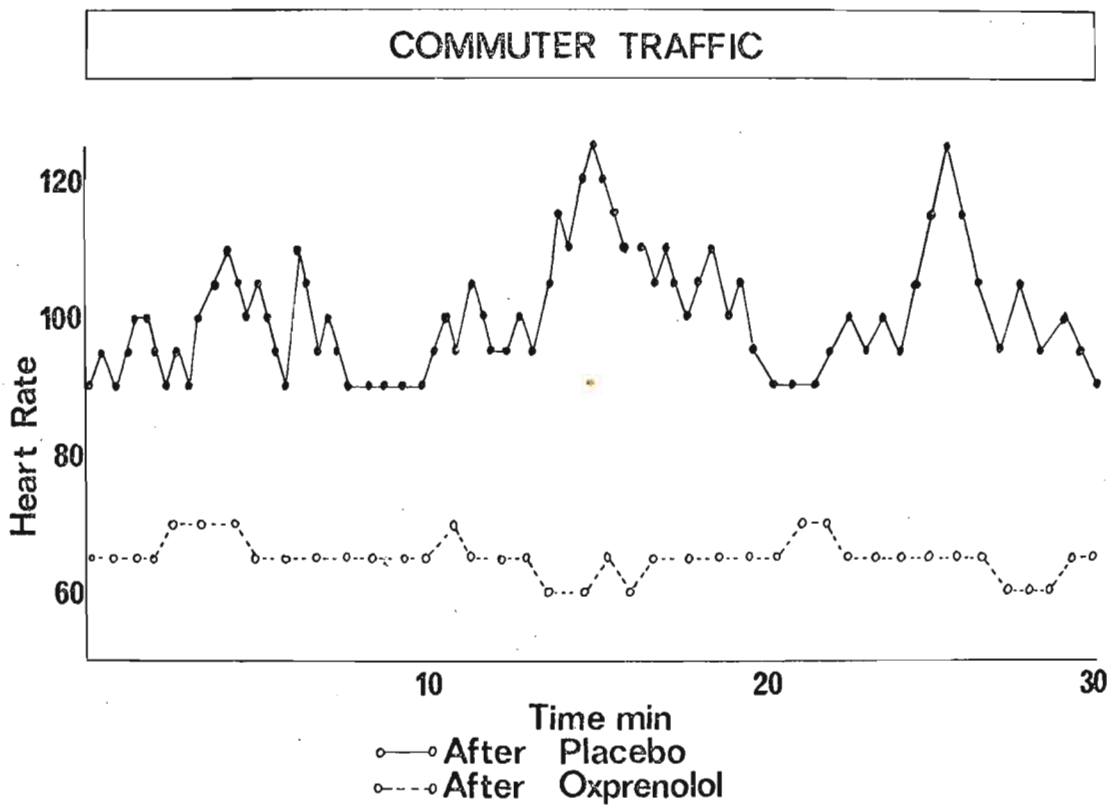
FIGURE 10

Record of the heart rate during city driving in a
normal subject before and after 40 mg oral oxprenolol.
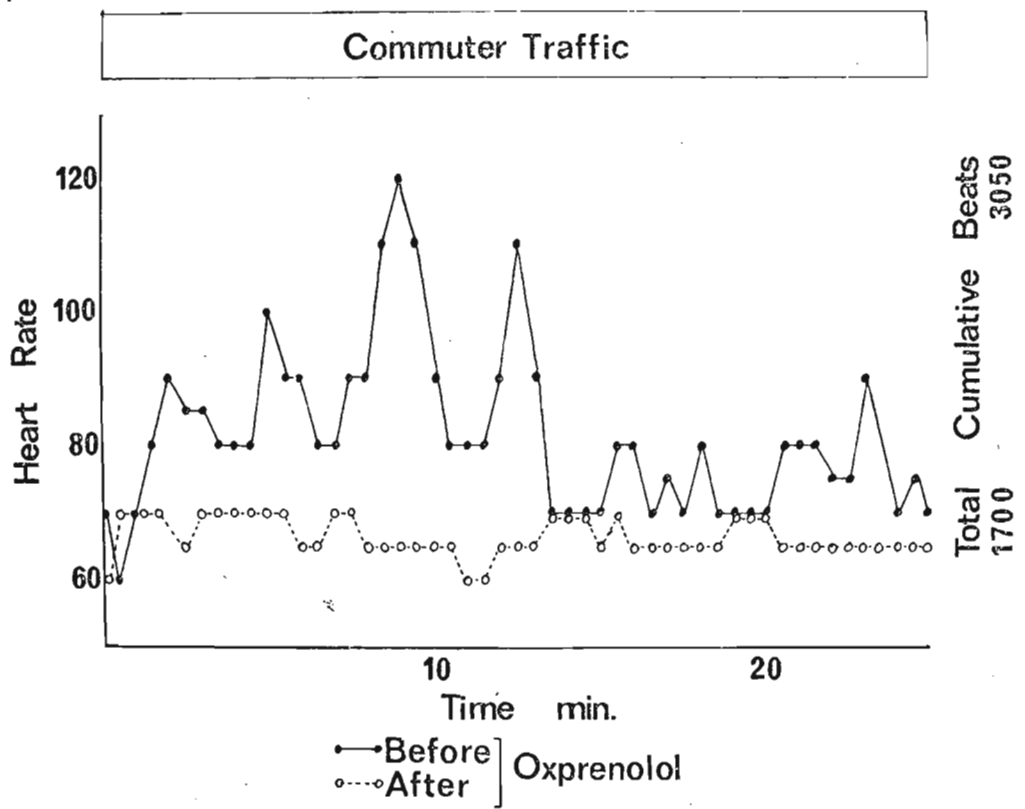
FIGURE 11

Record of the heart rate during city driving in a
normal subject before and after 40 mg oral oxprenolol.

TABLE 7 HEART RATE RESPONSE OF NORMAL CITY DRIVERS AND ITS MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate[1] per minute		Peak Heart Rate[2]		Cumulative Heart Rate[3] Total Heart Rate		Heart rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Before	After	Before	After
SHT	70	65	105	75	1575	1005	79	51
MKM	70	65	100	75	1615	1230	81	62
MP	80	60	120	65	2375	1445	95	58
AF	65	60	125	65	1995	1275	80	51
PH	72	60	125	70	3050	1700	122	68
GHK	80	70	120	80	3029	2250	101	75
MEAN	73	63	116	72	2273	1484	93	61
SEM ±	± 2	± 2	± 4	± 2	± 270	± 180	± 7	± 4

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.

COMMUTER TRAFFIC


Time min
o———o After Placebo
o----o After Oxprenolol
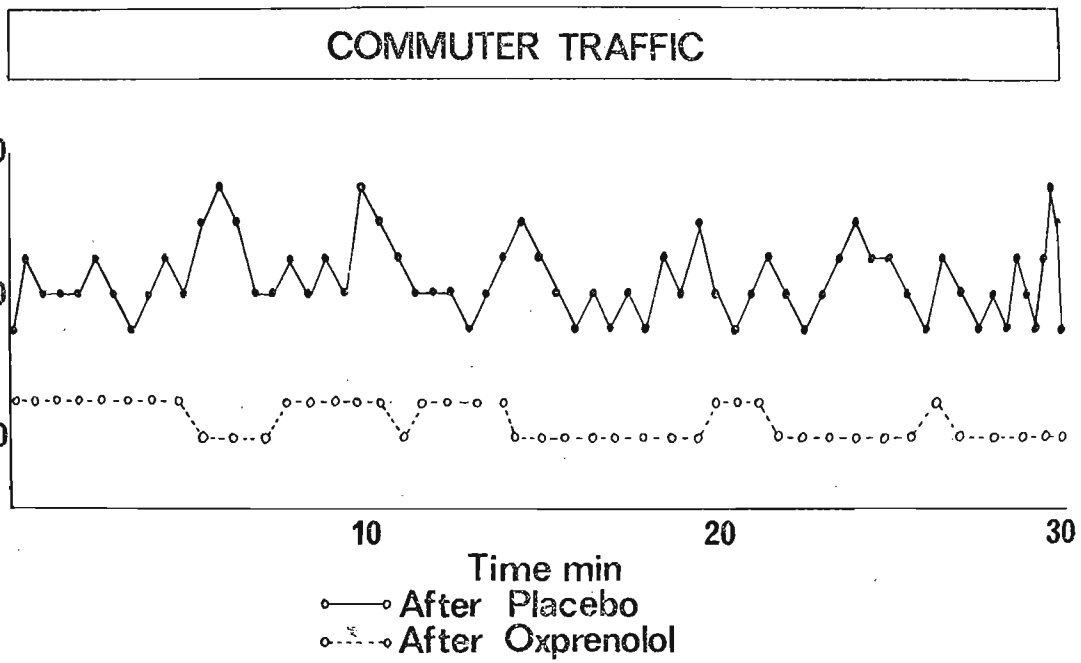
FIGURE 12

Record of heart rate during city driving in a
patient with ischaemic heart disease before and after
40 mg oral oxprenolol.
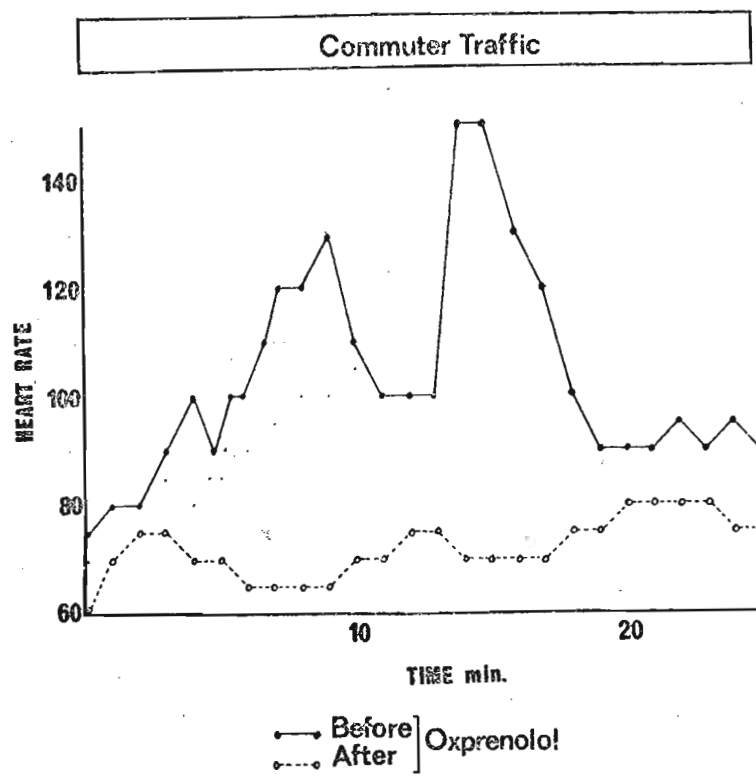
FIGURE 13

Record of heart rate during city driving in a patient with ischaemic heart disease before and after 40 mg oral oxprenolol.

TABLE 8   HEART RATE RESPONSE OF CITY DRIVING IN PATIENTS WITH ISCHAEMIC HEART DISEASE AND ITS

MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate[1] per minute		Peak Heart Rate[2]		Cumulative Heart Rate[3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
JR	70	65	130	75	2775	2110	93	70
LG	80	60	120	80	2355	1560	94	62
AS	70	60	120	70	8027	1832	101	61
SB	75	60	150	80	2740	1940	110	78
JM	80	70	120	75	4885	2740	122	69
DM	75	70	105	75	4045	2560	101	64
McCaa	75	70	125	80	3227	1941	108	65
GA	70	65	120	70	3107	1840	104	61
MEAN	74	65	124	76	3270	2065	104	66
SEM ±	± 1	± 2	± 5	± 1	± 288	± 140	± 3	± 2

1. Heart rate during control period sitting still before test.
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.
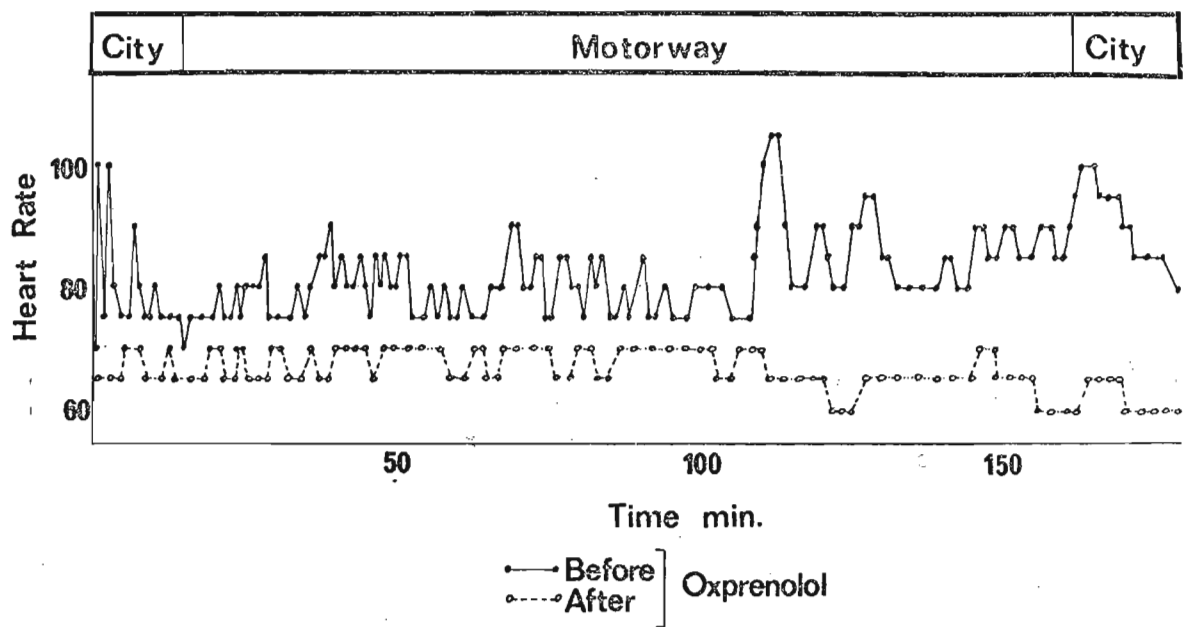
FIGURE 14

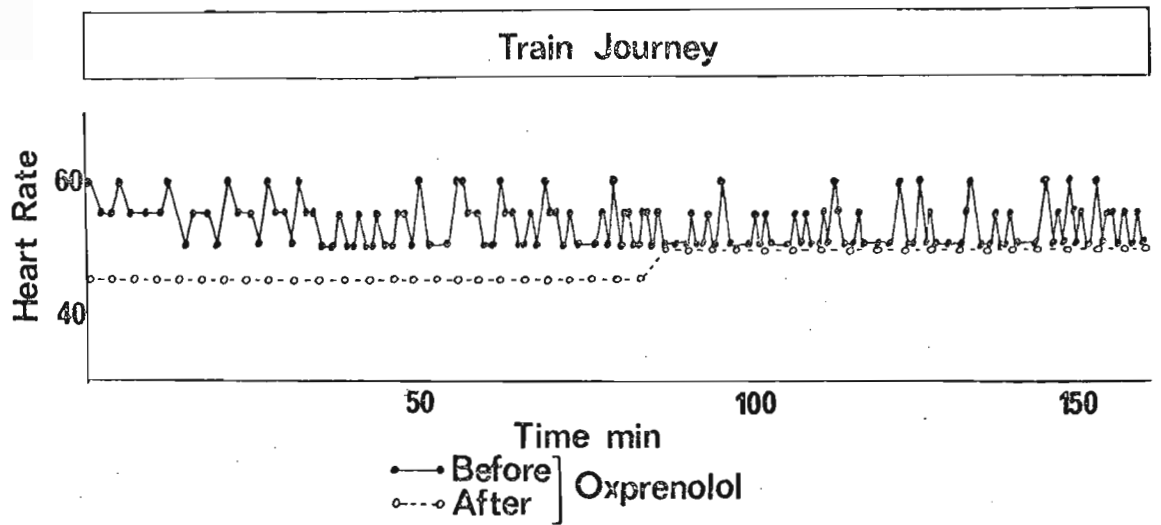Record of the heart rate in a normal motor car passenger between Leeds and London during placebo and after 40 mg oral oxprenolol.
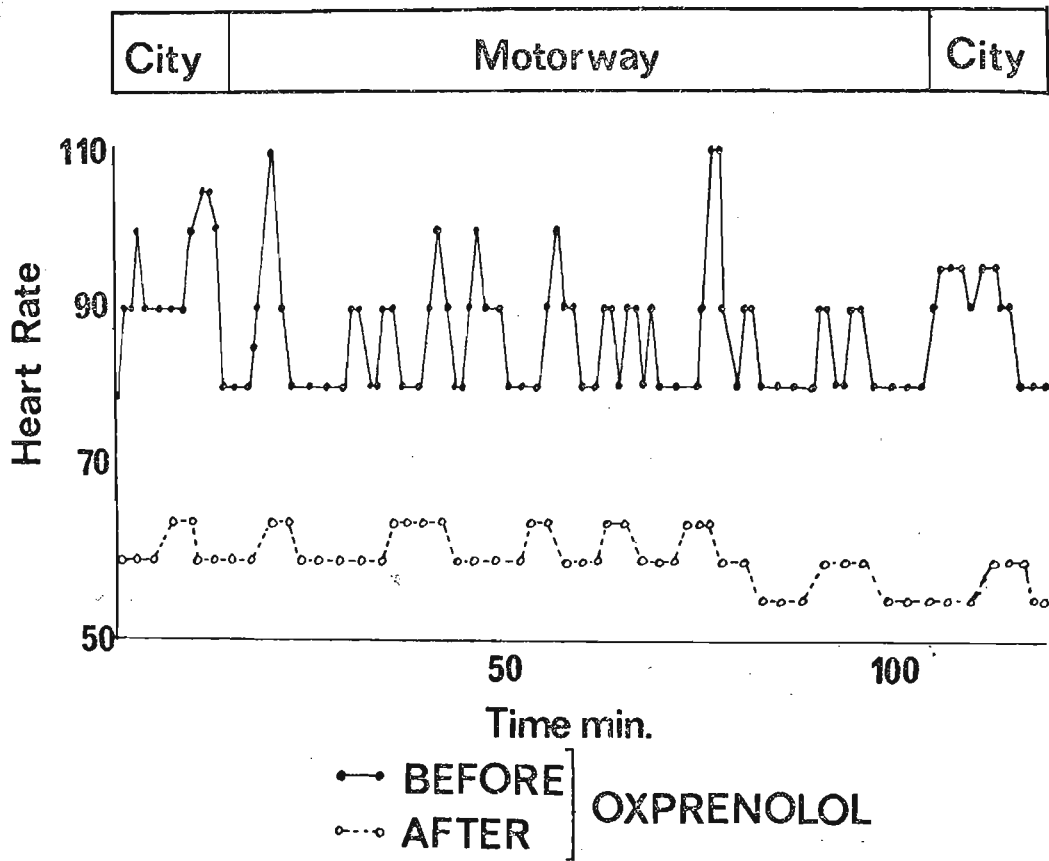
FIGURE 15

Record of heart rate in a normal motor-car passenger between Leeds and London during placebo and after 40 mg oral oxprenolol.

TABLE 9   HEART RATE RESPONSE OF NORMAL MOTOR CAR PASSENGERS DURING MOTORWAY DRIVING AND

ITS MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate [1]		Peak Heart Rate [2]		Cumulative Heart Rate [3]		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
SHT	70	60	90	75	23926	22271	68	64
HT	60	55	90	60	13506	10189	75	57
MKM	60	55	100	70	11007	7880	73	53
MP	80	60	110	65	10210	6970	85	58
PH	70	60	105	70	13290	8898	83	56
GAP	80	60	90	70	17080	12760	71	53
GHK	80	60	110	65	10210	6970	85	58
MEAN	71	59	99	68	14176	10848	77	57
SEM ±	± 3	± 1	± 4	± 2	± 1866	± 2054	± 3	± 1

1. Heart rate during control period sitting still before test.
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.
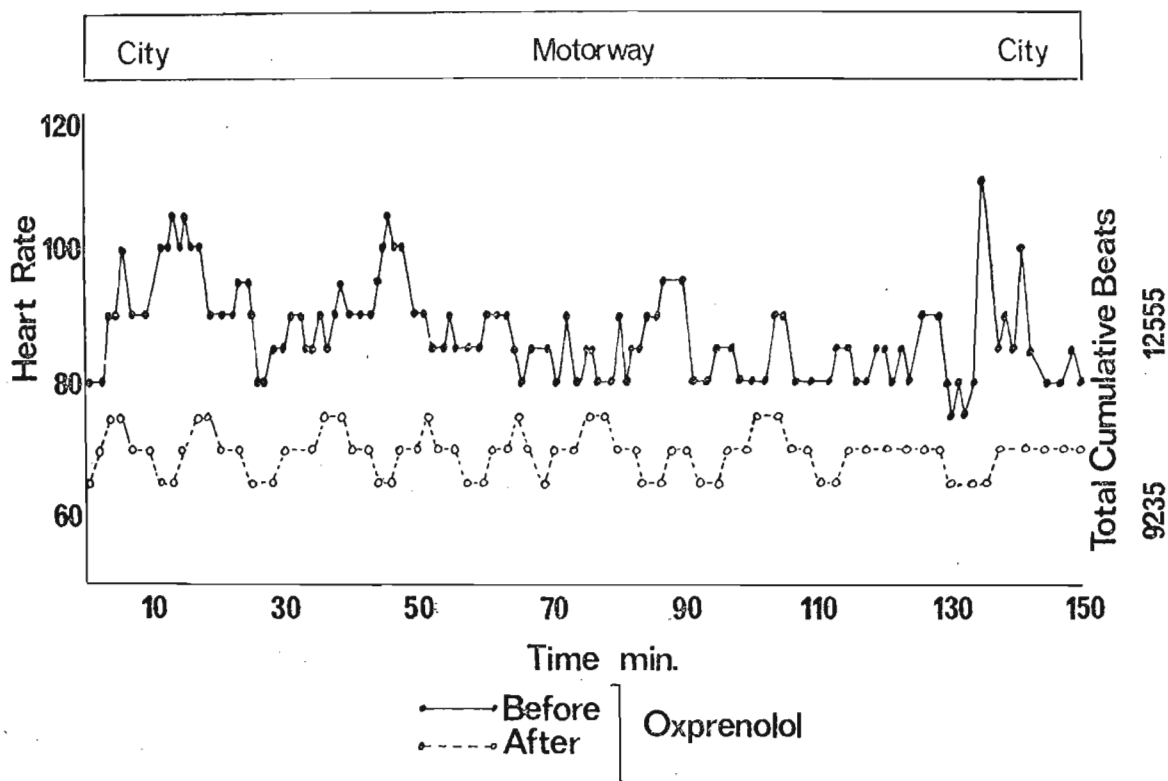
FIGURE 16

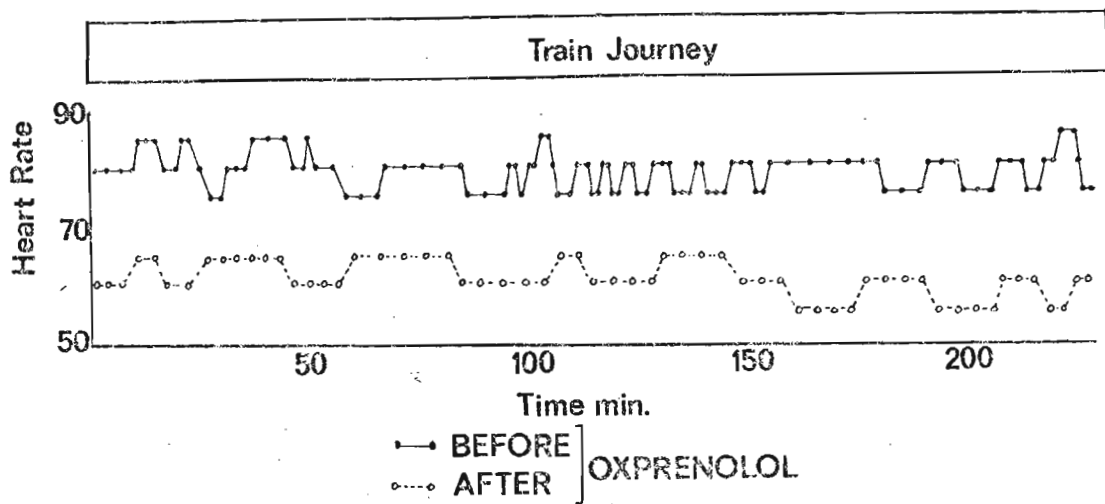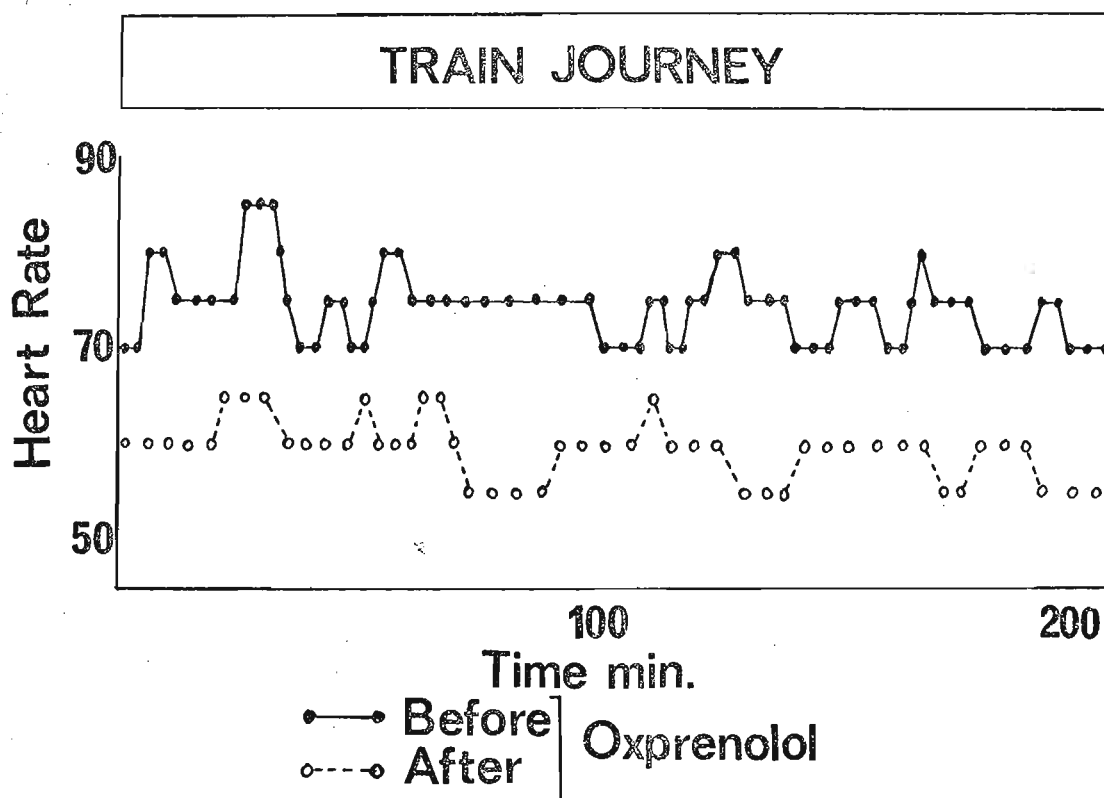Record of the heart rate in a passenger with ischaemic heart disease between Leeds and London, during placebo and after 40 mg oral oxprenolol.
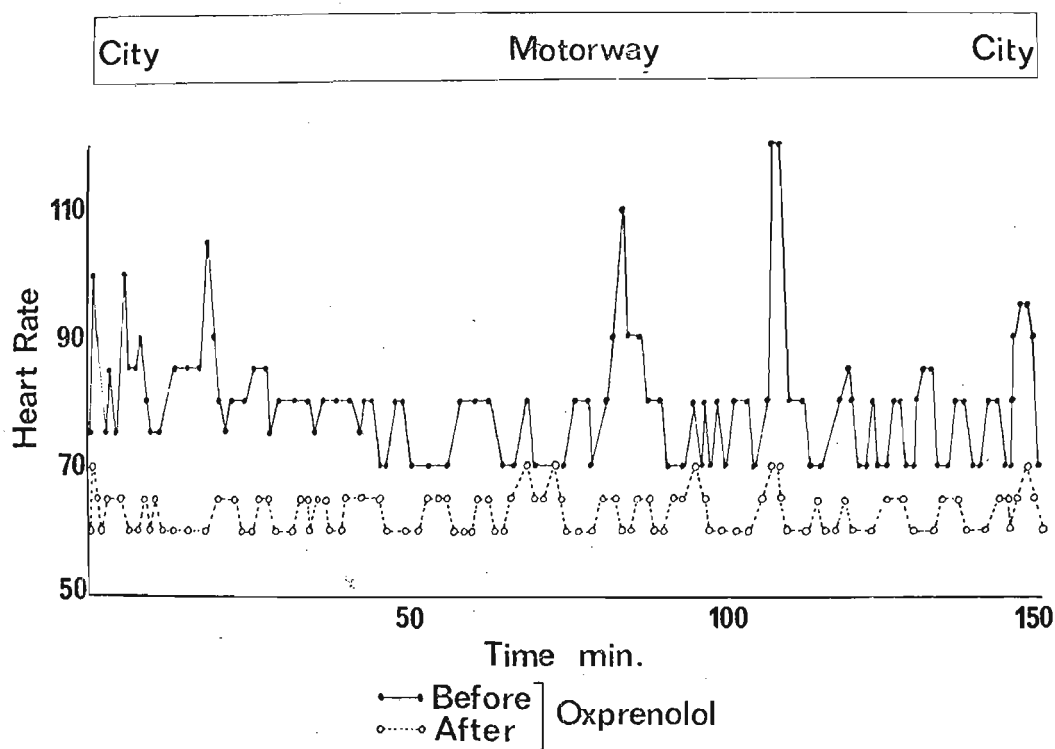
FIGURE 17

Record of the heart rate in a passenger with ischaemic heart disease between Leeds and London during placebo and after 40 mg oral oxprenolol.

TABLE 10   HEART RATE RESPONSE OF PASSENGERS WITH ISCHAEMIC HEART DISEASE AND ITS MODIFICATION

BY ORAL OXPRENOLOL

| Subjects | Control Heart Rate[1] | | Peak Heart Rate[2] | | Cumulative Heart Rate[3] | | | |
| | | | | | Total Heart Rate | | Heart Rate per minute | |
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
JR	80	65	120	75	12555	9235	84	62
LG	75	60	95	70	14416	11077	88	66
AS	75	70	90	75	12185	9890	80	65
SB	70	60	120	70	10810	8010	72	54
JM	70	65	90	70	12190	10010	87	72
SD	80	60	135	70	18851	12380	94	62
MEAN	75	63	108	72	13501	10100	84	64
SEM ±	± 2	± 2	± 8	± 1	± 1170	± 614	± 3	± 2

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
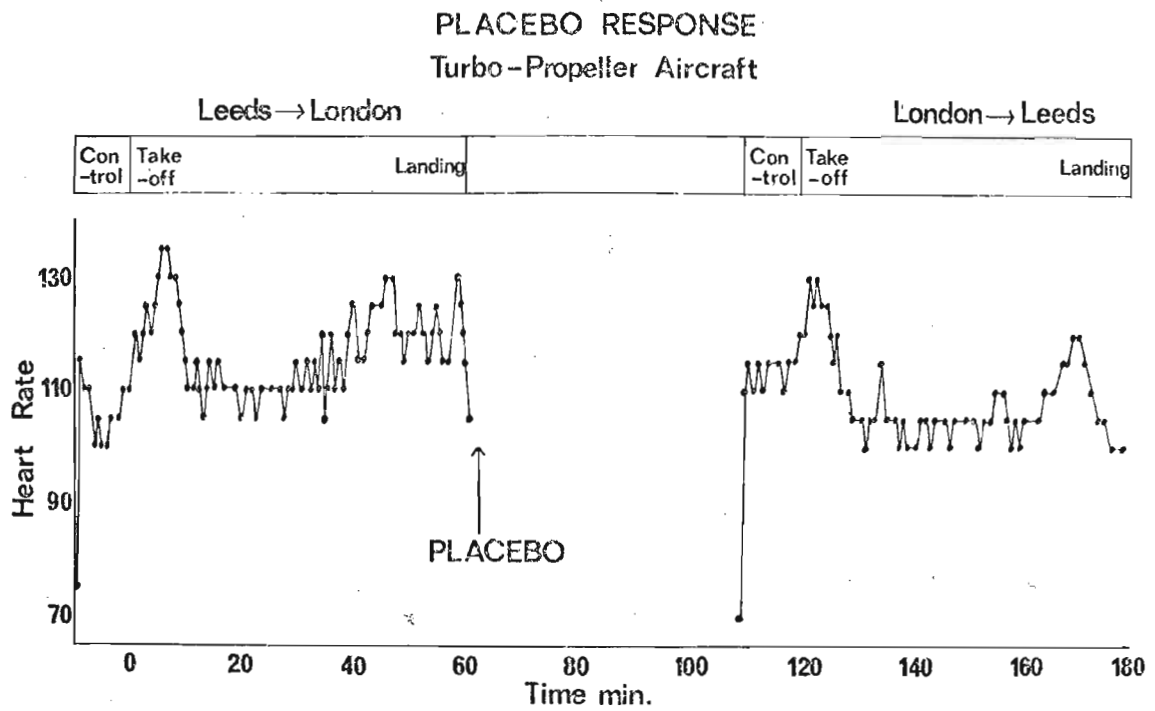3. The total heart rate over the journey.

FIGURE 18

Record of the heart rate in a normal subject travelling by
rail between Leeds and London before and after 40 mg oral oxprenolol.
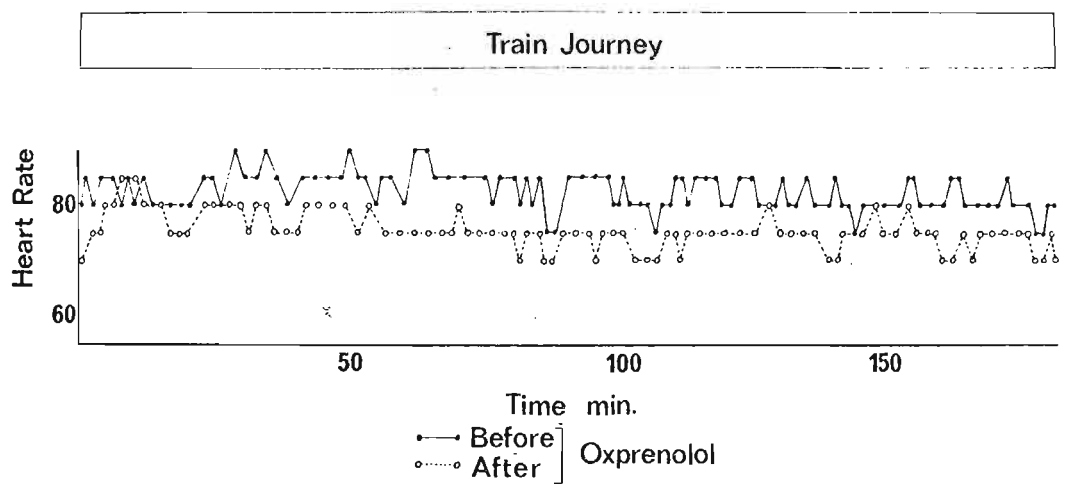
FIGURE 19

Record of the heart rate in a normal subject travelling by rail between Leeds and London before and after 40 mg oral oxprenolol.

TABLE 11   HEART RATE RESPONSE OF NORMAL RAIL PASSENGERS AND ITS MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate[1] per minute		Peak Heart Rate[2]		Cumulative Heart Rate[3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
SHT	75	60	95	80	12630	10612	79	66
MKM	50	45	60	50	8944	8135	56	51
MP	70	65	80	70	14496	11519	81	64
AF	65	60	90	70	13386	11639	74	65
PH	75	60	90	70	17326	14549	72	61
GAP	65	60	65	60	13386	11639	82	65
MEAN	67	58	80	67	13361	11349	74	62
SEM ±	± 4	± 3	± 6	± 4	± 1111	± 843	± 4	± 2

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.

FIGURE 20

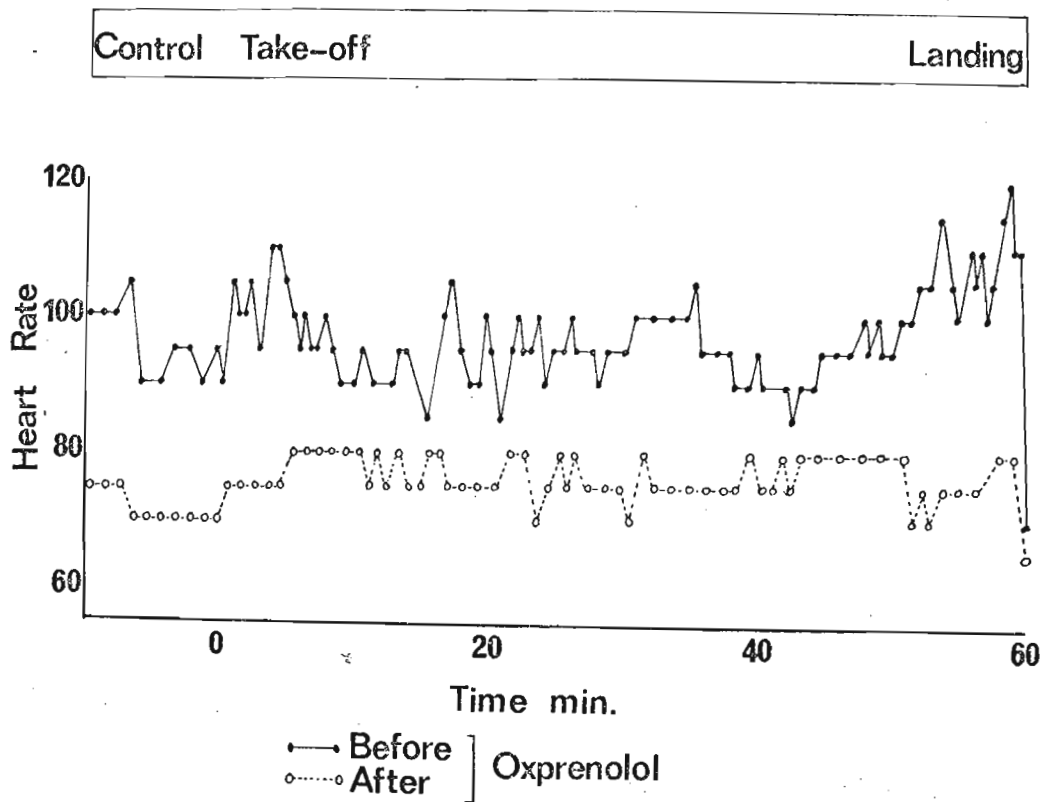Record of the heart rate in a subject with ischaemic heart disease travelling by rail between Leeds and London during placebo and after 40 mg oral oxprenolol.

FIGURE 21

Record of the heart rate in a subject with ischaemic heart disease travelling by rail between Leeds and London during placebo and after 40 mg oral oxprenolol.

TABLE 12   HEART RATE RESPONSE OF PATIENTS WITH ISCHAEMIC HEART DISEASE DURING RAIL TRAVEL

AND ITS MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate [1] per minute		Peak Heart Rate [2]		Cumulative Heart Rate [3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
JR	75	65	90	70	18760	15470	83	69
LG	70	70	85	75	15666	13385	78	67
JM	75	65	80	70	14770	10290	82	57
JB	70	60	85	65	15860	13167	76	63
DM	70	65	85	70	14910	10890	83	61
GA	72	60	80	65	13560	11112	75	62
MEAN	72	64	84	69	15587	12385	80	63
SEM ±	± 1	± 4	± 2	± 2	± 716	± 804	± 1	± 2

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.
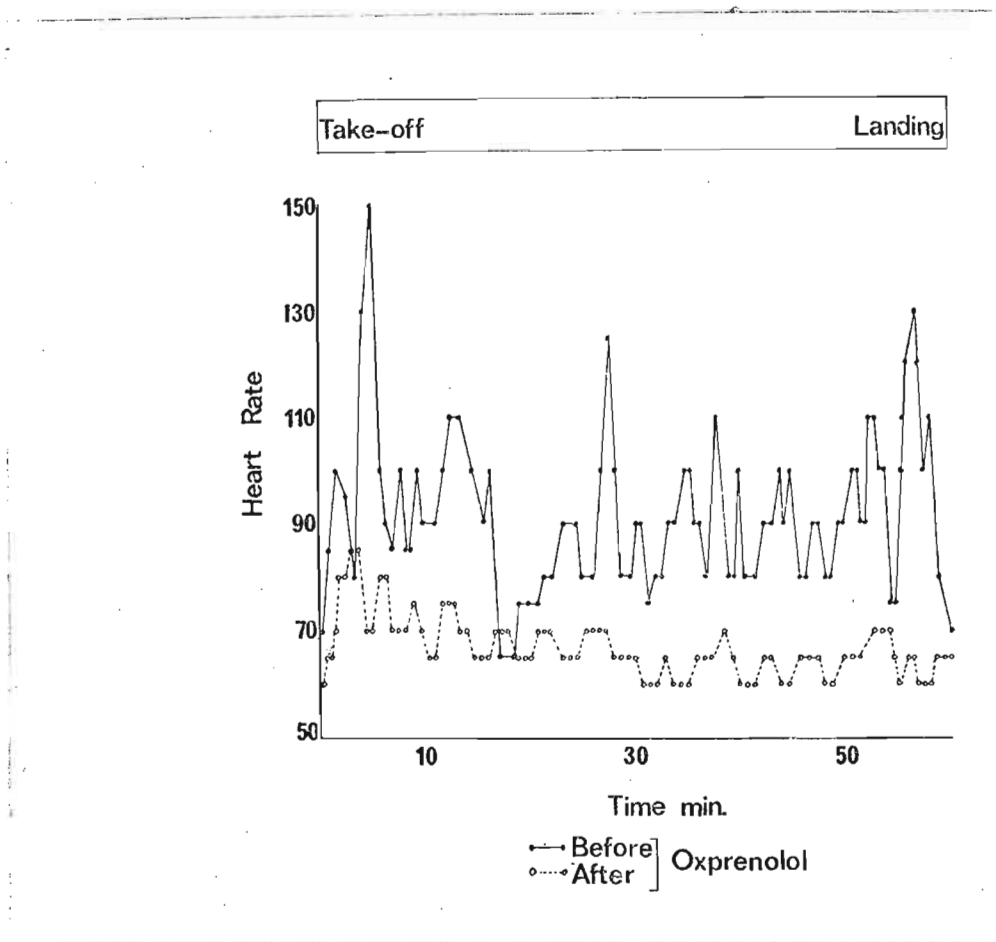
PLACEBO RESPONSE
### Turbo–Propeller Aircraft

Record of the heart rate in a patient with ischaemic heart disease travelling by turbopropeller aircraft between Leeds and London during placebo on both the outward and return journeys.

FIGURE 22

Record of the heart rate in a patient with ischaemic heart disease travelling by turbopropeller aircraft between Leeds and London during placebo on both the outward and return journeys.
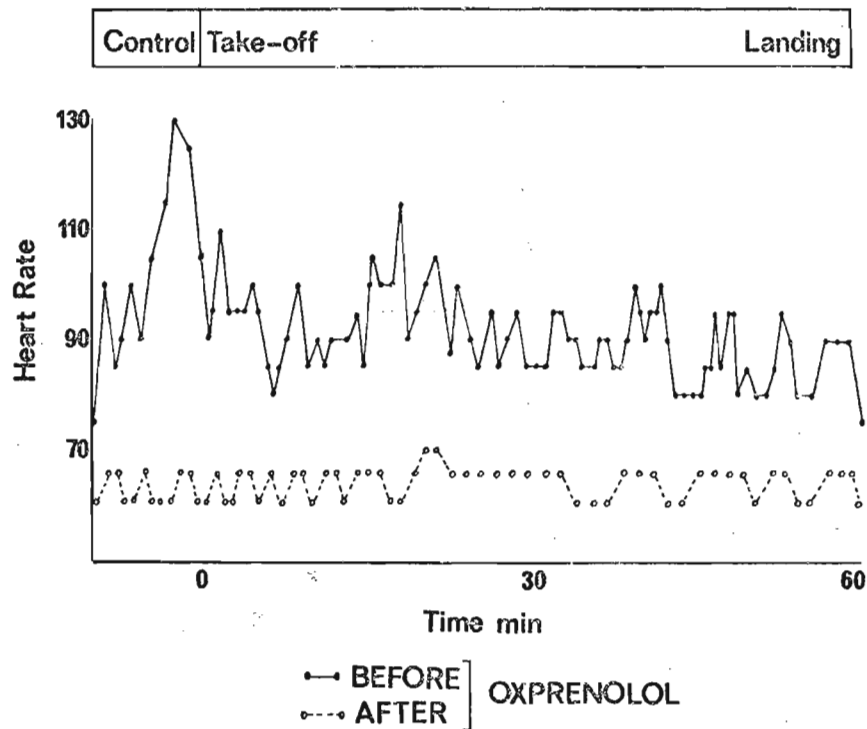
FIGURE 23

Record of the heart rate in a normal subject travelling
by passenger turbo-propeller aircraft between Leeds and London
and the modulation of the response by 40 mg oral oxprenolol taken
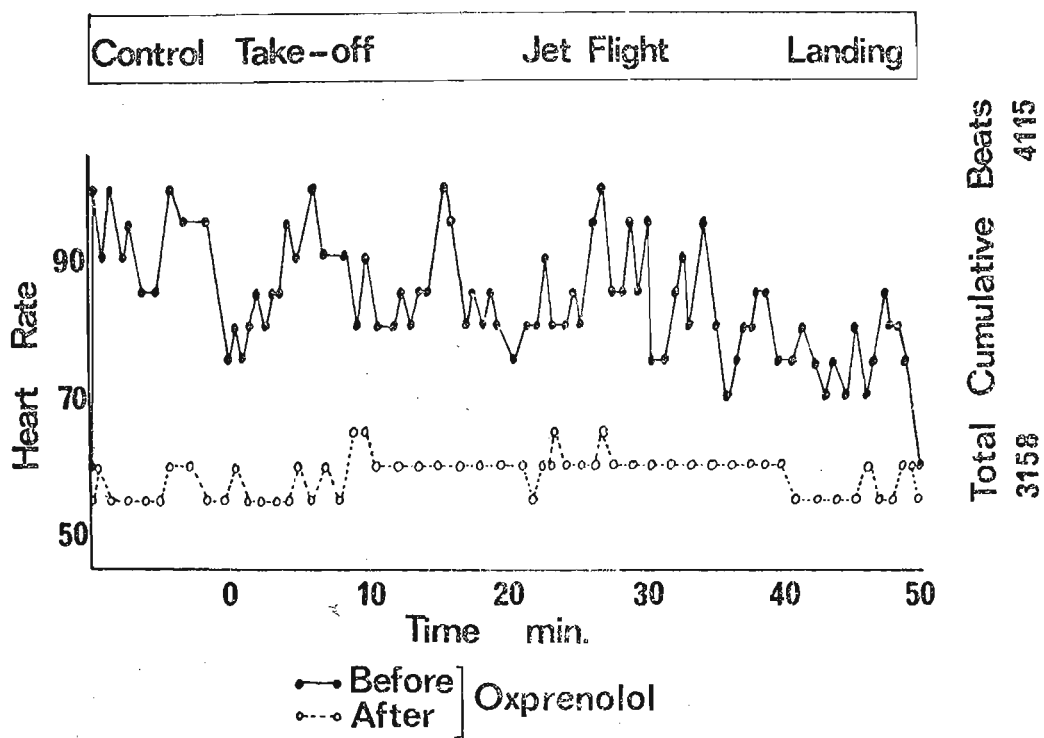one hour before the flight.
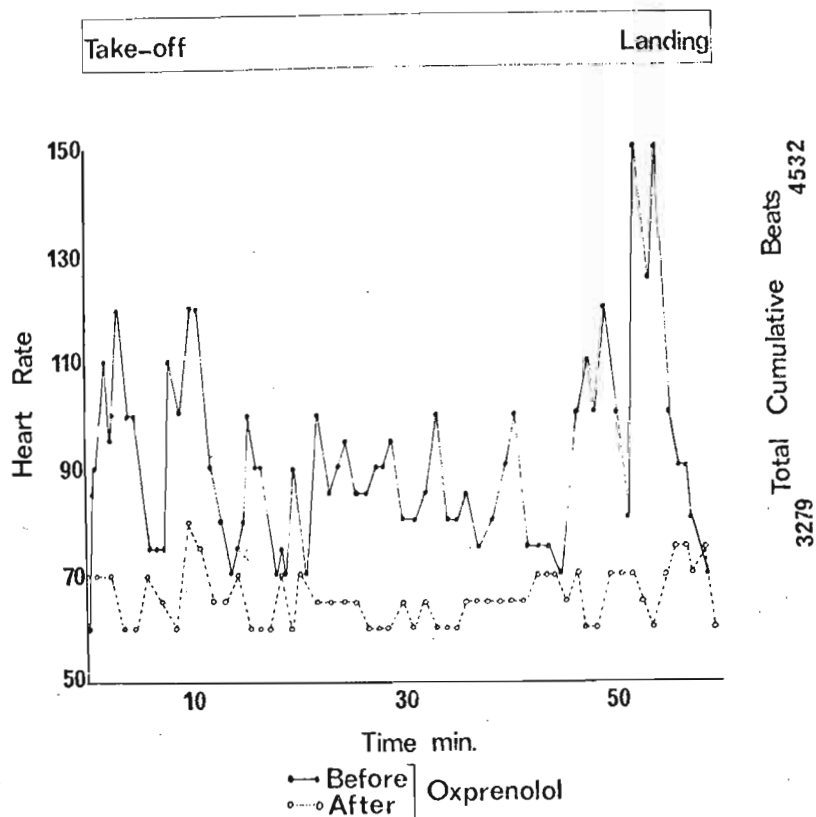
FIGURE 24

Record of the heart rate in a normal subject travelling by passenger turbo-propeller aircraft between Leeds and London and the modulation of the response by 40 mg oral oxprenolol taken one hour before the flight.

TABLE 13   HEART RATE RESPONSE OF NORMAL TURBO-PROPELLER AIR-FLIGHT PASSENGERS AND ITS

MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate[1] per minute		Peak Heart rate[2]		Cumulative Heart Rate[3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
SHT	70	60	140	65	5238	3858	95	70
MKM	60	50	150	60	4222	2933	77	53
MP	70	60	150	80	4532	3279	82	60
AF	75	60	115	70	5304	3165	96	58
PH	60	50	100	60	3984	2903	72	53
GAP	75	60	130	75	5063	3239	92	59
MEAN	68	57	131	68	4724	2230	86	59
SEM ±	± 3	± 2	± 3	± 3	± 227	± 140	± 4	± 3

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.

FIGURE 25

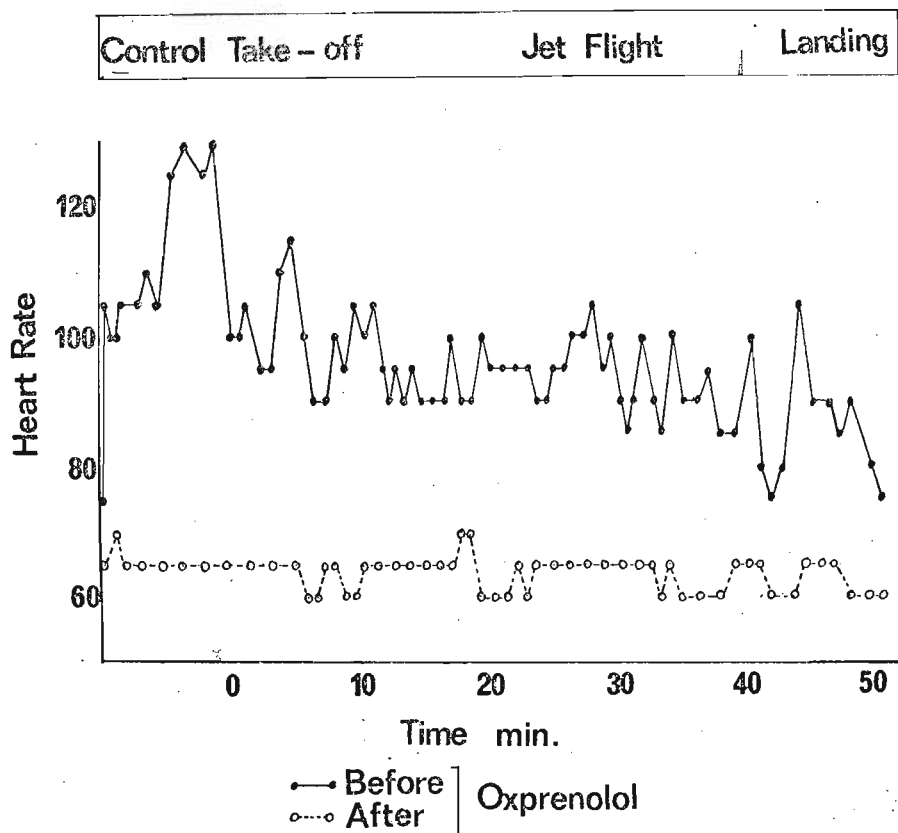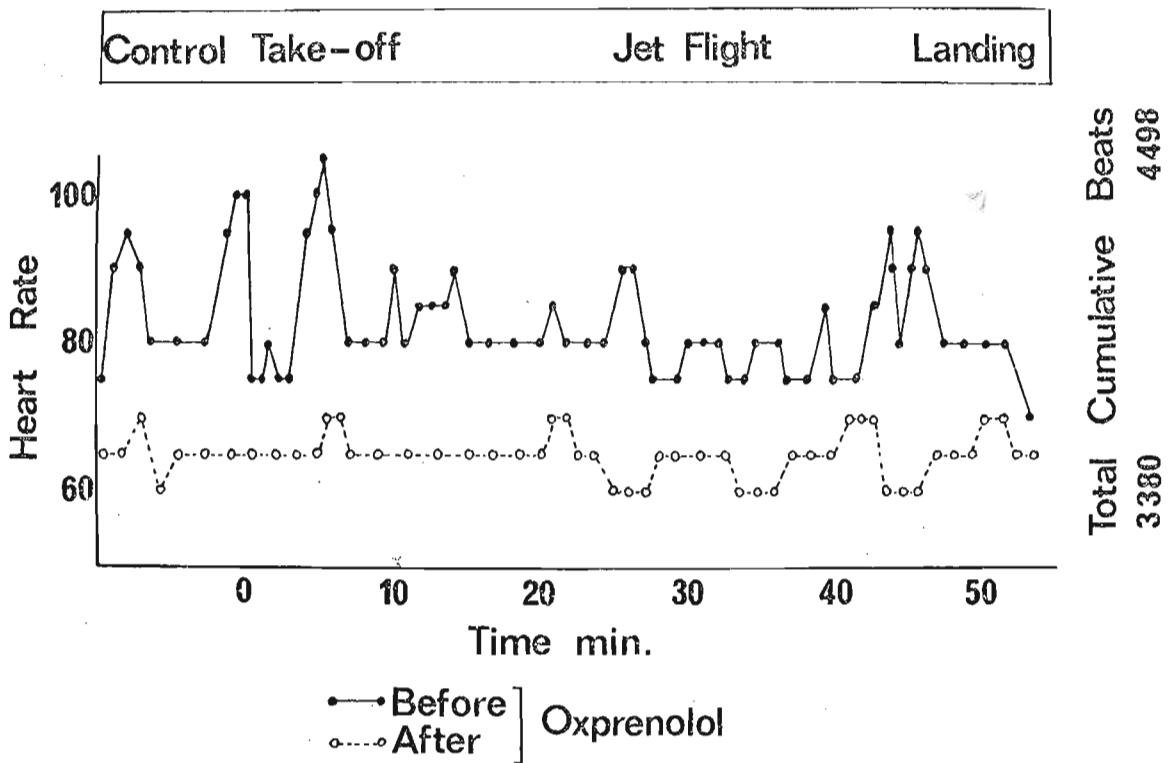Record of the heart rate in a patient with ischaemic heart disease travelling by turbo-propeller aircraft between Leeds and London during placebo and one hour after 40 mg oral oxprenolol.

FIGURE 26

Record of the heart rate in a patient with ischaemic heart
disease travelling by turbo-propeller aircraft between Leeds and
London during placebo and one hour after 40 mg oral oxprenolol.

TABLE 14   HEART RATE RESPONSE OF PATIENTS WITH ISCHAEMIC HEART DISEASE TRAVELLING BY TURBO-

PROPELLER AIRCRAFT AND ITS MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate [1] per minute		Peak Heart Rate [2]		Cumulative Heart Rate [3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
JR	70	55	100	55	4003	3200	73	58
LG	75	60	120	70	5166	3686	94	67
JM	75	70	120	80	5233	3985	95	72
McCaa	75	60	140	80	5415	3224	98	59
GA	70	65	125	80	5225	3950	95	72
MEAN	73	62	126	74	4951	3524	90	64
SEM ±	± 1	± 2	± 7	± 4	± 216	± 163	± 4	± 3

1.   Heart rate during control period sitting still before test
2.   Values relate to the maximal heart rate during the trip
3.   The total heart rate over the journey.
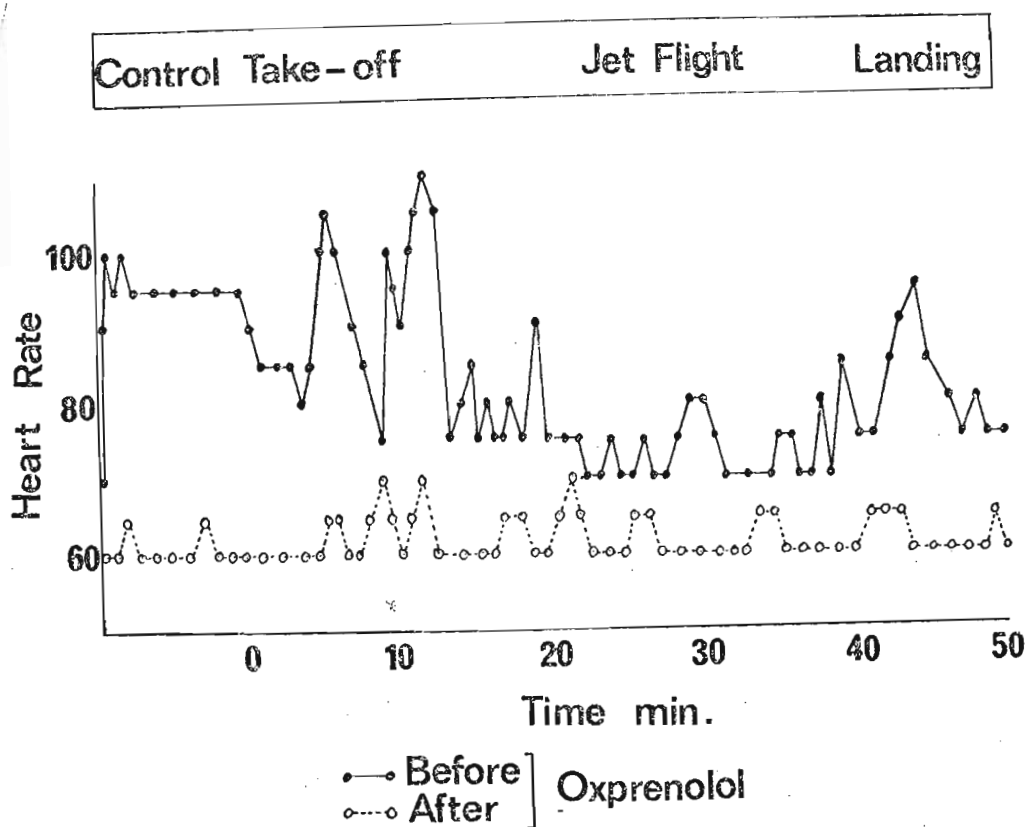
FIGURE 27

Record of the heart rate in a normal subject travelling by jet aircraft between Newcastle and London and the modulation of the response by 40 mg oral oxprenolol taken one hour before the flight.

FIGURE 28

Record of the heart rate in a normal subject travelling by jet
aircraft between Newcastle and London and the modulation of the response
by 40 mg oral oxprenolol taken one hour before the flight.

TABLE 15   HEART RATE RESPONSE OF NORMAL JET AIR FLIGHT PASSENGERS AND ITS MODIFICATION BY

ORAL OXPRENOLOL

Subjects	Control Heart Rate [1] per minute		Peak Heart Rate [2]		Cumulative Heart Rate [3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
SHT	70	65	110	75	4467	3194	89	64
MKM	60	50	90	60	3400	2670	68	53
PH	75	65	100	65	4115	3158	82	63
GAP	75	65	115	70	4473	3313	89	66
MEAN	70	61	104	68	4114	3084	82	62
SEM ±	± 4	± 4	± 6	± 3	± 252	± 142	± 5	± 3

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.

FIGURE 29

Record of the heart rate in a patient with ischaemic heart disease travelling by jet aircraft between Newcastle and London during placebo and one hour after 40 mg oral oxprenolol.

FIGURE 30

Record of the heart rate in a patient with ischaemic heart disease travelling by jet aircraft between Newcastle and London during placebo and one hour after 40 mg oral oxprenolol.

TABLE 16   HEART RATE RESPONSE OF PATIENTS WITH ISCHAEMIC HEART DISEASE TRAVELLING BY JET

AIRCRAFT AND ITS MODULATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate [1] per minute		Peak Heart Rate [2]		Cumulative Heart Rate [3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
JR	70	65	115	70	4498	3380	90	68
LG	75	70	100	80	4320	3942	86	79
JM	70	60	110	70	4783	3425	96	69
GA	60	55	90	60	4439	3043	89	61
MEAN	69	63	104	70	4510	3448	90	69
SEM ±	± 3	± 3	± 6	± 4	± 98	± 186	± 2	± 4

1. Heart rate during control period sitting still before test
2. Values relate to the maximal heart rate during the trip
3. The total heart rate over the journey.

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LIVE FOOTBALL MATCH
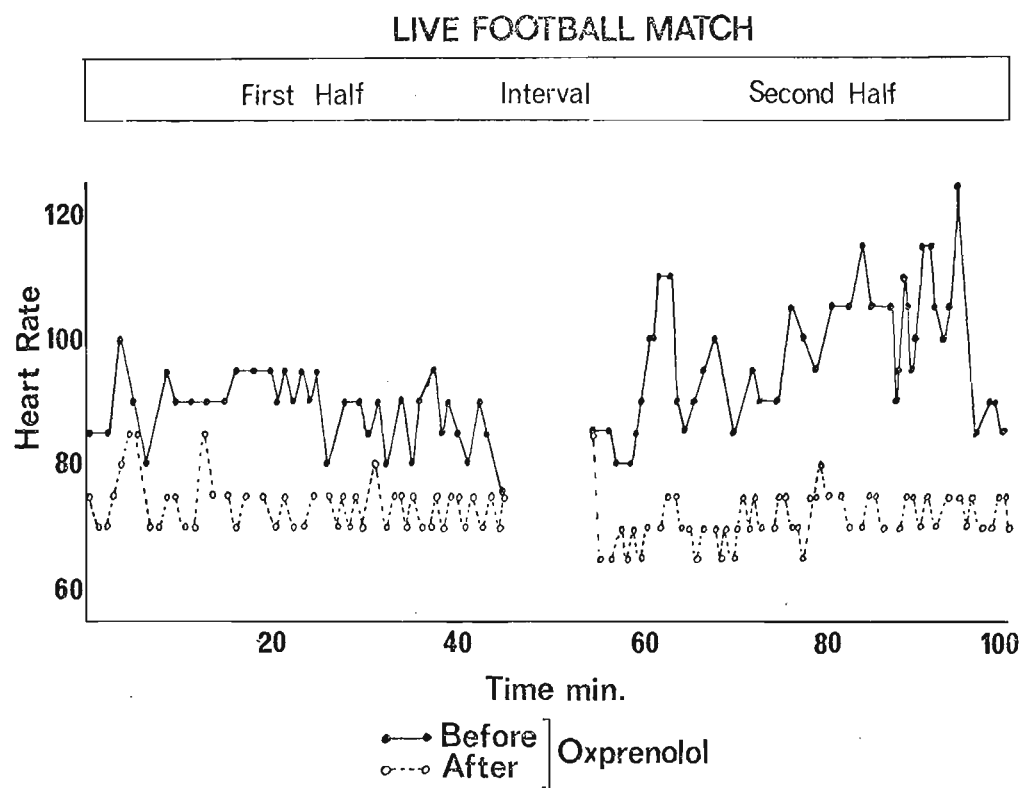
FIGURE 31

Record of the heart rate in a normal subject watching a soccer match after the ingestion of placebo and the modulation of the response produced by 40 mg oral oxprenolol taken one hour before a similar match.
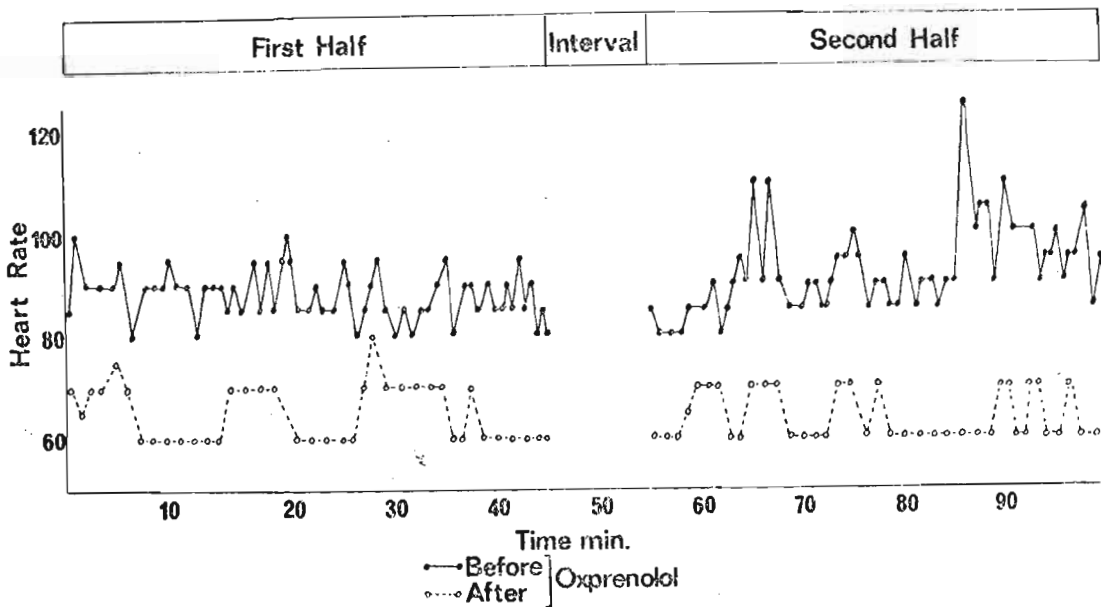
FIGURE 32

Record of the heart rate in a normal subject watching
a soccer match after the ingestion of placebo and the modulation of the
response produced by 40 mg oral oxprenolol taken one hour before a
similar match.
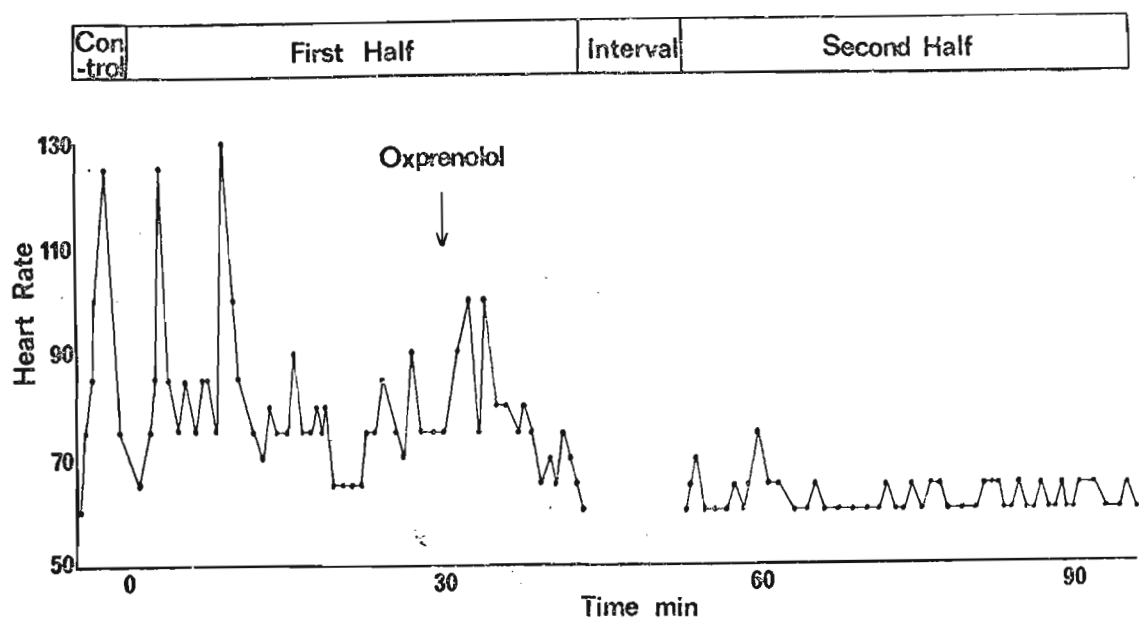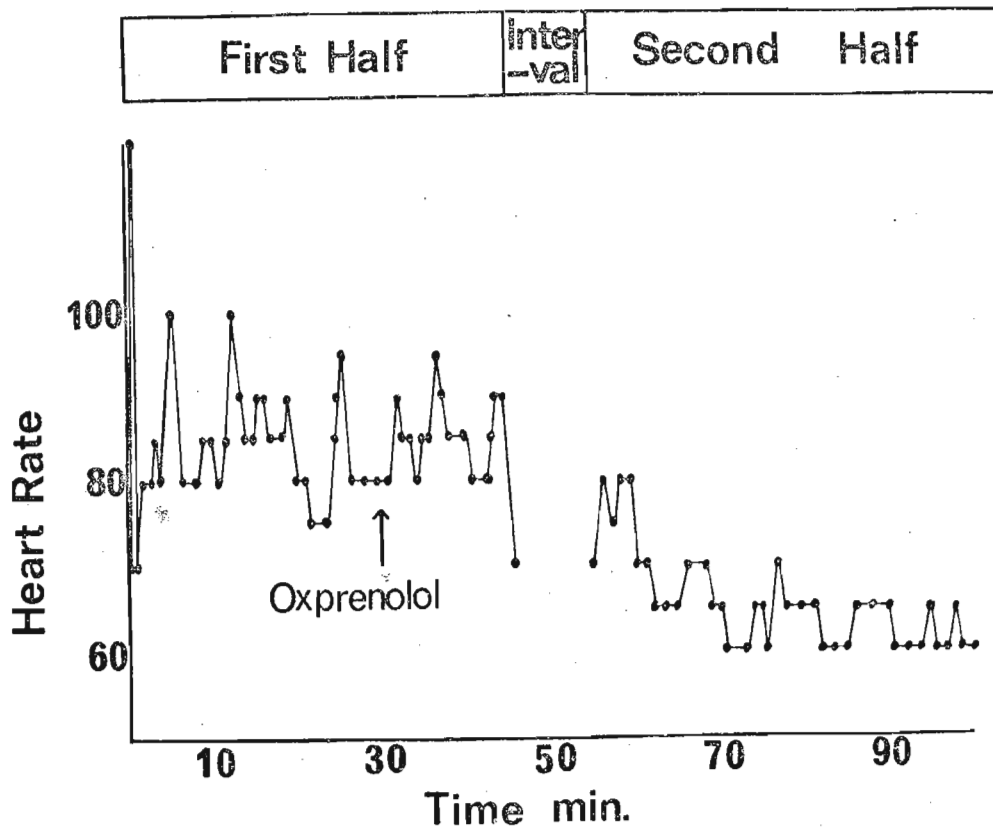
FIGURE 33

Record of the heart rate in a normal subject watching a
televised live football match and the effect of 40 mg oral oxprenolol.
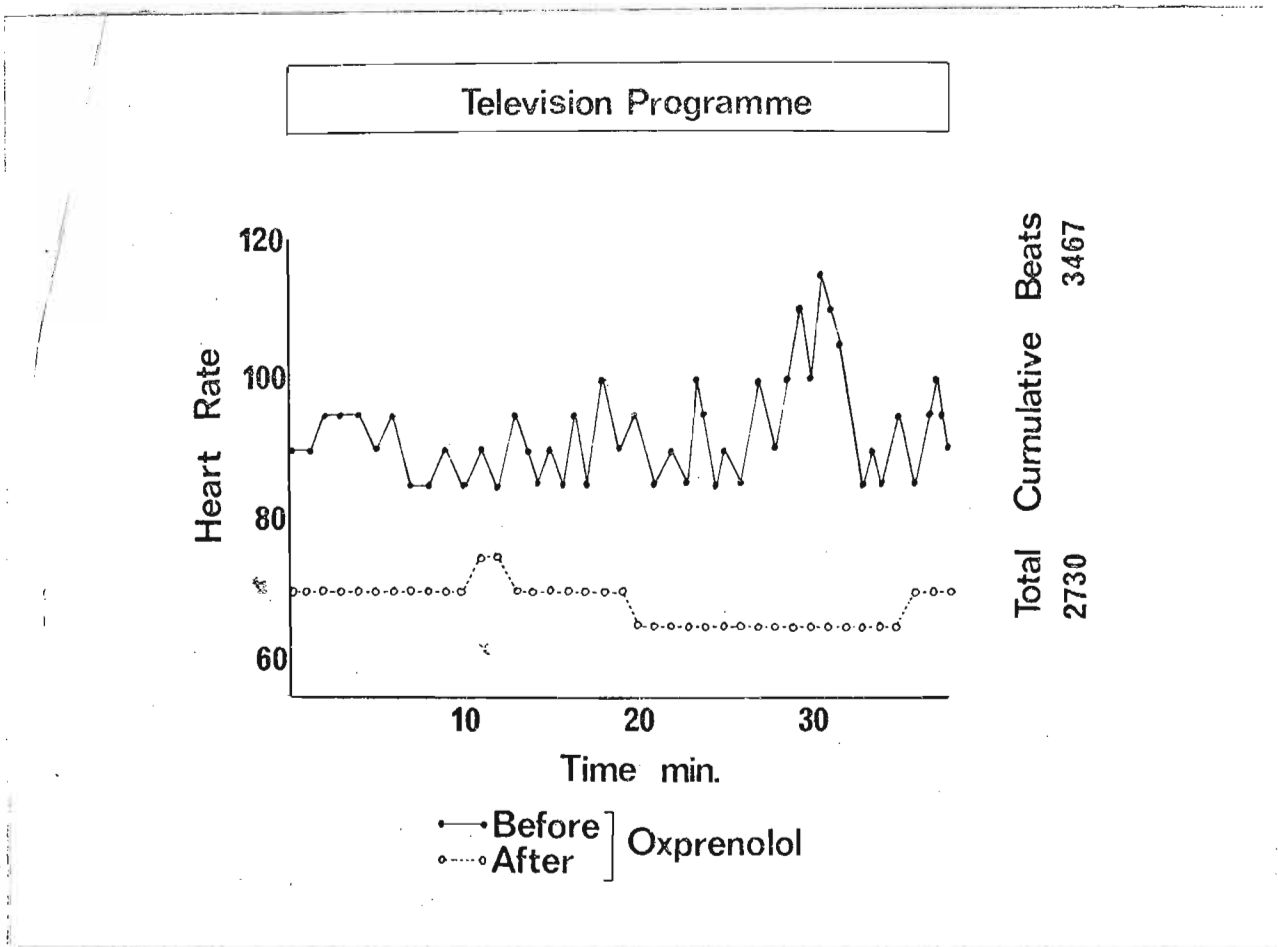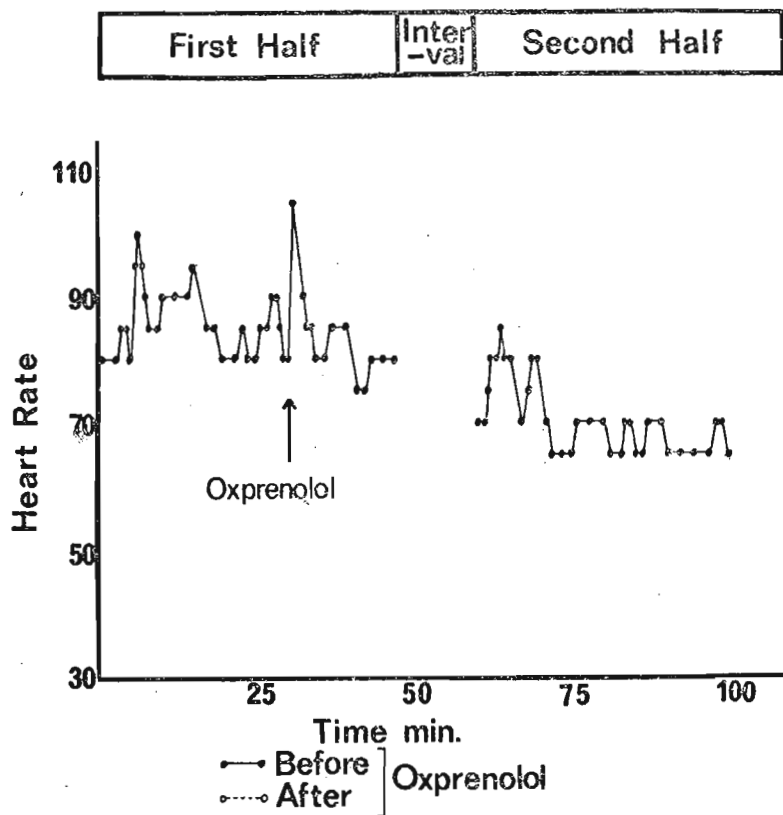
FIGURE 34

Record of the heart rate in a normal subject watching a televised live football match and the effect of 40 mg oral oxprenolol.
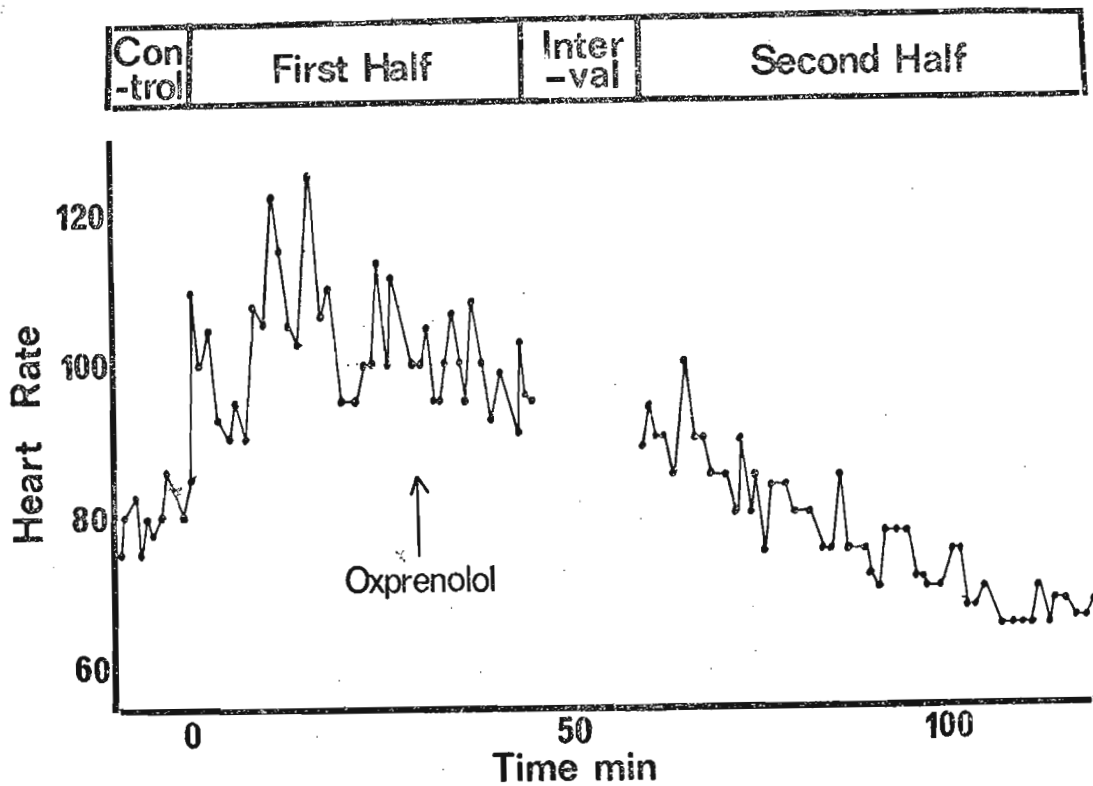
FIGURE 35

Record of the heart rate in a normal subject watching
a soccer match and its modification produced by 40 mg oral
oxprenolol taken 30 minutes after the commencement of the
match.
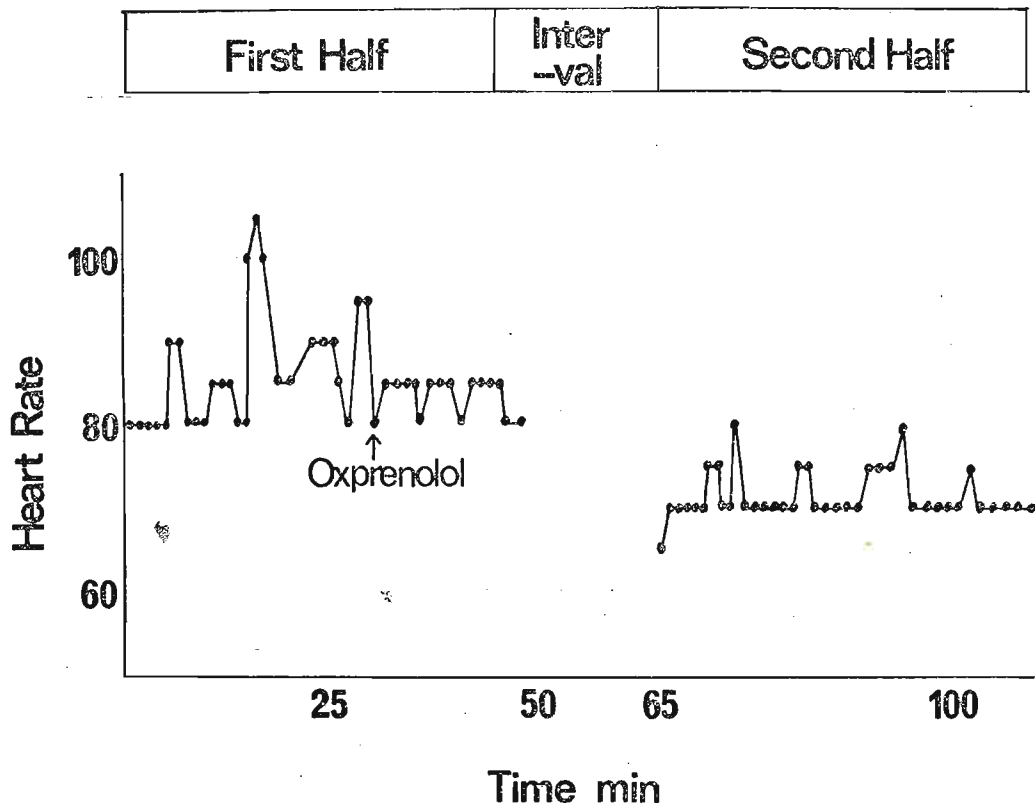
FIGURE 36

Record of the heart rate in a normal subject watching a televised live football match and the effect of 40 mg oral oxprenolol taken 30 minutes after the commencement of the match.

TABLE 17   HEART RATE RESPONSE OF NORMAL SUBJECTS DURING A LIVE FOOTBALL MATCH AND ITS

MODIFICATION BY ORAL OXPRENOLOL

| Subjects | Control Heart Rate [1] per minute | | Peak Heart Rate [2] | | Cumulative Heart Rate [3] | | | |
| | | | | | Total Heart Rate | | Heart Rate per minute | |
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
SHT	75	60	115	65	6921	5570	87	70
MKM	80	70	130	80	9187	6947	102	73
MP	80	70	120	80	8890	7177	111	76
PH	80	75	105	80	9367	7475	99	79
CNR	75	60	125	75	4777	3132	106	70
GAP	80	70	130	85	11178	7878	124	88
GHK	70	65	110	80	7004	5673	88	71
MEAN	77	67	119	78			102	75
SEM ±	± 1	± 2	± 4	± 2			± 5	± 2

1.   Heart rate during control period sitting quietly 30 minutes before the match
2.   Values relate to maximal heart rate during the match.
3.   Total heart rate during the match.
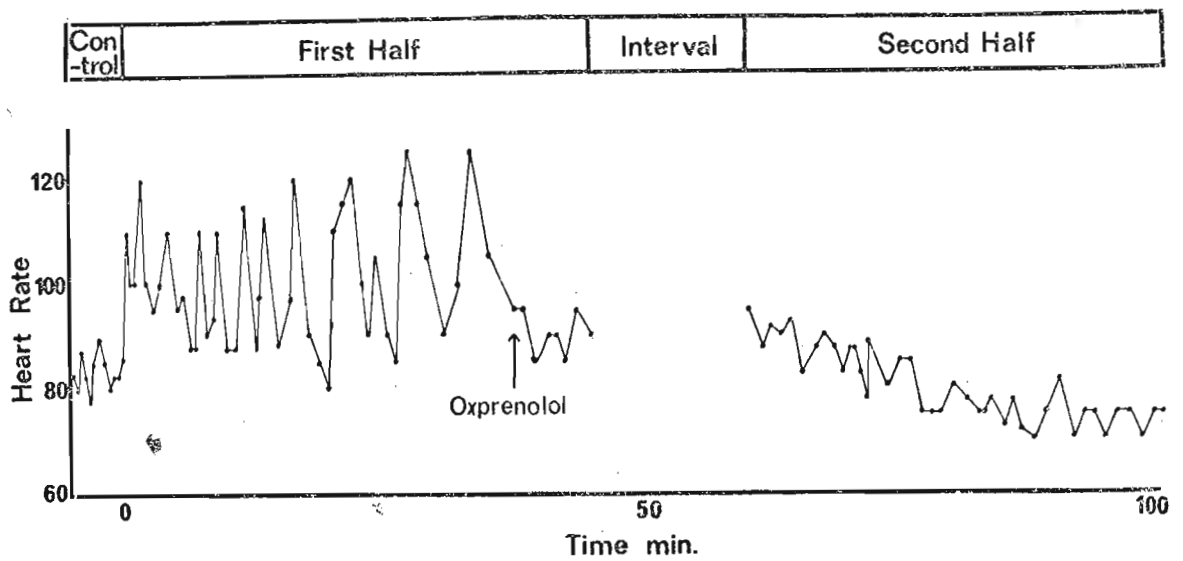
FIGURE 37

Record of the heart rate in a patient with ischaemic heart disease watching a soccer match and the modulation of the response by 40 mg oral oxprenolol taken 30 minutes after the commencement of the match.
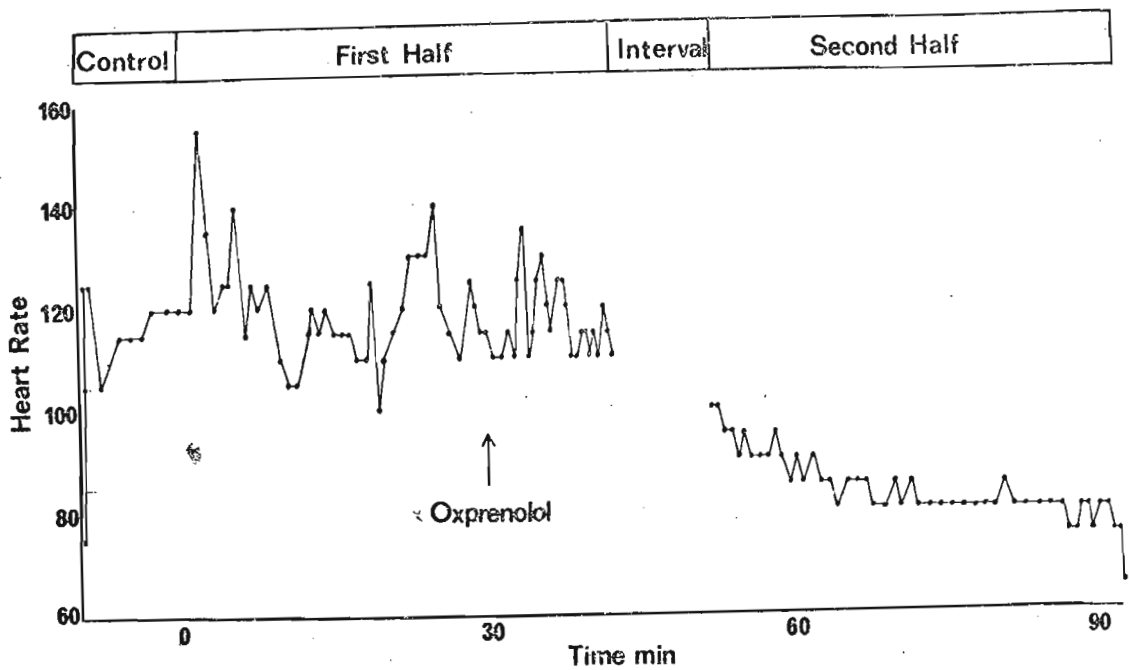
FIGURE 38

Record of the heart rate in a patient with ischaemic heart disease watching a soccer match and the modulation of the response by 40 mg oral oxprenolol taken 30 minutes after the commencement of the match.

FIGURE 39

Record of the heart rate in a patient with ischaemic heart disease watching a televised live football match and the effect of 40 mg oral oxprenolol taken 30 minutes after the commencement of the match.

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FIGURE 40

Record of the heart rate in a patient with ischaemic heart disease watching a televised live football match and the effect of 40 mg oral oxprenolol taken 30 minutes after the commencement of the match.

TABLE 18   HEART RATE RESPONSE OF PATIENTS WITH ISCHAEMIC HEART DISEASE DURING A LIVE FOOTBALL

MATCH AND ITS MODIFICATION BY ORAL OXPRENOLOL

Subjects	Control Heart Rate[1] per minute		Peak Heart Rate[2]		Cumulative Heart Rate[3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
JR	70	65	120	75	3805	2445	95	61
LG	80	70	125	95	3685	2209	123	74
JM	75	60	90	60	3005	1555	100	52
SD	70	60	120	70	3027	1832	101	61
DM	80	70	130	80	11188	6760	124	75
McCaa	75	65	140	85	4643	3277	103	73
GA	75	60	120	80	3770	2560	126	85
MEAN	75	64	121	78			110	69
SEM ±	± 2	± 2	± 6	± 4			± 5	± 4

1. Heart rate during control period sitting quietly 30 minutes before the match
2. Values relate to maximal heart rate during the match.
3. Total heart rate during the match.
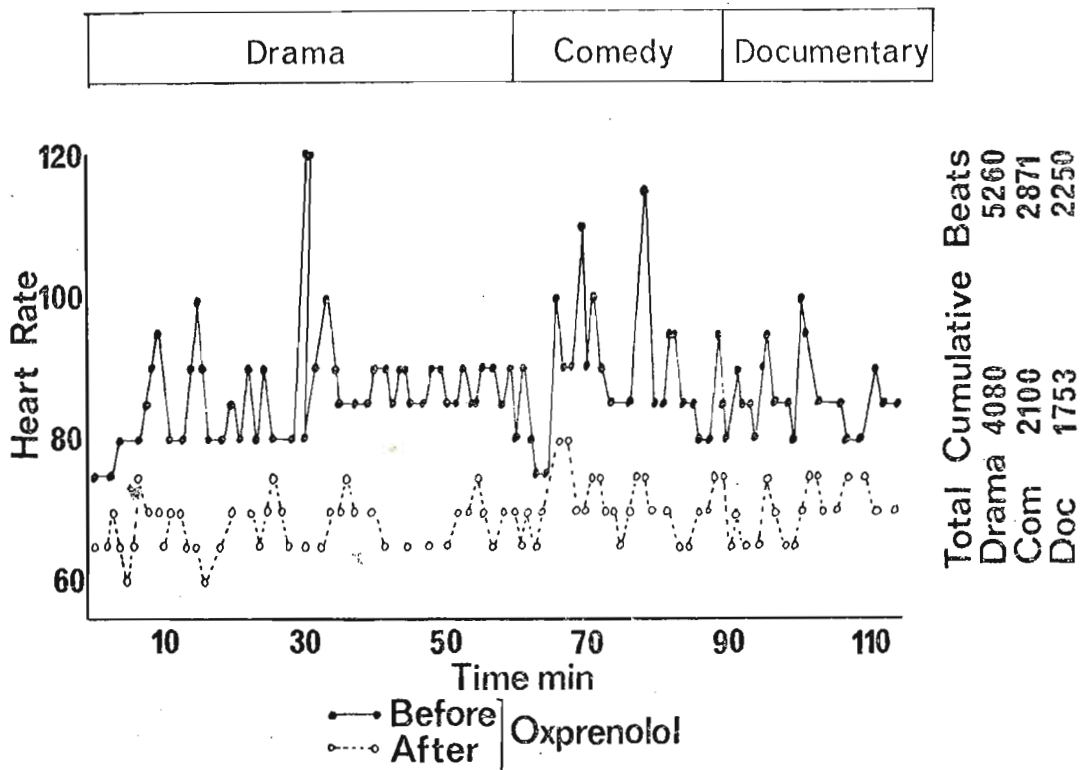
FIGURE 41

Record of the heart rate in a normal subject watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.
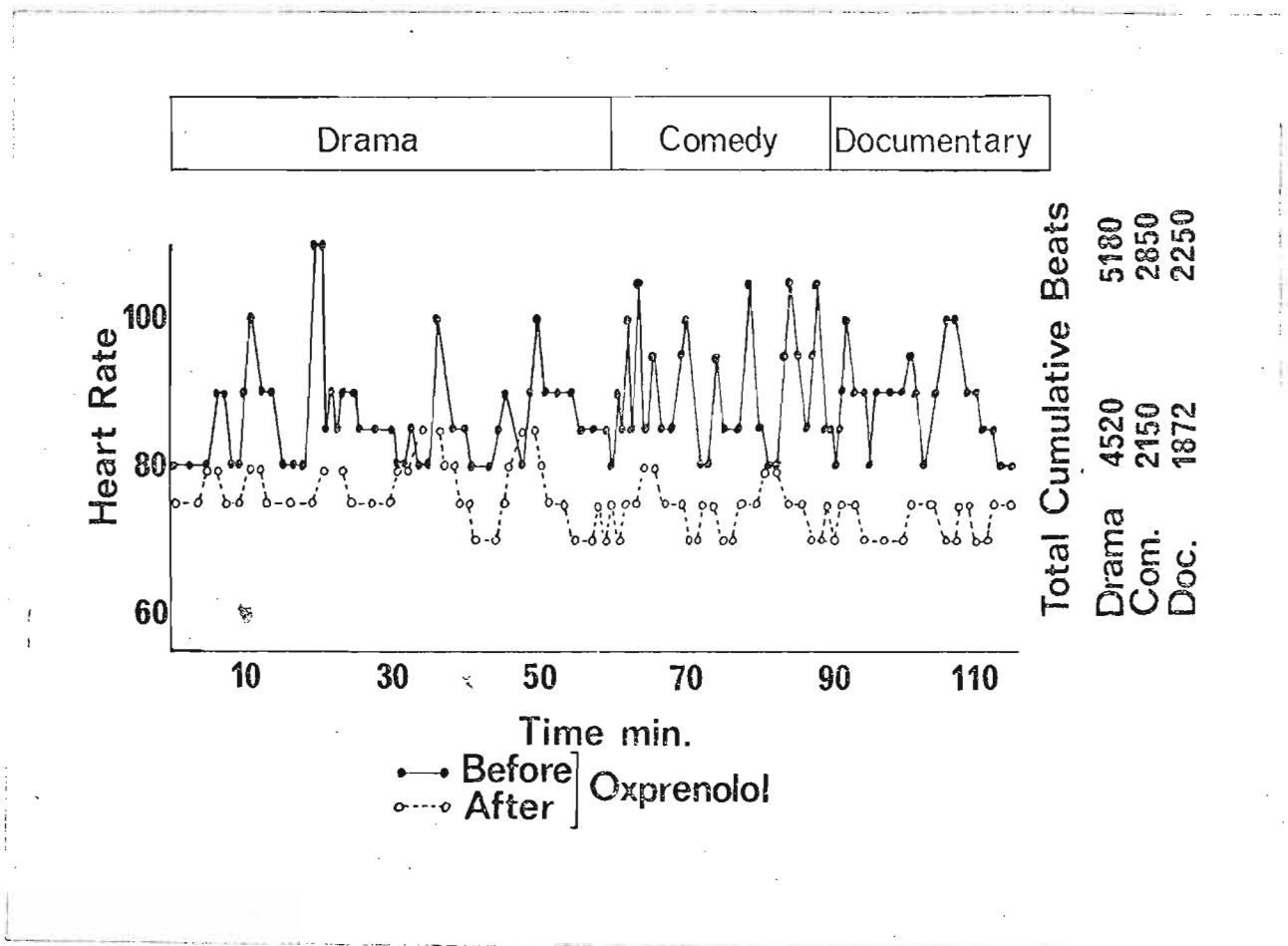
FIGURE 42

Record of the heart rate in a normal subject watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.
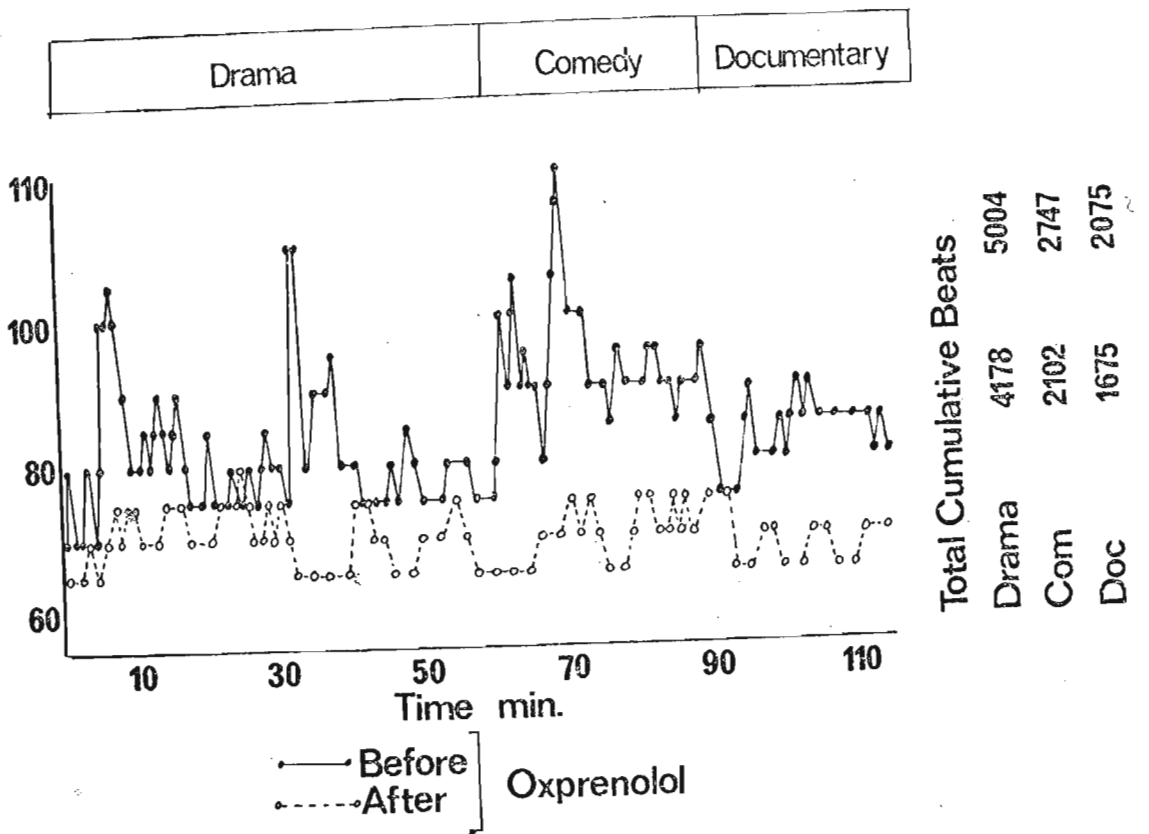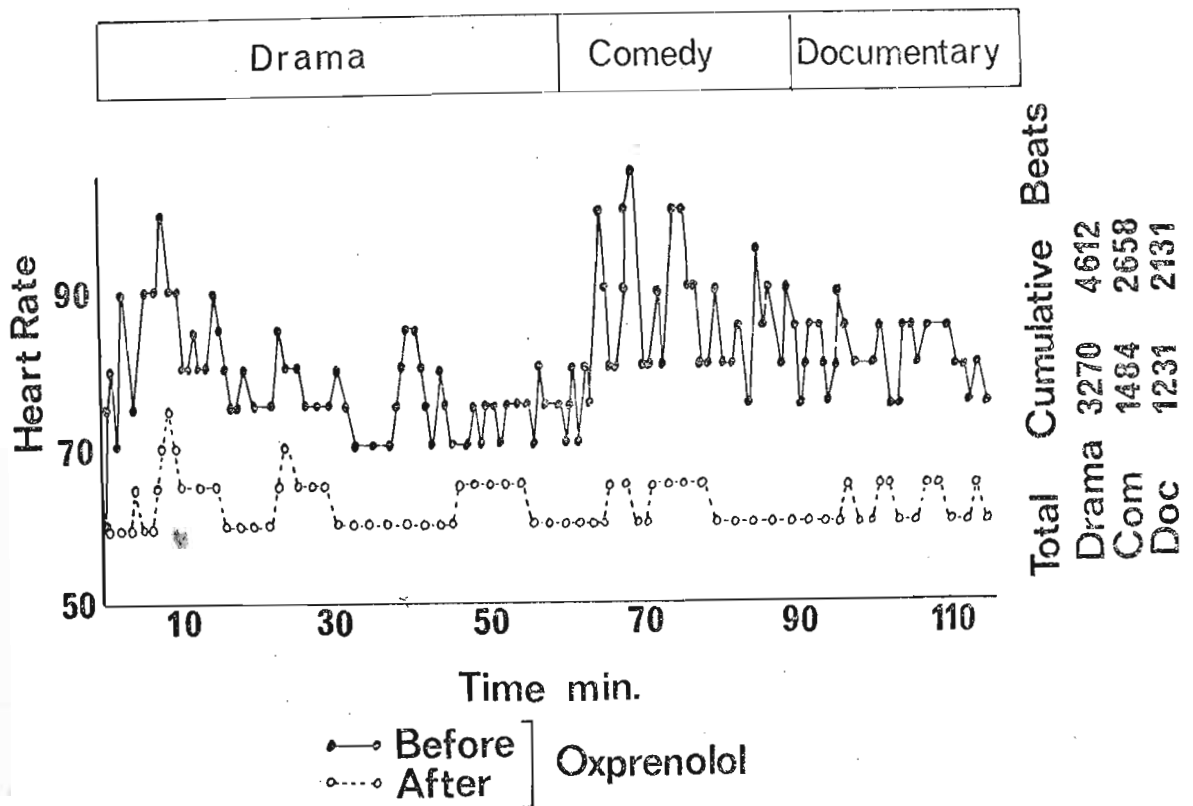
FIGURE 43

Record of the heart rate in a normal subject watching programmes
of Drama, Comedy and Documentary on television during placebo and
the modification of the response by 40 mg oral oxprenolol taken one hour
before the programme.
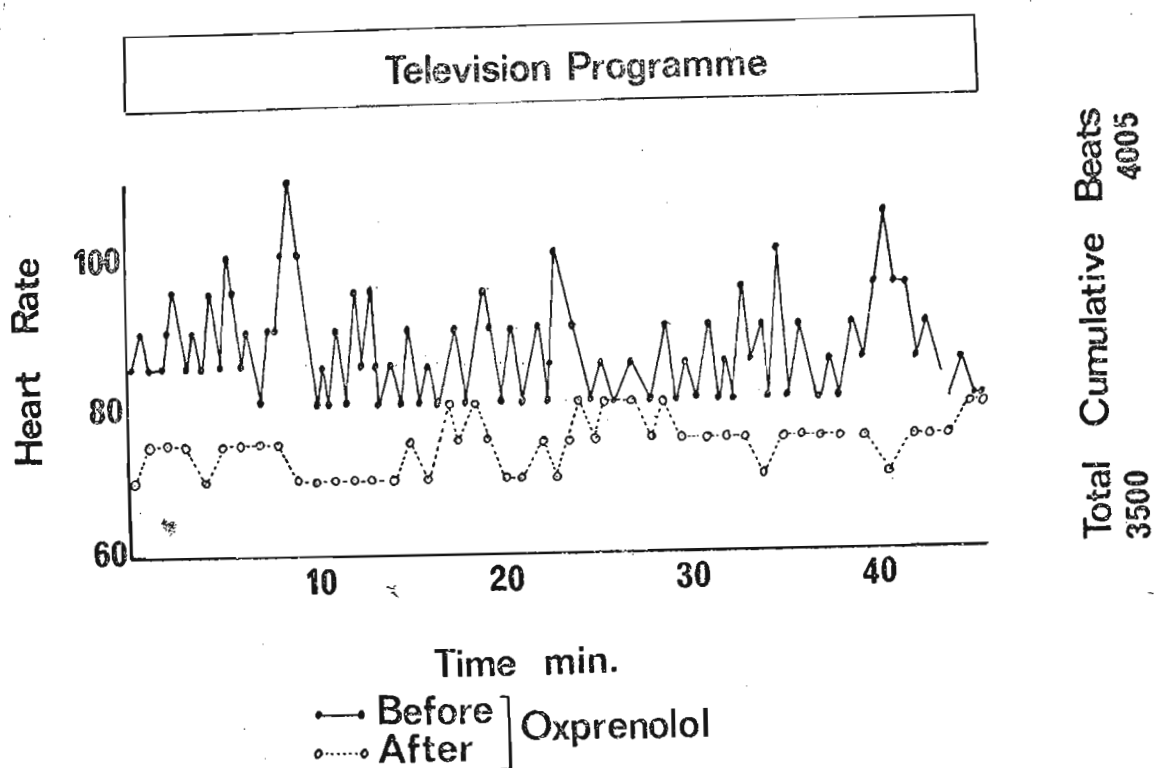
FIGURE 44

Record of the heart rate in a sensitive subject watching a mystery
television film and the modulation of the response by 40 mg oral oxprenolol
taken one hour before a similar programme.
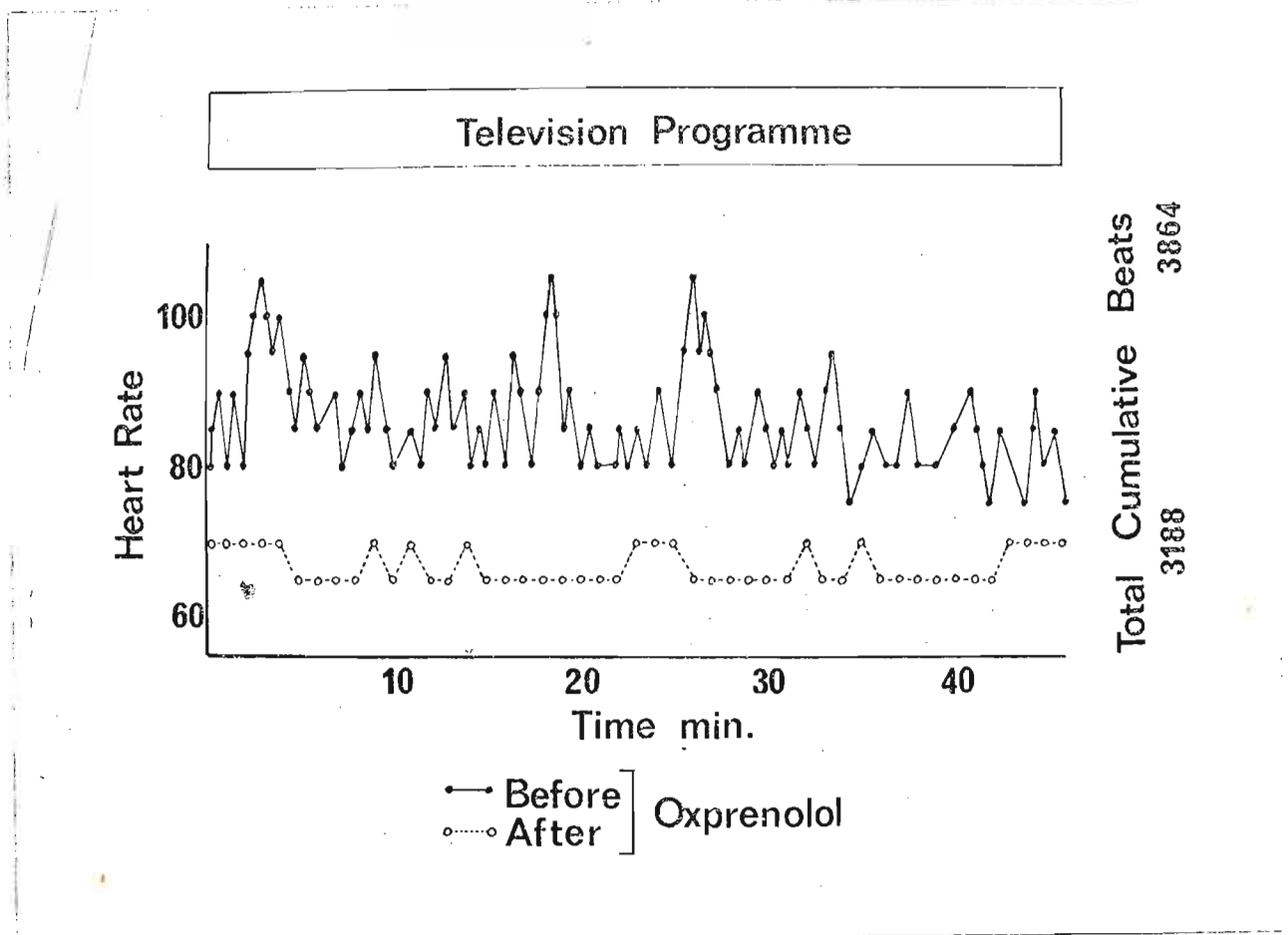
FIGURE 45

Record of heart rate in a sensitive subject watching a horror
television film. after 40 mg oral oxprenolol.
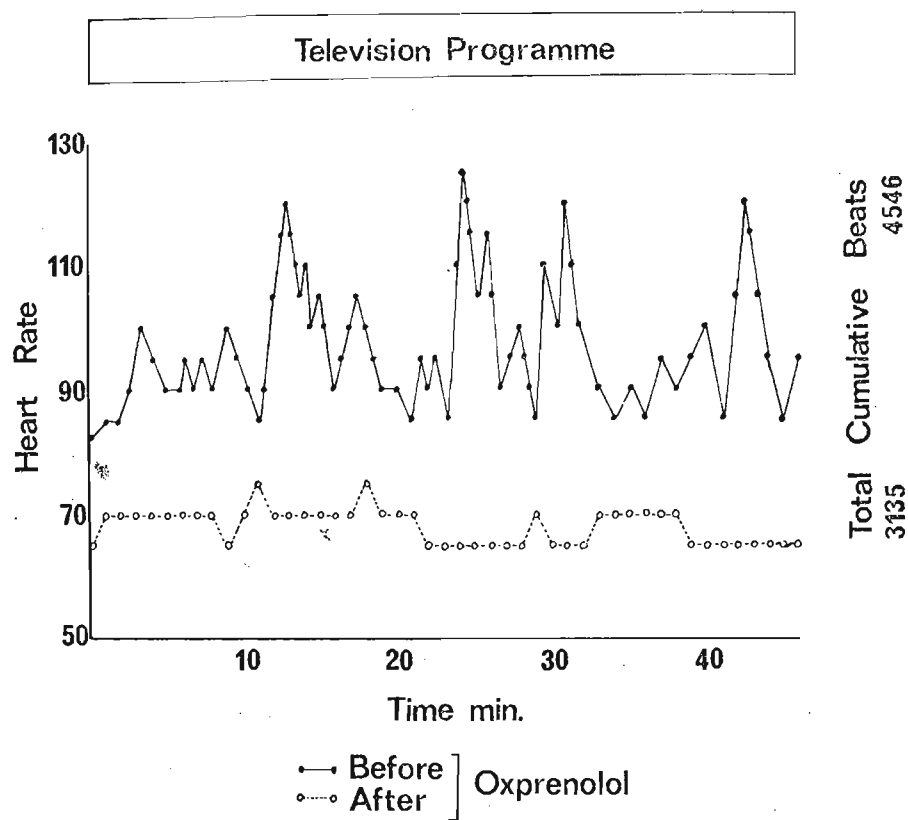
FIGURE 46

Record of the heart rate in a sensitive subject watching a televised
live boxing match, after 40 mg oral oxprenolol.

TABLE 19 HEART RATE RESPONSE OF NORMAL SUBJECTS TO TELEVISION VIEWING AND ITS MODIFICATION BY OXPRENOLOL

Subjects	CONTROL HEART RATE PER MINUTE[1]						PEAK HEART RATE[2]						CUMULATIVE HEART RATE[3]											
	Drama (60 min)		Comedy (30 min)		Documentary (25 min)		Drama (60 min)		Comedy (30 min)		Documentary (25 min)		Drama				Comedy				Documentary			
													Total H.R.		HR/min		Total H.R.		HR/min		Total H.R.		HR/min	
	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O
MKM	60	55	60	55	60	55	100	75	105	80	95	65	4750	3901	79	65	2500	2060	83	69	2014	1220	81	49
MP	72	65	72	65	72	65	110	80	120	75	90	75	5004	4178	84	70	2749	2102	92	70	2075	1675	83	67
AF	80	75	80	75	80	75	110	85	110	80	100	75	5180	4520	86	75	2850	2150	95	72	2250	1872	90	75
PH	76	65	76	65	76	65	120	75	115	80	100	75	5260	4080	88	68	2871	2100	96	70	2250	1753	90	70
GAP	82	65	82	65	82	65	110	75	110	75	100	70	5468	4102	91	68	2951	2001	98	67	2200	1620	88	65
GHK	84	70	80	70	80	70	120	80	110	75	100	75	5668	4380	94	73	2670	2160	97	72	2150	1702	86	64
MEAN	76	66	75	65	75	65	112	78	113	78	98	73	5222	4194	87	70	2765	2496	94	70	2157	1640	86	65
SEM ±	± 4	±3	±3	±3	±3	±3	±3	±2	±2	±1	±2	±2	±134	±91	±2	±1	±66	±24	±2	±1	±39	±91	±2	±4

1 Heart rate during control period sitting still before test.
2. Values relate to maximal heart rate during television viewing
3. Total heart rate during television viewing.
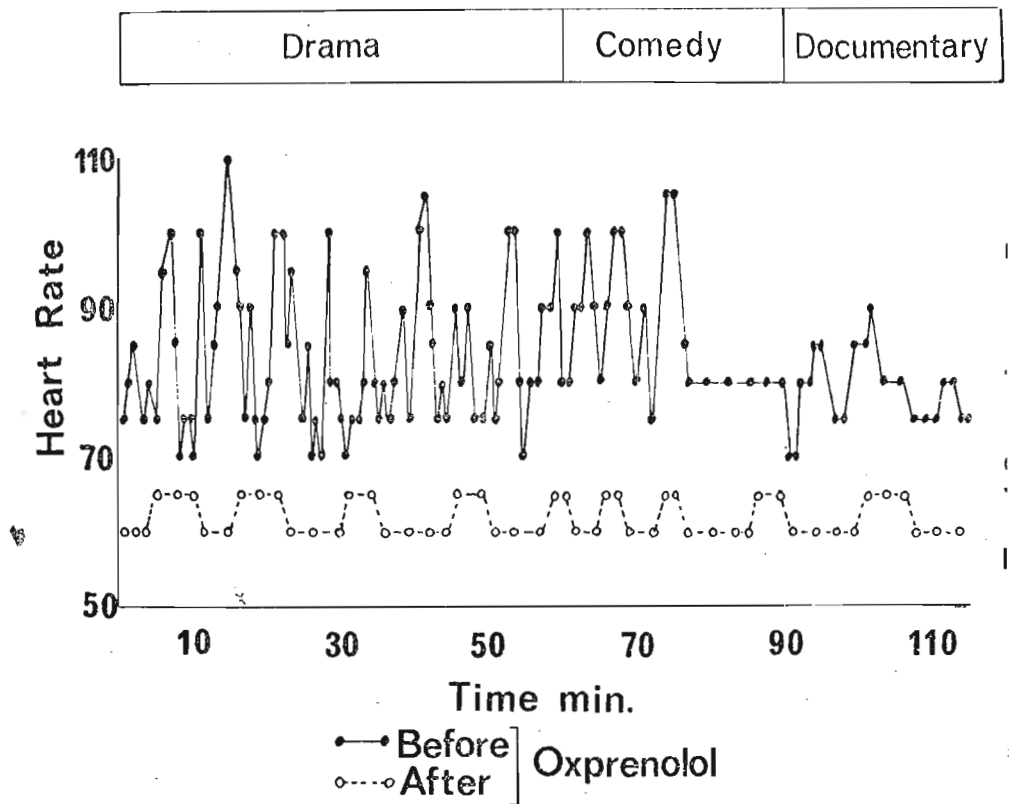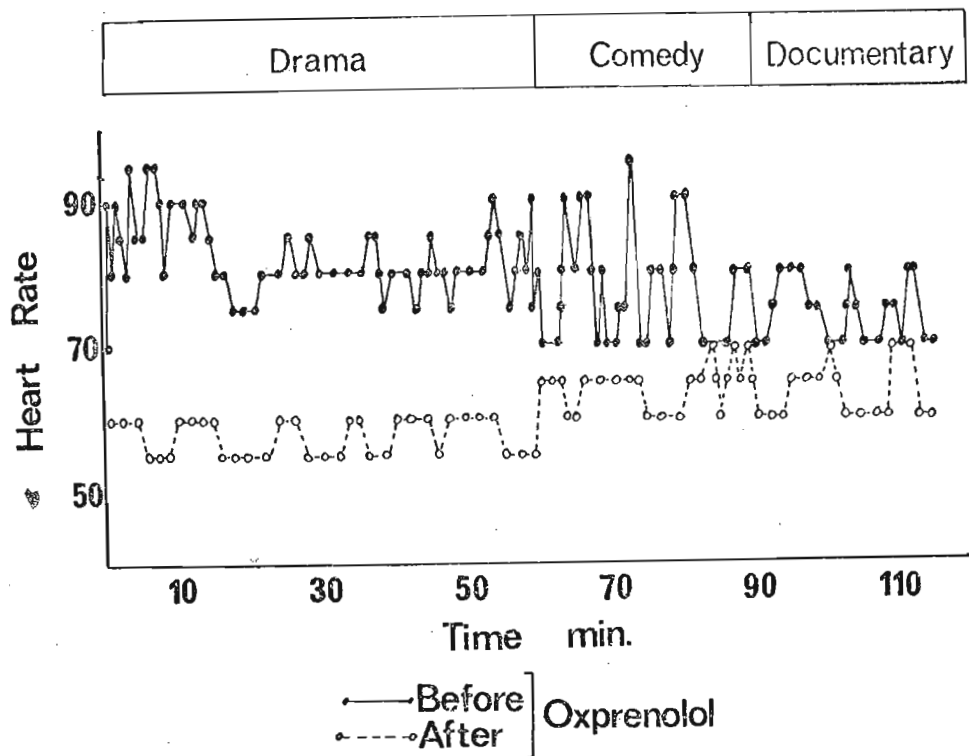
P - Placebo
O - Oxprenolol

FIGURE 47

Record of the heart rate in a patient with ischaemic heart disease watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.

FIGURE 48

Record of the heart rate in a patient with ischaemic heart disease watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.

FIGURE 49

Record of the heart rate in a patient with ischaemic heart disease
watching programmes of Drama, Comedy and Documentary on television
during placebo and the modification of the response by 40 mg oral oxprenolol
taken one hour before the programme.

Subjects	CONTROL HEART RATE PER MINUTE [1]						PEAK HEART RATE [2]						CUMULATIVE HEART RATE [3]											
	Drama (60 min)		Comedy (30 min)		Documentary (25 min)		Drama (60 min)		Comedy (30 min)		Documentary (25 min)		Drama				Comedy				Documentary			
													Total H.R.		HR/min		Total HR		HR/min		Total HR		HR/min	
	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O
JR	70	60	70	65	70	60	95	60	95	70	80	70	5278	3775	88	63	2565	1980	86	66	1930	1435	77	57
AS	80	65	76	65	80	65	120	70	100	65	90	70	5280	3728	88	62	2880	1995	96	67	2025	1610	81	64
SB	70	60	70	60	70	60	80	65	80	60	100	65	4793	3485	80	58	2668	1680	89	56	2205	1617	88	65
JM	70	60	70	60	75	60	100	70	105	65	90	65	4612	3270	77	55	2658	1484	89	63	2131	1631	85	65
SD	72	65	70	65	70	65	100	70	100	60	85	60	4682	3673	78	61	2784	1994	93	66	1975	1619	79	65
JB	72	60	70	62	70	60	105	65	80	70	90	65	4710	3485	79	58	2160	1860	72	62	2050	1546	82	62
DM	74	66	74	65	70	65	110	80	120	75	95	70	5875	4160	98	69	2838	1812	95	60	2275	1555	91	62
GA	75	60	75	60	70	60	110	70	105	65	90	65	4925	3210	82	54	2724	1920	91	64	1945	1605	78	64
MEAN	73	62	72	63	72	62	103	69	101	66	90	66	5019	3598	84	60	2660	1892	86	63	2067	1577	83	63
SEM ±	±1	±1	±1	±1	±1	±1	±4	±2	±5	±2	±2	±1	±153	±108	±3	±2	±80	±38	±4	±1	±44	±23	±2	±1

1. Heart rate during control period sitting still before test
2. Values relate to maximal heart rate during television viewing
3. Total heart rate during television viewing.

P - Placebo
O - Oxprenolol

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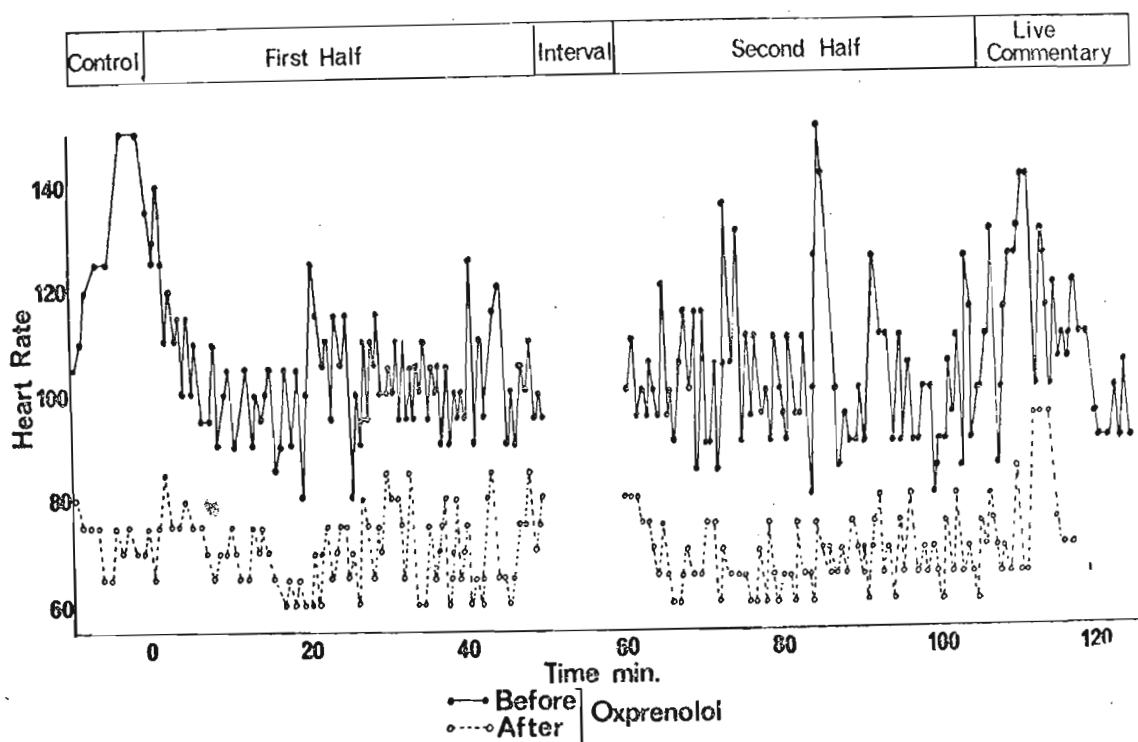
FIGURE 50

Record of heart rate of a radio and television commentator
during a live football match and the modification of the response produced
by 40 mg oral oxprenolol taken one hour before a similar match.
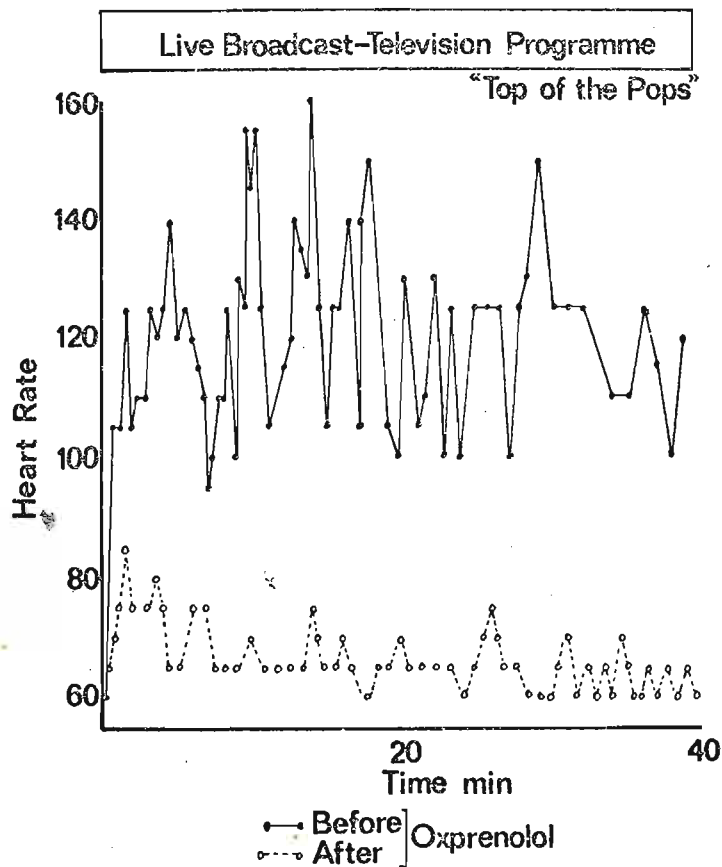
FIGURE 51

Record of heart rate in a radio and television personality during a
"pop" music show after ingestion of placebo and the modulation of the
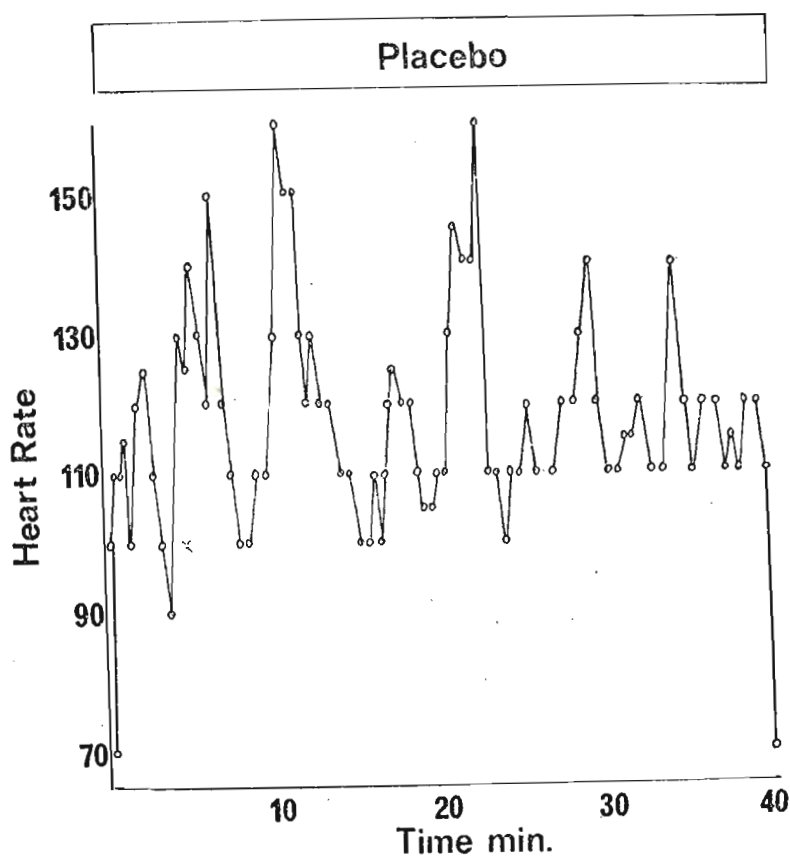response produced by 40 mg oral oxprenolol taken one hour before a
similar show.

FIGURE 52

Record of heart rate in the radio and television "pop"
personality during a show without the ingestion of any tablets.

TABLE 21 **HEART RATE RESPONSE OF RADIO AND TELEVISION COMMENTATORS AND PERFORMERS**

AND ITS MODIFICATION BY OXPRENOLOL

Subjects	Control Heart Rate [1] per minute		Peak Heart Rate [2]		Cumulative Heart Rate [3]			
					Total Heart Rate		Heart Rate per minute	
	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol	Placebo	Oxprenolol
B.D.	80	60	150	85	12778	8674	111	75
J.S. "pop" artist	76 (65)*	60	160 (160)*	85	4556	2315	114 (117)*	58

*   Denotes heart rate response without ingestion of any tablets.

1.   Heart rate during control period sitting still for 30 minutes before broadcasting/performance.
2.   Values relate to maximal heart rate during broadcasting/performance.
3.   Total heart rate during broadcasting/performance.
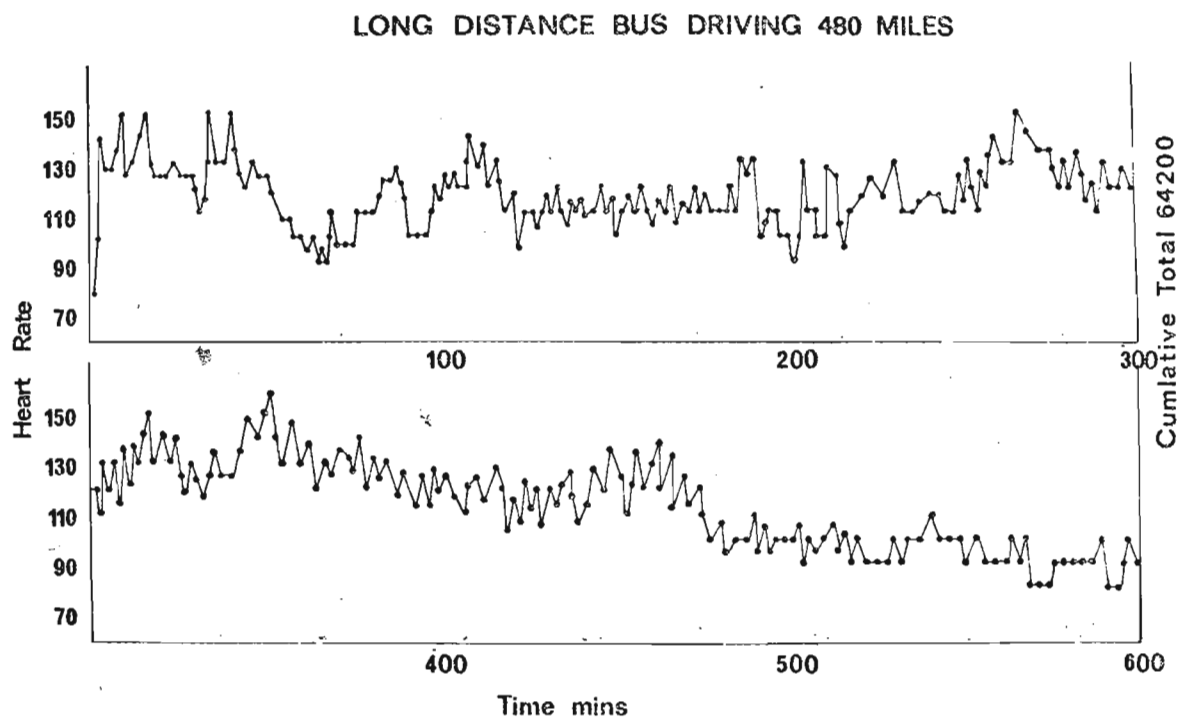
FIGURE 53

Record of heart rate during long distance bus driving.

EXCURSION BUS DRIVER
480 MILES
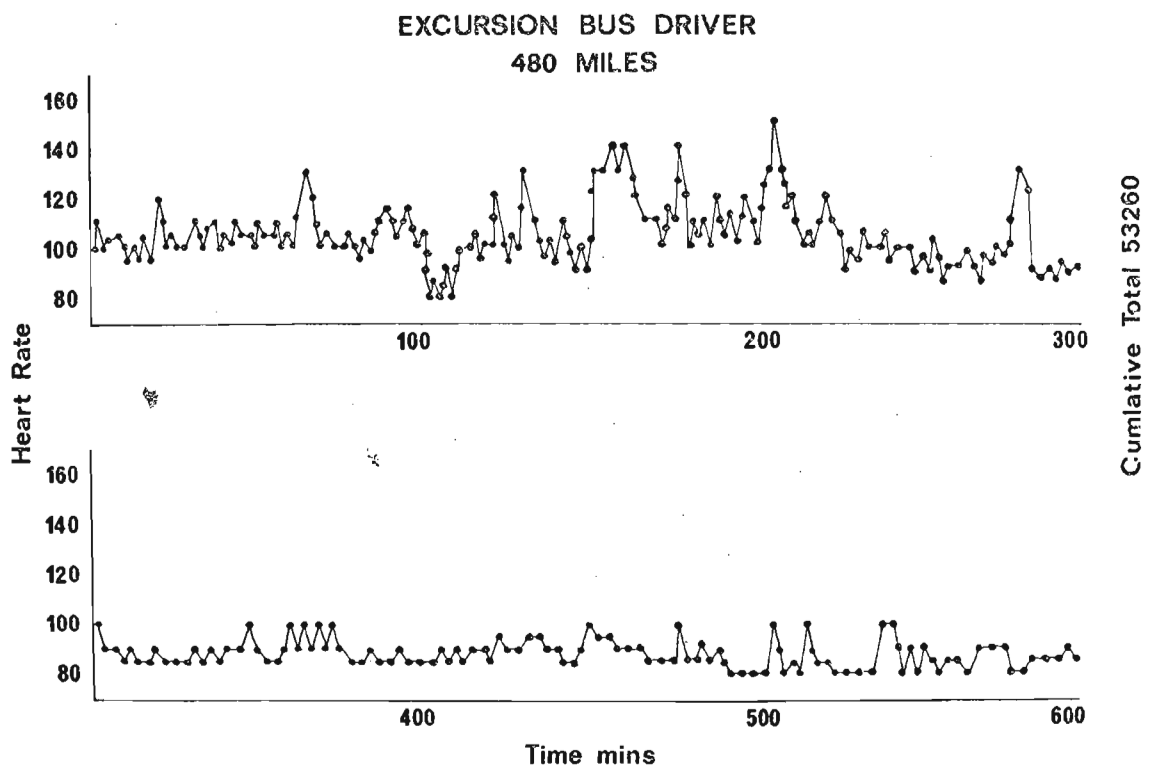
FIGURE 54

Record of heart rate during long distance bus driving.
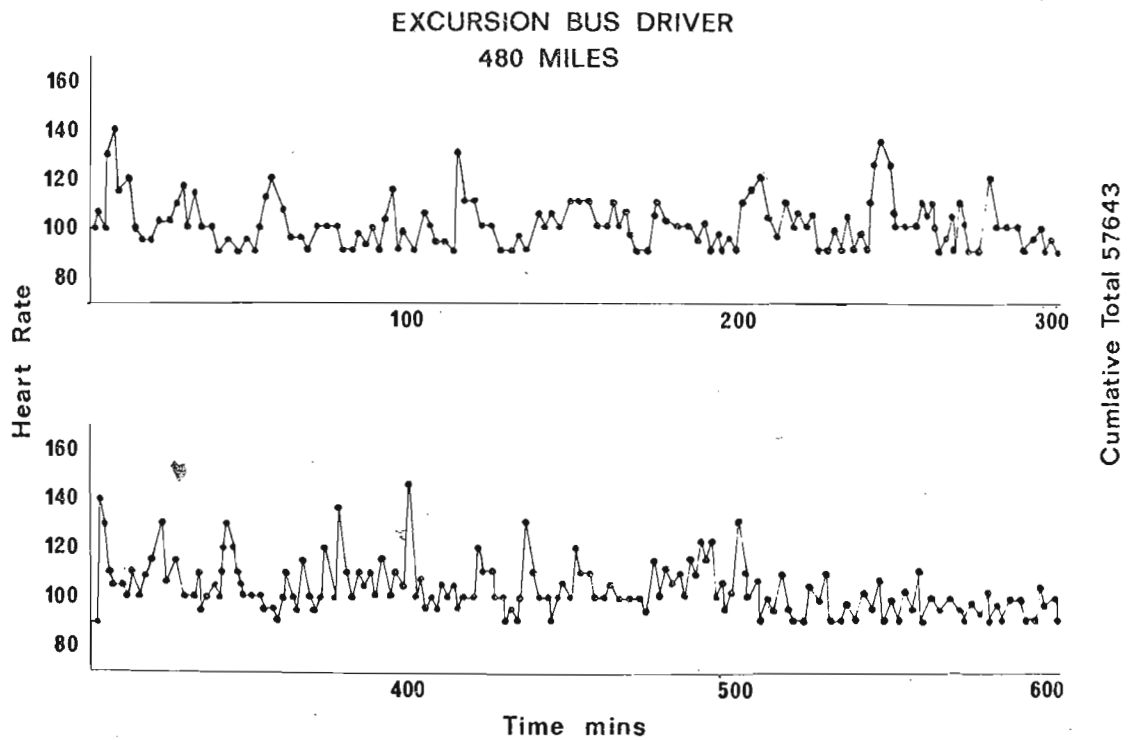
FIGURE 55

Record of heart rate during long distance bus driving .

TABLE 22   HEART RATE RESPONSE TO LONG DISTANCE BUS DRIVING

Subjects	Control Heart Rate [1] per minute	Peak Heart Rate [2]	Cumulative Heart Rate [3]		Increment. [4]
			Total Heart Rate	HR/min	
JB	78	150	64200 (600 mins)	107	27
JC	80	145	57643 (600 mins)	96	17
PJ	74	140	57893 (600 mins)	96	23
BC	68	150	48960 (480 mins)	102	33
BB	78	140	45450 (480 mins)	95	18
HS	80	150	53260 (600 mins)	89	10
SW	82	145	48800 (540 mins)	90	9
JS	72	135	62846 (600 mins)	105	14
HS	76	130	2428 (240 mins)	100	24
JB	78	130	9720 (90 mins)	108	28
HS	82	145	31600 (300 mins)	105	22
JCC	80	140	29586 (300 mins)	99	19
SW	80	120	11520 (120 mins)	96	17
MEAN	77	140		99	20
SEM ±	± 1	± 3		± 2	± 2

1. Heart rate during control period sitting still before start of journey.
2. Values relate to maximal heart rate during journey
3. Total heart rate during trip.
4. Percentage heart rate increment over control value during journey.
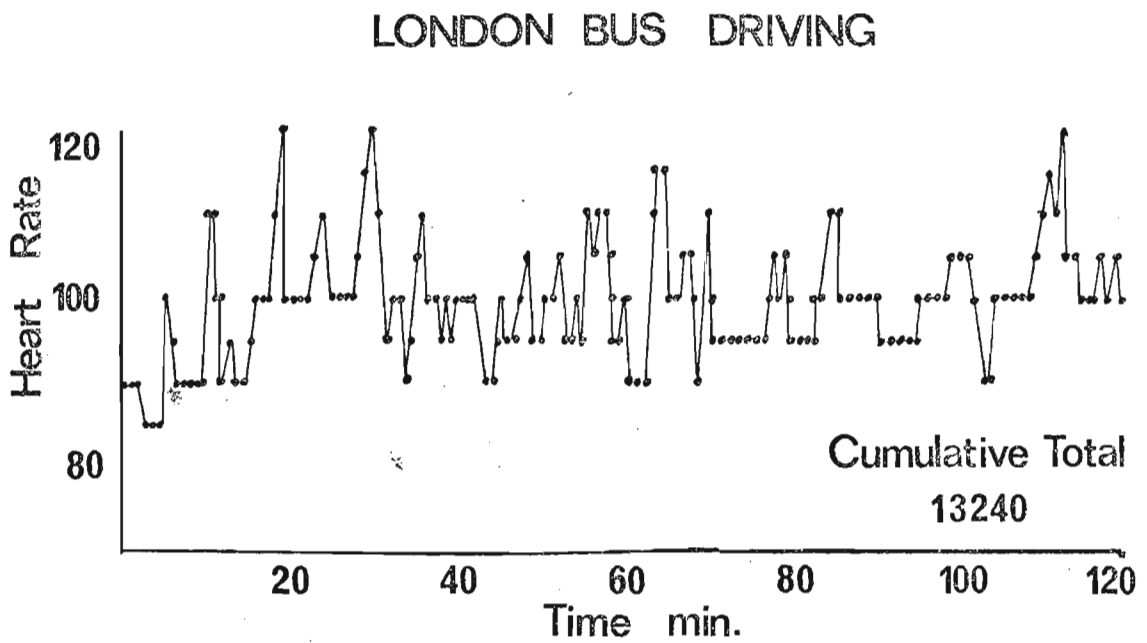
FIGURE 56

Record of heart rate during bus-driving in London.

FIGURE 57

Record of heart rate during bus-driving in London.

LONDON BUS DRIVING
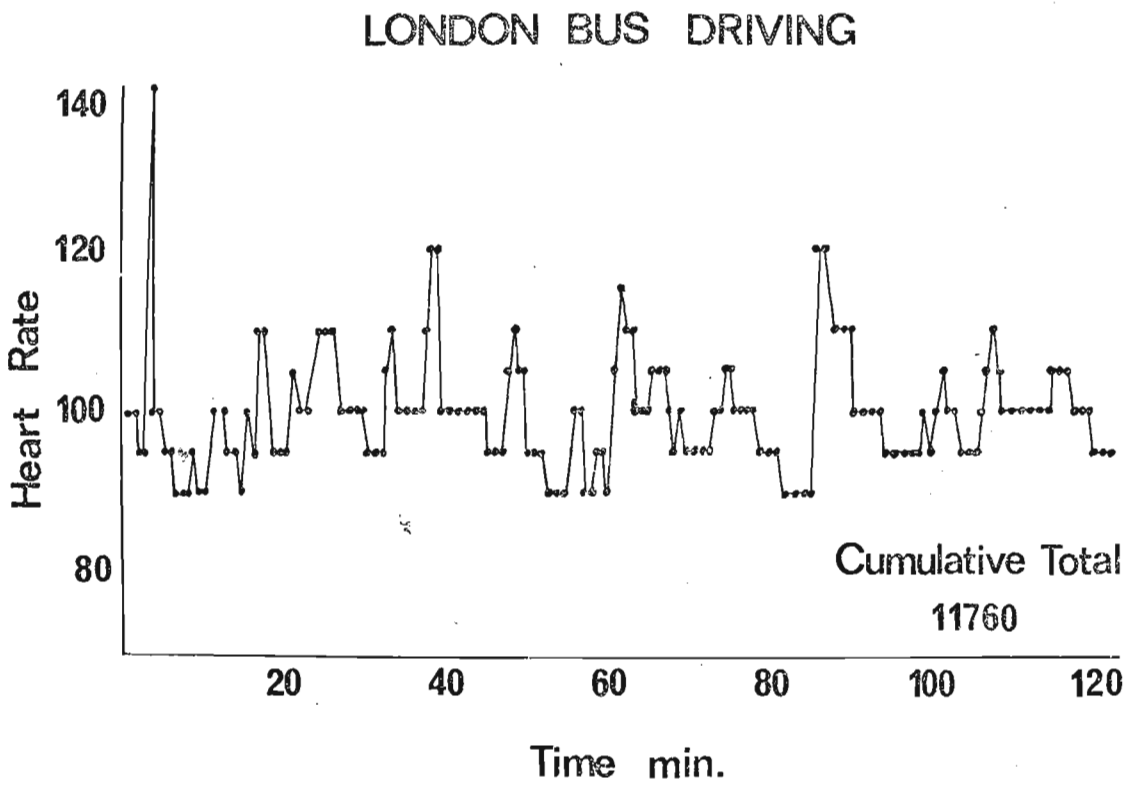
FIGURE 58

Record of heart rate during bus-driving in London.

TABLE 23   HEART RATE RESPONSE TO BUS DRIVING IN LONDON

	Control Heart Rate [1] per minute	Peak Heart Rate [2]	Cumulative Heart Rate [3]		Increment [4]
			Total Heart Rate	HR/min	
DP	80	140	11760 (120 mins)	98	22
TML	76	130	12780 (120 mins)	107	29
MJ	75	120	13240 (120 mins)	110	32
AC.	74	140	14720 (120 mins)	123	40
AW.	78	140	10200 (90 mins)	113	31
JS	70	130	9360 (90 mins)	104	33
MEAN	76	133	12010	109	31
SEM ±	±1	±3		±3	±2

1. Heart rate during control period sitting still before start of journey.
2. Values relate to maximal heart rate during journey
3. Total heart rate during trip
4. Percentage heart rate increment over control value during journey.

SUMMARY OF RESULTS

The following conclusions can be drawn from these studies:-

1) A number of everyday environmental situations were associated with a substantial increase in heart rate, i.e. motor-car and bus driving on a motorway and in city traffic, motor-car, rail and aircraft passenger, live and television viewing of soccer matches, television viewing of comedy, drama and documentary films, and radio and television commentators and performers.

2) These peaks of tachycardia were conspicuously reduced for up to 12 hours by 40 mg oral oxprenolol.

3) The peaks of tachycardia observed during motor-car driving were similarly suppressed by the same degree of beta-blockade as that resulting from the infusion of catecholamines.

4) None of the subjects noticed any appreciable effect on mental performance or any detectable change in their everyday skills after oxprenolol.

DISCUSSION

The discussion is arranged under the following headings:

1.   CRITIQUE of Method.

2.   INTERPRETATION of the Results

3.   CONCLUSIONS

CRITIQUE OF METHOD

In order that these studies may be placed in proper clinical perspective, it is important that their design and execution are critically examined. They may be criticised from the following view-points:

1) It may be argued that in the absence of a double-blind study the interpretation of the effects of oxprenolol is less valid. However, as was discussed in Study 1 a completely double-blind study undertaken during the stress of city motor driving showed that 40 mg oral oxprenolol conspicuously modified the peaks of tachycardia for up to 12 hours. It is impossible to hide the marked reductions in heart rate to a trained observer; only continuous blind E.C.G. recording would have answered the problem and this was impractical both technically and economically at the time. However, in the other more extensive single blind studies, the responses were measured objectively and were similar in all subjects, confirming their validity.

2) Ideally in the study of environmental stress on the heart, E.C.G. recordings over 24 hours and over several days is mandatory and would allow far more detailed study of the sympathetic stimulation of the heart. Unfortunately, during the time of this study, no such recording apparatus was available

3. The heart rate response recorded may have not been solely psychologically induced by in part the results of unnoticed

physical exertion. This criticism could be answered by the fact that the tachycardia response of the heart to psychologically induced stress (motor-car driving) and to the infusion of catecholamines was largely suppressed for up to 12 hours following 40 mg oral oxprenolol; the tachycardia induced by exercise in the same subjects was much less affected by the drug both in magnitude and duration (Study 1). Similar small doses of propranolol have also been shown to have relatively little effect on the tachycardia associated with isometric contraction of skeletal muscles, such as might be expected in gripping the arms of a chair (McDonald et al, 1966). Therefore the major portion of the tachycardia observed in these situations is a reaction to psychological stress and unassociated with significant physical exertion.

4) It could be argued that this pilot study consisted of a small number of male subjects. There is no reason to belive that the heart rate response to stress or its modulation by sympathetic antagonists is different in female subjects. Moreover, the environmental stresses studied were those frequently experienced by the same patients and subjects; all were studied during their normal everyday activities and none were subject to abnormal situations as many of the previous studies in the literature. Against this it

could be argued that because of extreme individual variations
in the heart rate response to environmental stress, this pilot
study should be extended to incorporate a larger cross-section
of the population.

5) There is a valid argument that the whole spectrum of environmental
stress on the heart should be studied; this was by necessity a limited
survey. It was not possible in such a pilot study to measure effects
of all situations in everyday life. The situations chosen were
thought to be the most stressful in the everyday life situation.

6) Anxiety is accompanied not only by an increase in heart rate but
perhaps also by an increase in cardiac output and the systemic
arterial pressure. Changes other than heart rate were not measured
as they were precluded by the design of the study. Even the
taking of the blood pressure by the cuff method besides being
unreliable would have caused some further anxiety under the
circumstances of study. All methods of measurement of cardiac
output involve procedures that can reasonably be expected to result
in additional mental stress. Therefore, although the measurement
of heart rate alone limits the interpretation of these results, at least
the non-invasive methods used were innocuous in this respect.

INTERPRETATIONS OF THE RESULTS

Accepting the validity of the foregoing criticisms of the methods used
the results of the present studies are clear-cut.

Many forms of everyday travel were consistently associated with

conspicuous peaks in heart rate. In this respect motor-car, bus

driving and airtravel were associated with greater tachycardia than motor

car travel as a passenger; rail travel was by far the least disturbing.

High peaks in heart rate were found on television viewing of drama and comedy

films than during documentary programmes. Similar responses were seen

in live radio and television commentators. There was no apparent

difference between the responses in normal subjects and patients with proven

ischaemic heart disease. The tachycardia found during these situations

was conspicuously suppressed by 40 mg oral oxprenolol in all subjects. The

rapidity of action of the drug was illustrated by observations during

spectator viewing whilst the exciting stimuli was maintained; the heart

rate increase was abolished within thirty minutes of its ingestion. The

modulation of stress-induced tachycardia by this dose of drug was

maintained for up to 12 hours.

Cardiac Work during Mental Stress

What do these repetative increases in cardiac sympathetic activity

mean in terms of increase in cardiac work?

There is little doubt that increases in heart rate are directly responsible

for substantial increments in myocardial oxygen consumption (Yeo, 1885,

Evans and Matsuoka, 1915; Laurent et al, 1956; Van Citters et al, 1957;

Maxwell et al, 1958; Mitchell et al, 1963; Van der Veen and Willebrands

1967; Boerth et al, 1969). But there are few comprehensive circulatory

studies of the overall haemodynamic consequences of emotionally induced

stress. Anxiety in subjects undergoing circulatory investigation has been

shown to be accompanied by increases in heart rate, cardiac output and

systemic arterial pressure (Grollman, 1929; Stead et al, 1945; Hickman

et al, 1948; Stevenson et al, 1949). These changes are increased by any

further psychological stress, such as forced mental arithmetic (Brod et al, 1959). The tachycardia, increase in cardiac output and blood pressure are accompanied by vasoconstriction in the skin and renal circulation (Brod et al, 1954; French et al, 1959) and by metabolically independent vasodilatation in muscle (Blair et al, 1959; Barcroft et al, 1960; Brod et al, 1962). These circulatory changes observed during stress imply substantial increases in left ventricular work. It must also be pointed out that the cardiac changes measured in these studies were in response to relatively mild stressful conditions which may give some indication of the extent and magnitude of the circulatory changes that may result from more stressful situations. The heart rate is one of the predominant variables related to the production of symptoms of myocardial ischaemia in patients with coronary heart disease (Robinson, 1971; Taylor, 1973), and is probably of more importance in this respect than changes in systemic arterial pressure (Sharma et al, 1973).

A further factor that must be taken into account in this respect is that in the majority of circumstances in which such measurements were made, the tachycardia associated with psychologically induced stress was accompanied by a high concentration of plasma catecholamines, particularly nor-adrenaline (Taggart et al, 1969; Taggart and Carruthers, 1971) or by their increased urinary secretion (Bogdonoff et al, 1960). It is perhaps relevant in this respect to point out that catecholamines appear to increase myocardial oxygen consumption over and above that purely related to their positive chronotropic and inotropic effects (Raab et al, 1962). Thus, there would appear to be no reasonable doubt that

stress induced by emotional or psychological factors results in substantial increases in cardiac work; these increases are probably underestimated by the use of the heart rate index alone. The peaks of tachycardia observed in these studies were of a similar order to those known to be associated with the production of myocardial ischaemia in patients in whom the coronary arterial blood supply is limited. Yet these were associated with <u>normal everyday conditions of living</u>. Whilst the effects of such increases in heart rate may be borne with impunity by the heart with normal arterial supply, it can be expected with reasonable confidence that the heart limited by coronary arterial disease will outstrip its available blood supply at these rates. In fact, this is the basis of the diagnostic atrial pacing test for the precipitation of angina pectoris. Furthermore, these heart rates imply very considerable sympathetic stimulation of the heart. The resulting direct increase in myocardial contractility can be expected to result in an increase in myocardial oxygen consumption considerably greater than that directly due to the increased rate alone. This is the clinical basis for the provocative isoprenaline infusion test for ischaemic heart disease. (Wexler et al, 1971).

<u>Pathophysiological effects of Stress on the Heart</u>

Are such increases in cardiac work immediately hazardous to the heart?

There are no haemodynamic studies which would suggest that the stress induced in subjects under cardiac investigation are associated

with impairment of left ventricular function;   no direct measurements
of left ventricular activity during emotional stress appear to have been
made.   The catheter studies of Hickman et al, 1948 can be used as
a guide;   anxiety induced in five "normal" subjects was not accompanied
by any abnormal increase in pulmonary artery pressure.   But there
was a rise of 12 mm Hg in the mean pulmonary artery pressure without
change in the cardiac output (2.2 4 min/sq.m) in a patient in congestive
heart failure during induced anxiety.   Although changes in pulmonary
artery pressure are at best an insensitive indicator of changes in left
ventricular filling pressure, directional changes in both pressures
are similar (Balcon et al, 1972).   Thus it is possible that mental
anxiety may adversely affect the pumping function of the failing or
ischaemic heart.

The heart rate peaks repeatedly seen during these everyday stressful
activities can with reasonable confidence, be expected to precipitate
a state of myocardial ischaemia in many patients with obstructive
coronary artery disease.

Of more definite relevance to my studies are the studies of
electrocardiographic changes in subjects during induced psychological
stress.   The evidence that the type of stressful situation under
consideration in this thesis induced pathological changes in the
electrocardiogram of "normal" subjects is difficult to evaluate.
Electrocardiographic changes suggestive of myocardial ischaemia
have been reported in association with the tachycardia induced by fear.

Mainze and Krause (1940) described electrocardiographic changes
suggestive of myocardial ischaemia in 16 of 25 patients without other
evidence of ischaemic heart disease and 8 of 12 patients with definite
evidence of such disease during the anxiety immediately before surgical
operations; the changes disappeared after induction of anaesthesia.
A number of reports have also described electrocardiographic changes
during spontaneous anxiety states in otherwise normal patients
(Loftus et al, 1945; Heyer et al, 1947; Magendantz and Shortsleeve,
1951) and during anxiety induced by cardiovascular investigations
(Stevenson et al, 1949). Even more relevant to my study was the
demonstration of a close association between the heart rate and
electrocardiographic ischaemic changes during motor car driving.
Hoffman (1965) in an extensive study of 600 healthy male drivers and
26 drivers with coronary artery disease, claimed to have demonstrated
no "pathological" electrocardiographic changes in healthy drivers
as compared to changes in 12 per cent in subjects with coronary
heart disease driving in low traffic densities. In city driving, with
high traffic density "pathological" changes occurred in 16 per cent of
healthy drivers and 46 per cent of drivers with coronary disease.
Unfortunately, the clinical categorization of the patients studied, the
exact definition of electrocardiographic evidence of abnormality and
the observer variation in interpretation of the electrocardiographic
findings was not given. Simonson and his colleagues (1968) described
"T-wave changes" during long distance motor car driving in five

healthy males aged 26 - 77 years with normal post-exercise electrocardiograms. However, "T-wave changes" are not pathognomonic of myocardial "hypoxia" although they have been observed during infusion of adrenaline (Mitchell and Shapiro, 1954; Lepeschkin et al, 1960) and it has been claimed that such changes are a reflection of subendocardial ischaemia (Sodi Polares et al, 1971) there is no categoric evidence of this supposition particularly in the presence of high heart rates. Bellet and his co-markers (1968) reported that no significant changes were noticed in the electro-cardiogram recorded continuously in 65 normal subjects during a period of two and a half hours driving in "favourable conditions". In similarly easy driving conditions electrocardiographic changes probably significant of myocardial ischaemia, e.g. S-T segment depression multifocal premature contractions, ventricular bigeminal or trigeminal rhythm, were observed in 11 of 66 patients with known coronary heart disease. More recently Taggart et al (1969) reported a close association between the heart rate and electrocardiographic ischaemic changes during motor car driving in dense commuter traffic in 13 of 24 patients with ischaemic heart disease and 3 of 32 normal subjects. Furthermore, it should not be ignored that it is common clinical experience that many patients with established ischaemic heart disease suffer typical anginal symptoms during the stress of motor car driving, during the excitement of live football matches, watching exciting television programmes or viewing mystery films.

Despite the variability in observer recognition and oral interpretation of electrocardiographic changes, certain conclusions can be drawn from these and my studies. Although the increase in cardiac sympathetic stimulation associated with extremely stressful situations may give rise to myocardial ischaemia even in the normal heart, there is no conclusive evidence that this results from everyday emotional stimuli. However, in patients with coronary heart disease, even such common everyday tasks such as motor car or bus driving may precipitate myocardial ischaemia, and it is of relevant interest that similar symptomatic and electrocardiographic changes may be produced in such patients by raising the heart rate to similar levels by the infusion of catecholamines (Wexler et al, 1971).

This evidence, together with that of the foregoing, suggests that while the everyday psychological stresses met in modern urban existence probably have no immediately deleterious effects on the normal heart, there is reasonable evidence that they result in myocardial ischaemia in subjects with coronary artery disease.

There was a conspicuous suppression of the tachycardia associated with stressful situations in all subjects after 40 mg oral oxprenolol. Both studies confirm this conclusion.

Study I suggests the similarity in the magnitude and duration of the stress and isoprenaline tachycardia to the same degree of beta-receptor antagonism suggests that the heart rate response to both stimuli may be due to the same mechanism, namely stimulation of

the cardiac beta-receptors by circulating catecholamines.

Although such a supposition should be susceptible to direct proof by the measurements of circulating catecholamines the practical and technical difficulties in making such measurements precludes their valid use at the present time. The quite different pattern of response of exercise tachycardia to the same degree of beta-receptor blockade would suggest that a difference mechanism is responsible for heart rate response to exertion. This differential effect of beta-receptor antagonism on the cardiac response to psychological stress and exercise has also been observed in other situations. Eliasch et al, (1967) observed that propranolol inhibited the heart rate increase during simulated flight in pilots but had much less effect on the tachycardia of exercise. Imhoff and his colleagues (1969) found similar differential effects of oxprenolol on the tachycardia associated with pre-jump anxiety and that associated with the physical exertion of ski-jumping. The response of the heart rate to exercise in this range of exertion is preponderantly due to vagal withdrawal (Donald and Shepherd, 1963: Robinson, 1966). Thus the small doses of oral oxprenolol that completely suppressed catecholamine or stress induced tachycardia had relatively little effect on exercise performance of the heart. Thus the effects on the heart of such environmental stresses as were studied in the present investigation may be largely suppressed with doses of beta-receptor antagonists that could be expected to have little noticable effect on patients' exercise

capability during normal everyday life.

The Effect of Emotional Stress on the Course of Established Ischaemic Heart Disease

Do these responses aggravate the course of established ischaemic heart disease? The factors associated with the progression of established coronary heart disease are unknown. There is, at present, no evidence that the frequency of emotionally induced or exercise induced myocardial ischaemia has any bearing on the natural history of the disease. But as the pain sometimes associated with ischaemic heart disease is often accompanied by enzyme changes in the peripheral blood probably indicative of myocardial cell death, and as the majority of patients dying from ischaemic heart disease usually exhibit widespread myocardial fibrosis, there is every reason to suppose that recurrent attacks of myocardial ischaemia, however induced, are deleterious in the long term. Even more speculative is the association between these circulatory responses and the 'sudden death' associated with coronary artery disease. In an autopsy study of the causes of sudden natural death in motor car drivers, Peterson and Petty (1962) found the large majority of deaths to be associated with severe coronary heart disease or actual myocardial infarction. Chiang and his colleagues (1969) found distinct correlation between the prevalence of ventricular premature contractions, coronary artery disease and sudden death. It is of interest that extrasystoles are commonly noted in anxiety states, are frequently precipitated by

catecholamine infusions (Lapeschkin et al, 1960) and have been

noticed during motor car driving (Taggart et al, 1969). Although this

evidence relating mental stress, its effects on the heart and sudden

death is speculative, it is based on reasonable logic. Fortunately,

the beta-receptor antagonists provide a socially acceptable medical

tool for putting this important thesis to the test.

The Relationship between Mental Stress and Precocious Coronary Heart Disease

Despite many speculative hypotheses and assertions(Wolff, 1950;

Morris and Crawford, 1958; Carruthers, 1969), there is, as yet,

no acceptable evidence that stress and coronary heart disease are

casually related. A number of studies on bus drivers, train drivers,

aircraft pilots and subjects in sedentary occupations have all claimed

a connection between occupation and an increased incidence of ischaemic

heart disease. But the validity of these conclusions is in serious

doubt due to two main factors; the personal characteristics of the

subjects in each occupational group and the basis on which the clinical

diagnosis of coronary heart disease was made. These problems

are highlighted by the early studies of Morris and his colleagues (1953).

These authors concluded that there was an increased incidence of

"coronary heart disease" in London bus drivers as compared to bus

conductors. But the clinical diagnoses were "obtained from general

practitioners" and "hospital certificates" or from medical officers'

reports of examinations carried out 28 days or more after the illness.

The quality of such information, presumably much of it subjective, is unacceptable for the present day diagnosis of ischaemic heart disease. Later it was reported that at the time of taking up their occupation, the bus drivers were already considerably fatter men than the conductors (Morris et al, 1956). It may be that the recurrently high heart rate of bus drivers does indeed predispose them to coronary heart disease, but there is no convincing evidence of such a relationship. A similar argument may be levelled at the claim that stress on telephonists predisposes them to precocious coronary heart disease as compared to postmen (Morris et al, 1953). However, although such critical reasoning is essential if such findings are to be placed in proper clinical and social perspective, it is equally important that the potential value of such studies in the evaluation of the effects of urbanized living on the heart is not ignored.

Although the demonstration of such a relationship does not necessarily implicate a cause-effect relationship, the findings in this thesis that small doses of beta-receptor antagonists completely suppress the cardiac effects of such stress, again suggests that these drugs may provide a useful tool in the test of such a hypothesis.

CONCLUSION

The results of this study of the effects of emotional and psychological stress on the heart must be placed in clinical and social perspective. Although the observations made raise many exciting questions in the coronary heart disease scene, their interpretation

must be tempered by critical consideration of the design and objective findings of the study. The results of any single report such as this, designed as a limited pilot study, must necessarily be treated with reserve until confirmed by observations in a larger population. The stresses selected for study were arbitrarily chosen from a wide range of possible situations; the effects of many other types of everyday stress require similar evaluation. These results concern only changes in heart rate; other less accessible circulatory variables must be measured before the full spectrum of the circulatory responses to everyday life situations are known. But within these critical limitations these studies indicate that the stresses of everyday life, many of which are accepted as normal in a Western urbanized society result in substantial sympathetic stimulation of the heart. There is no evidence that such psychological or emotional stresses are damaging to the normal heart or associated with precocious coronary heart disease. But there are suggestive indications that such responses may be harmful to the heart afflicted by coronary artery obstruction. However, there is as yet no evidence that suppression of these effects stays or reverses the natural course of ischaemic heart disease. Furthermore, these studies have shown that the effect of such stresses on the heart may be completely prevented by small doses of beta-receptor antagonists which have little effect on everyday exercise performance. The beneficial effects of such agents on the amelioration of symptoms in angina pectoris is

well established.   The results of this study, if confirmed, would

suggest that their evaluation in progressive ischaemic heart disease

and perhaps in its prevention is also worthy of serious consideration.

APPENDIX

1.   Summary Tables of the subject studied.

2.   Remaining illustrations from the results of the main text.

TABLE 24   SUBJECTS (ONLY MALE SUBJECTS WERE STUDIED)

I - NORMAL SUBJECTS

A)   Healthy Normal Subjects

Subjects	Age	Height in ft and ins.	Weight in stones	B.P.	Occupation
SHT	46	5' 10"	11.00	120/80	Consultant Physician
MKM	35	5' 10"	11.80	115/75	Physician
MP	28	5' 11"	11.50	120/70	Senior Technician
AF	26	5' 9"	10.50	120/70	Physician
PH	26	5' 11"	11.00	115/70	Senior Technician
CNR	56	5' 10"	12.00	130/80	Physician
GAP	36	5' 9"	12.00	125/80	Company Director
GHK	26	5' 11"	11.00	120/80	Physician

B)   Normal Subjects Sensitive to
Television Viewing

JS	23	5' 9"	11.00	120/80	School Teacher
AC	25	5' 9"	10.00	115/80	Salesman
WL	50	5' 8"	10.00	130/70	Works Foreman
AC	30	5' 9"	10.50	115/75	Salesman

TABLE 25 PATIENTS WITH ISCHAEMIC HEART DISEASE

A) Patients with Exercise induced Angina Pectoris

Subjects	Age	Ht. in ft and ins.	Wt in stones	B.P.	Occupation	Clinical Diagnosis
JR	35	5' 10"	12.00	110/80	Company Director	Exercise induced angina pectoris for 12 months.
LG	60	5' 8"	11.50	135/80	Business Executive	Exercise induced angina pectoris for six months.
AS	53	5' 11"	13.00	140/80	Company Director	Exercise induced angina pectoris for nine months
JB	60	5' 6"	10.50	130/70	Business Executive	Exercise induced angina pectoris for nine months
JO	40	5' 10"	11.75	140/75	Company Director	Exercise induced angina pectoris for 12 months
DB	45	5' 9"	11.00	135/80	Company Director	Exercise induced angina pectoris for six months

B) Patients with Myocardial Infarction

Subjects	Age	Ht. in ft and ins.	Wt in stones	B.P.	Occupation	Clinical Diagnosis
SB	58	5' 9"	11.00	110/70	Retired Business Executive	Posterior Myocardial Infarction 9 months prior to study; confirmed by E.C.G. changes and elevated serum enzymes
JM	35	5' 8"	12.00	120/80	Company Director	Anterior myocardial infarction 6 months prior to study; confirmed by E.C.G. changes and elevated serum enzymes
SD	38	5' 8"	12.50	130/75	Branch Manager of Motor Factory	Anterolateral infarction 12 months prior to study confirmed by E.C.G. changes and elevated serum enzymes
DM	36	5' 10"	13.00	120/80	Works Manager British Leyland	Inferior myocardial infarction 12 months prior to study; confirmed by E.C.G. changes and elevated serum enzymes.
McCaa	50	5' 11"	12.25	130/80	Factory Director	Inferior myocardial infarction 12 months prior to study; confirmed by E.C.G. changes and elevated serum enzymes.
GA	50	5' 9"	11.00	130/80	Company Director	Anterior myocardial infarction 6 months prior to study; confirmed by E.C.G. changes and elevated serum enzymes

TABLE 26 BUS DRIVING

A) Long Distance Bus Drivers					B) City Bus Drivers				
Subjects	Age	Height in ft and ins.	Weight in stones	B.P.	Subjects	Age	Height in ft and ins.	Weight in stones	B.P.
JB	50	5' 8"	10.00	135/85	DP	32	5' 10"	12.00	130/70
JC	34	5' 10"	12.00	120/80	TML	30	5' 9"	11.50	120/80
PJ	48	5' 9"	11.50	120/75	MJ	26	5' 9"	11.00	115/75
BC	36	5' 8"	9.75	130/70	AC	28	5' 8"	11.25	115/70
BB	36	5' 11"	10.50	120/75	AW	40	5' 11"	12.25	125/80
HS	58	5' 10"	12.00	130/80	JS	36	5' 10"	10.50	120/80
SW	32	5' 8"	10.00	115/70					
JS	46	5' 10"	11.75	120/80					
HS	46	5' 7"	10.00	125/75					
JB	30	5' 9"	12.00	115/80					
HS	30	5' 7"	11.00	120/80					
JCC	45	5' 8"	9.75	130/70					
SW	50	5' 10"	12.00	130/85					

TABLE 27   B.B.C. RADIO AND TELEVISION COMMENTATORS AND PERFORMERS

Subject	Age	Height in ft. ins.	Weight in stones	B.P.	Occupation
BD	36	5' 10"	11.00	120/75	Radio and Television Commentator
JS	48	5' 9"	10.50	130/80	Radio and Television Performer

MOTOR-CAR DRIVING
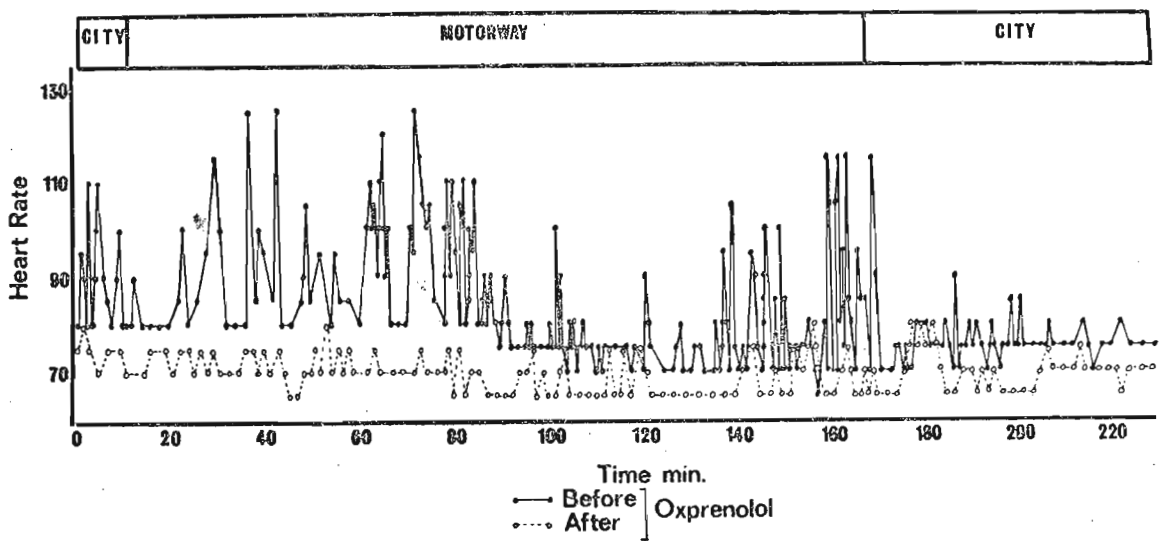
FIGURE 59

Records of the heart rate in a normal subjet driving a motor-
car between Leeds and London before and after 40 mg oral oxprenolol.
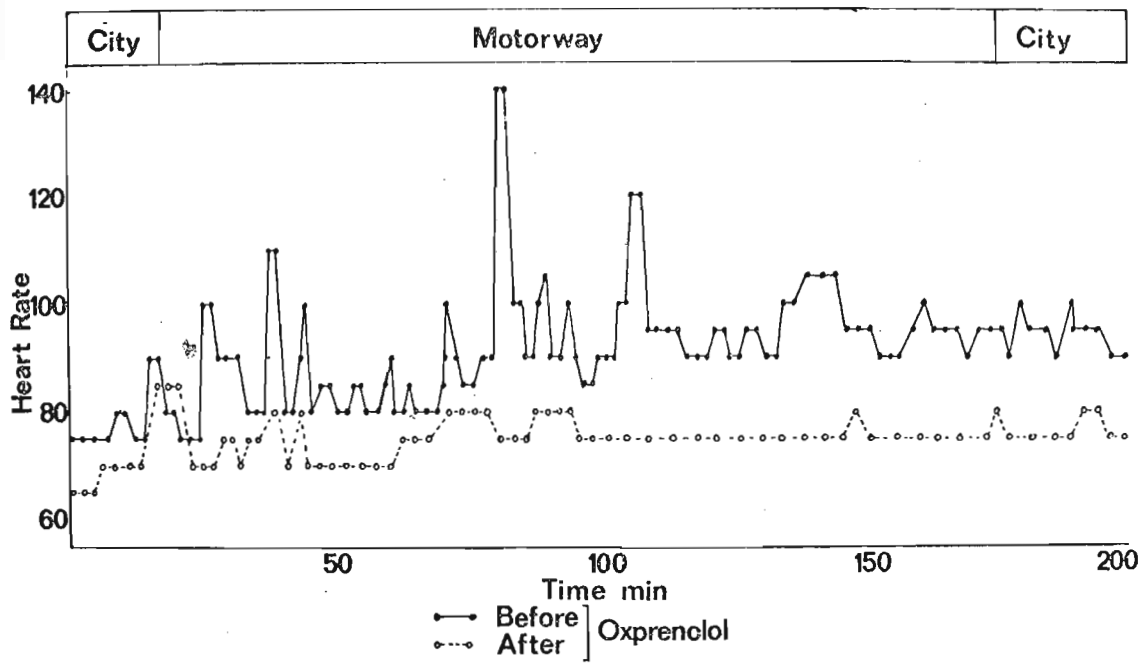
FIGURE 60

Records of the heart rate in a normal subject driving a motor-car between Leeds and London before and after 40 mg oral oxprenolol.
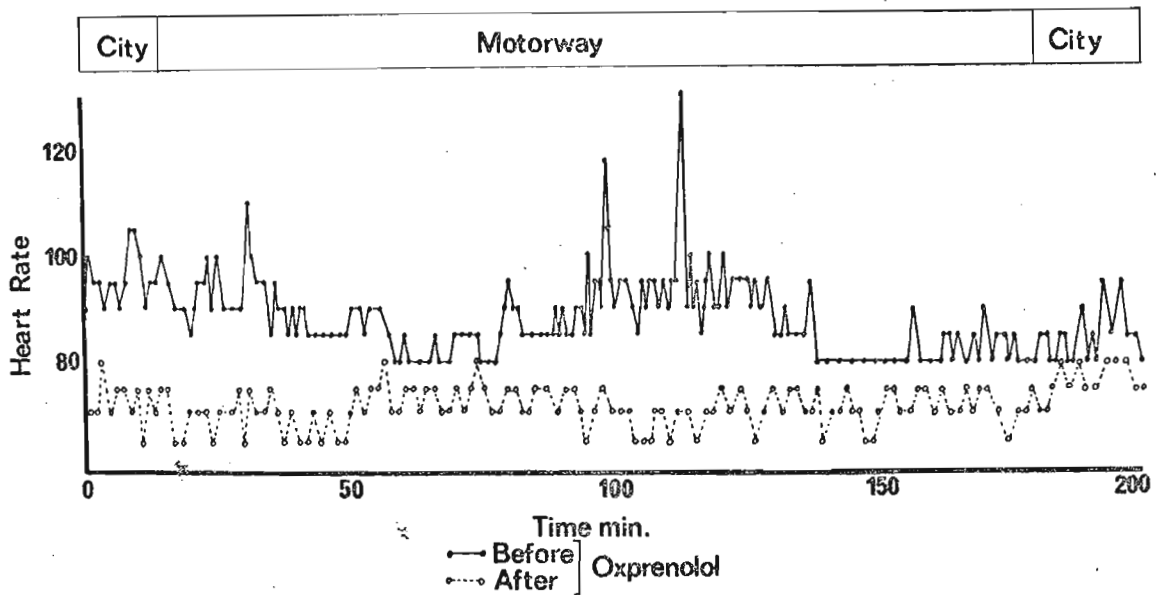
FIGURE 61

Records of the heart rate in a normal subject driving a motor-
car between Leeds and Newcastle before and after 40 mg oral oxprenolol.
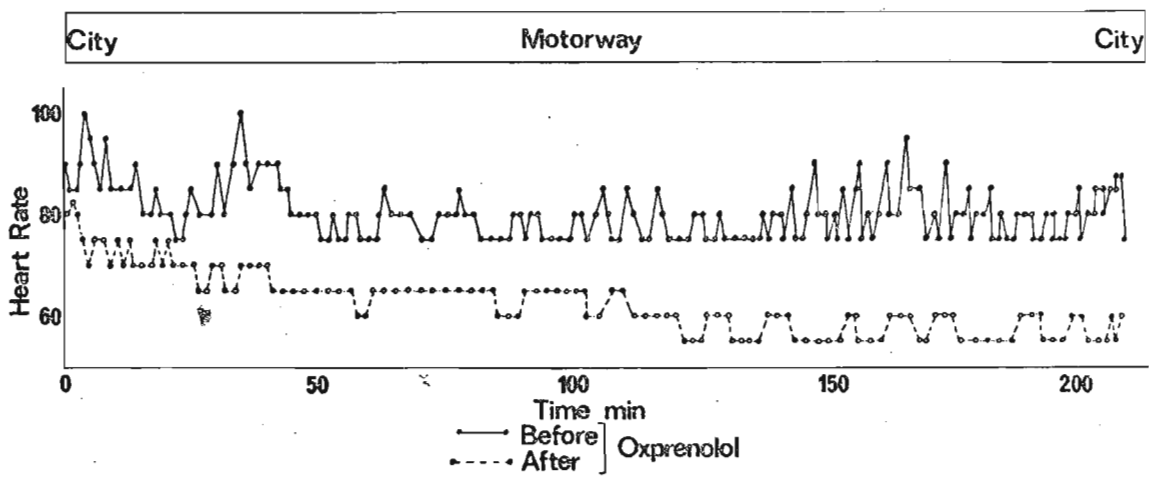
FIGURE 62

Records of the heart rate in a normal subject driving a motor-car between Leeds and Newcastle before and after 40 mg oral oxprenolol.
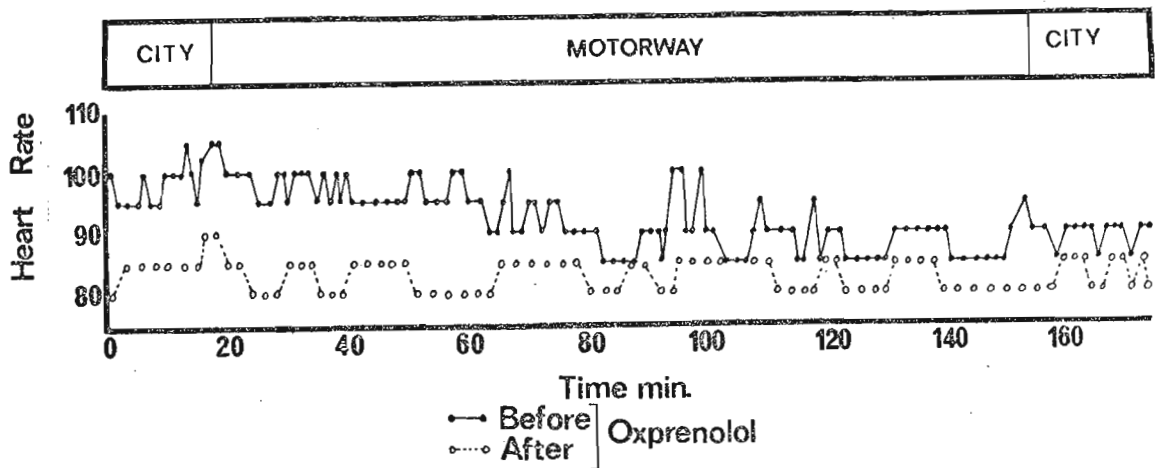
FIGURE 63

Record of the heart rate in a patient with ischaemic heart disease driving a motor-car between Leeds and London before and after 40 mg oral oxprenolol.
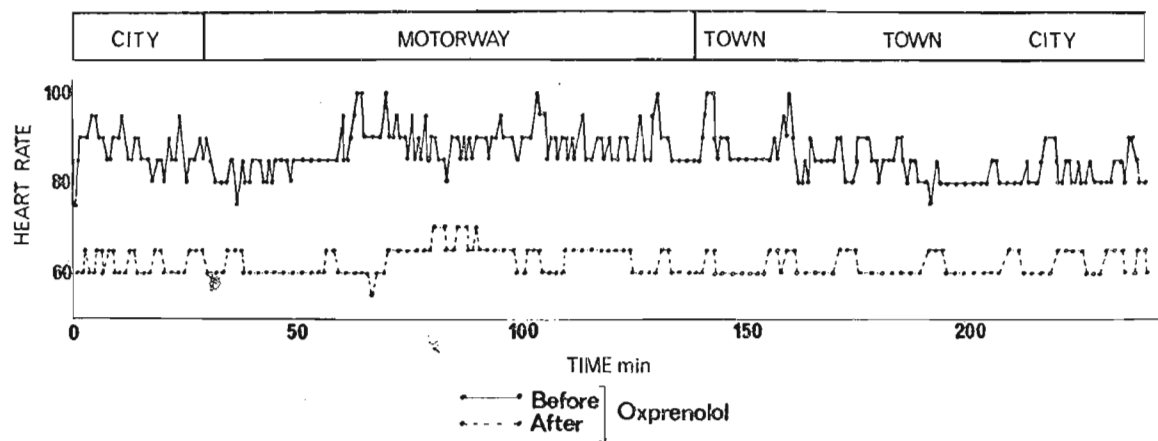
FIGURE 64

Record of the heart rate in a patient with ischaemic heart disease driving a motor-car between Leeds and London before and after 40 mg oral oxprenolol.
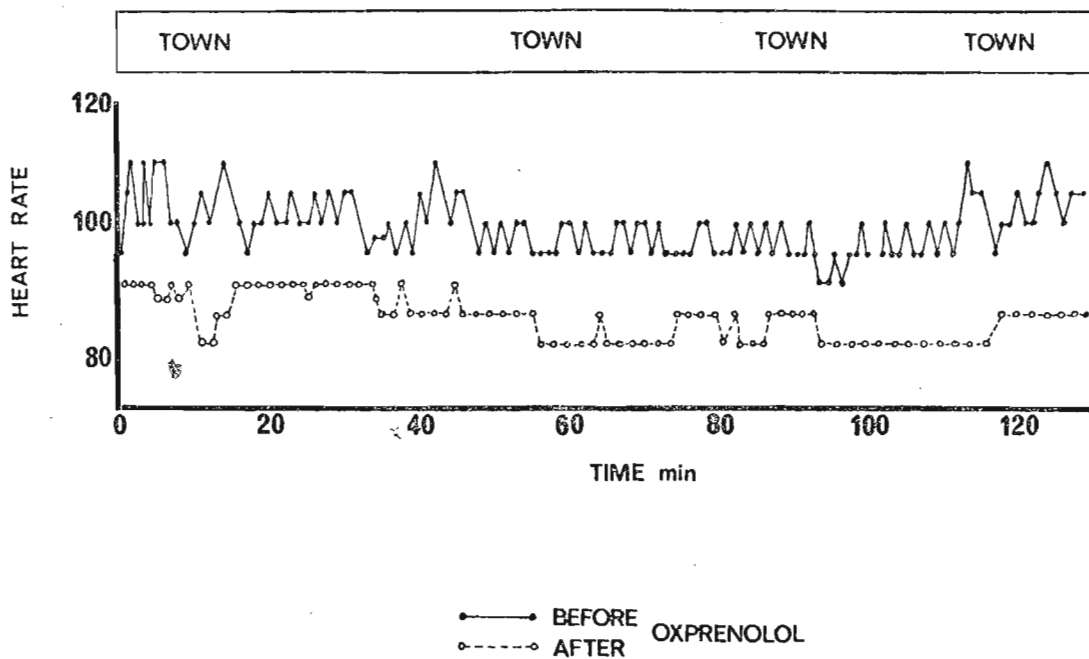
FIGURE 65

Record of the heart rate in a patient with ischaemic heart disease driving a motor-car between Leeds and Newcastle before and after 40 mg oral oxprenolol.
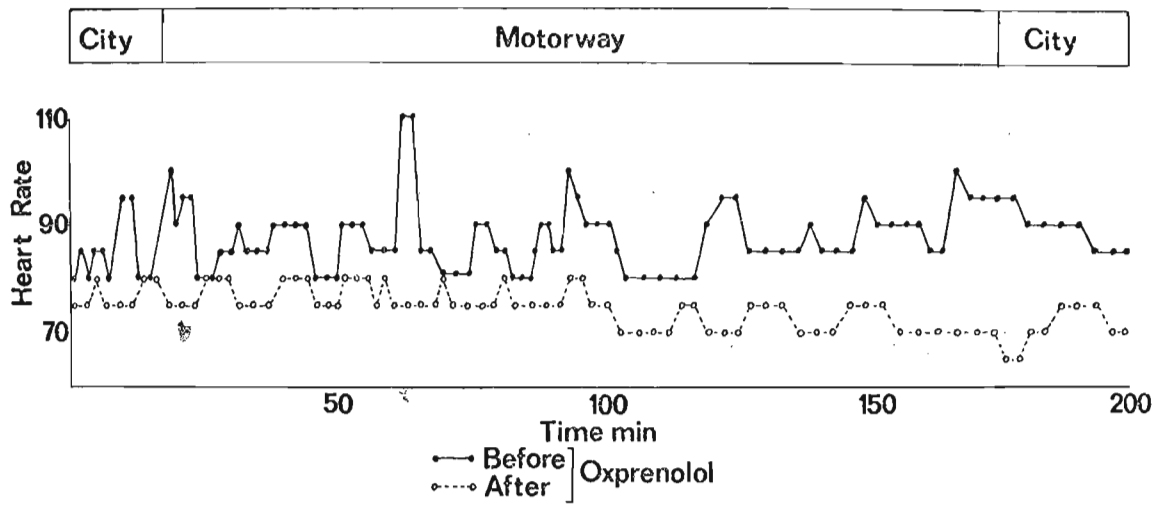
FIGURE 66

Record of the heart rate in a patient with ischaemic heart disease driving a motor-car between Leeds and Newcastle before and after 40 mg oral oxprenolol.
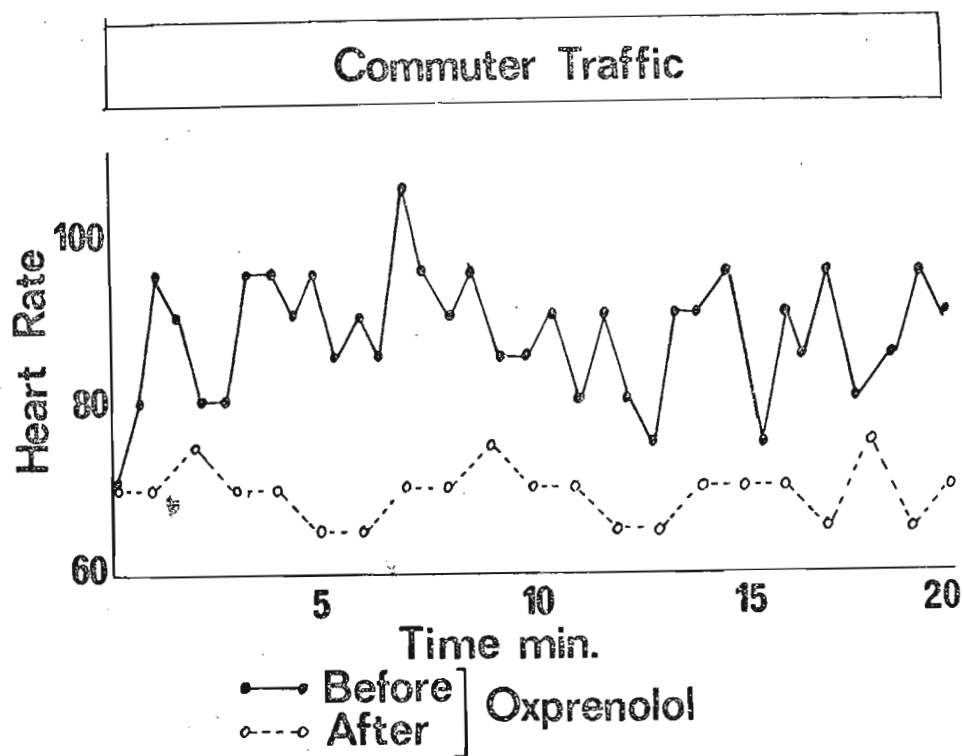
FIGURE 67

Record of the heart rate during city driving in a normal subject before and after 40 mg oral oxprenolol.
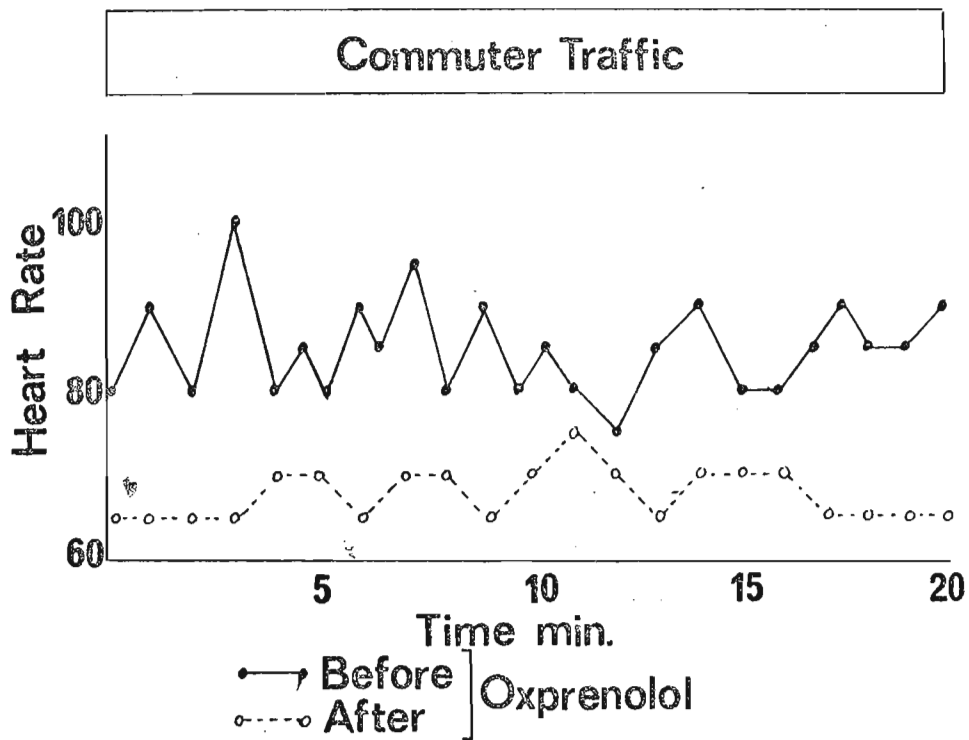
FIGURE 68

Record of the heart rate during city driving in a normal subject before and after 40 mg oral oxprenolol.
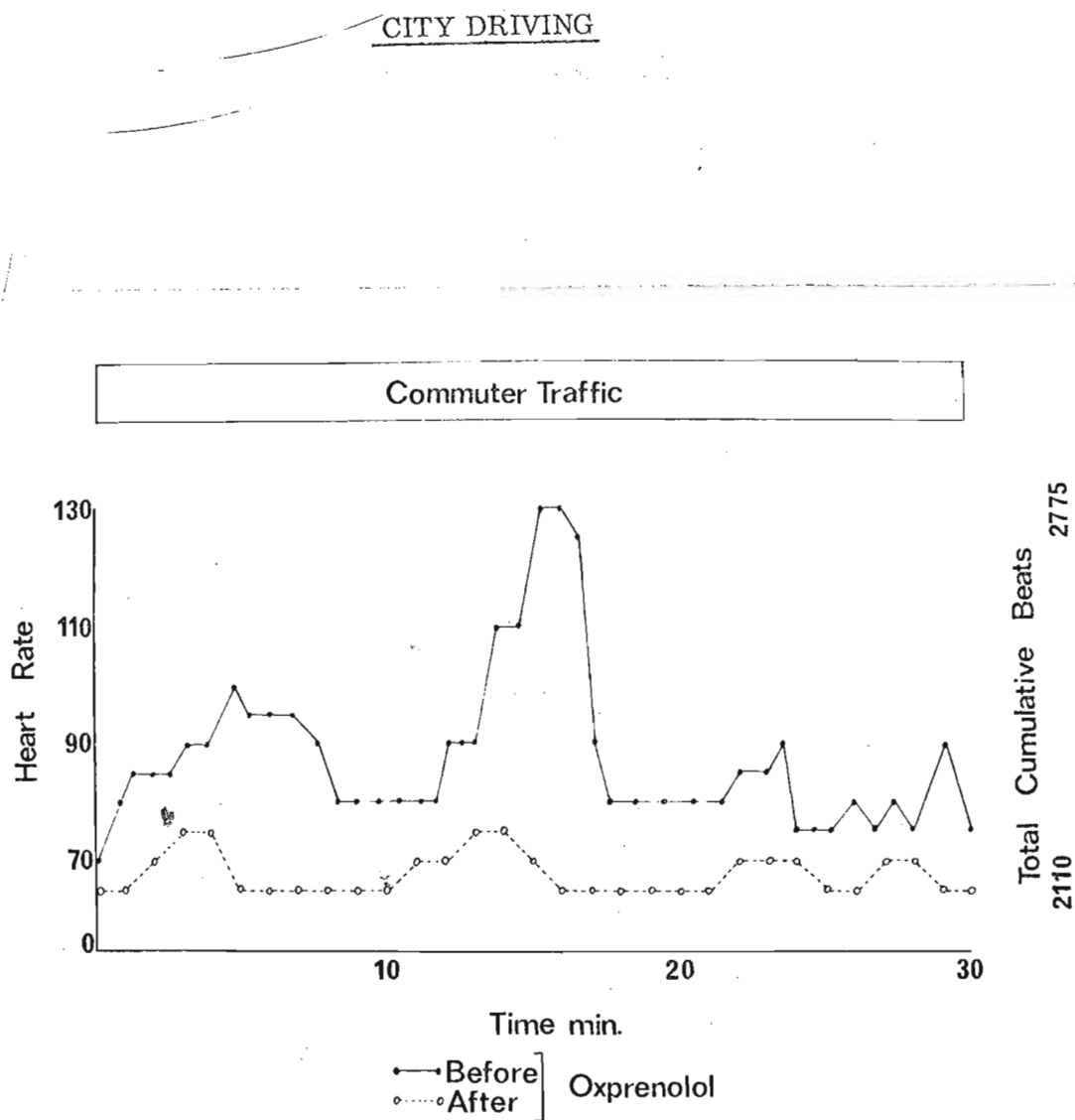
FIGURE 69

Record of heart rate during city driving in a patient with ischaemic heart disease before and after 40 mg oral oxprenolol.
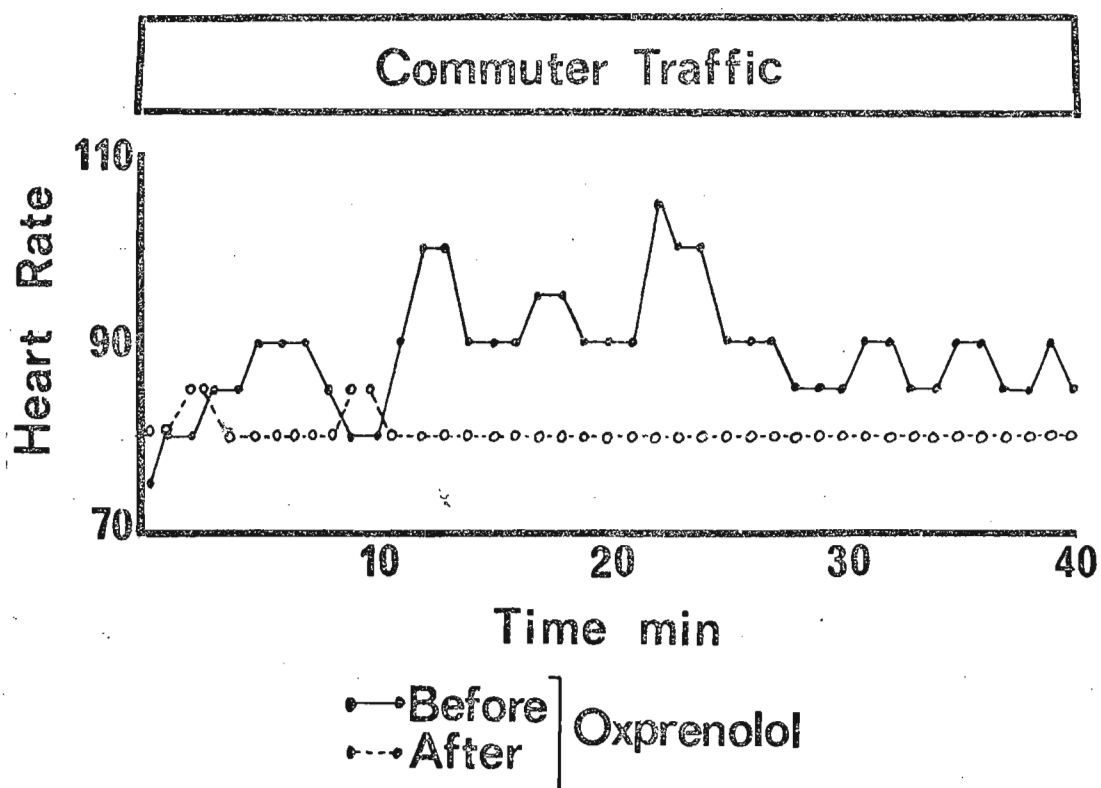
FIGURE 70

Record of heart rate during city driving in a patient with ischaemic heart disease before and after 40 mg oral oxprenolol.
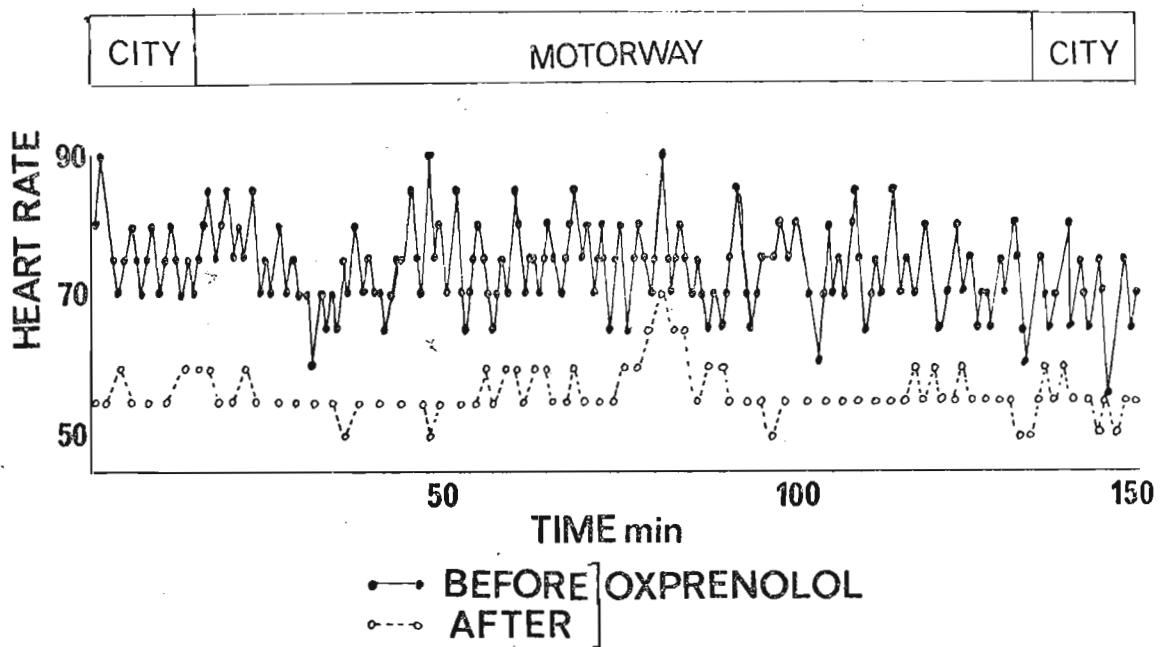
FIGURE 71

Record of the heart rate in a normal motor car passenger between Leeds and London during placebo and after 40 mg oral oxprenolol.
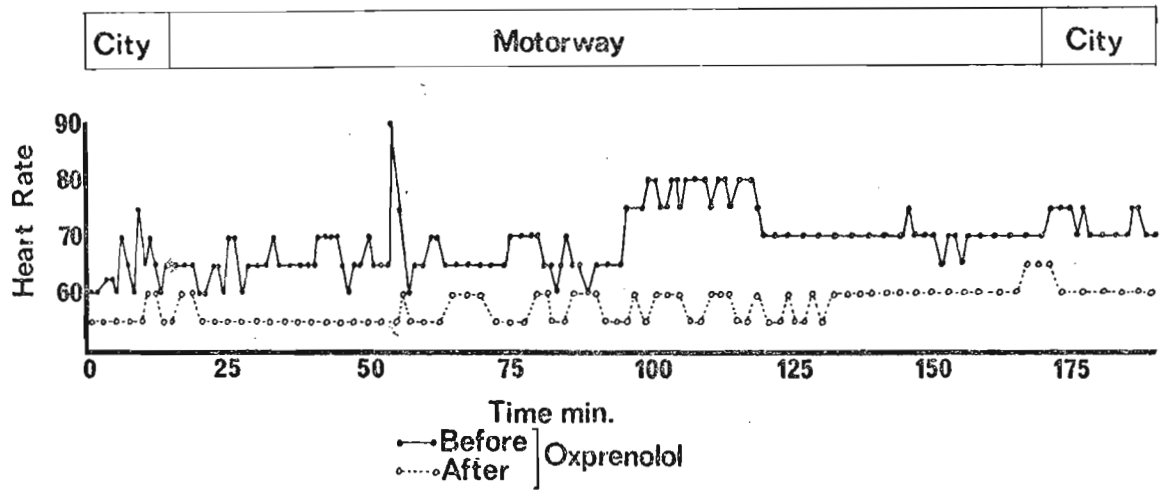
FIGURE 72

Record of the heart rate in a normal motor car passenger between Leeds and London during placebo and after 40 mg oral oxprenolol.
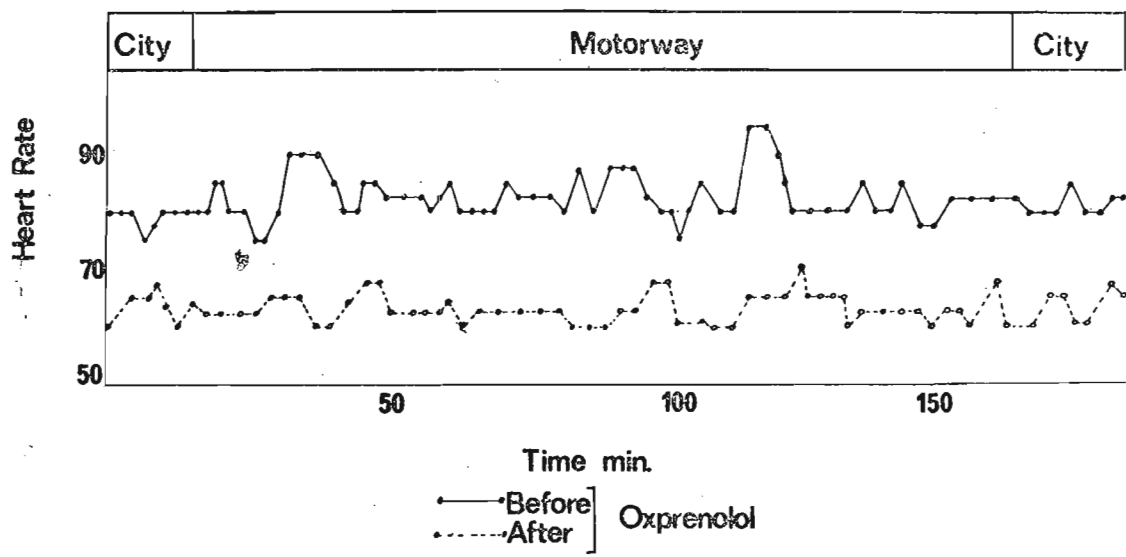
FIGURE 73

Record of the heart rate in a normal motor car passenger between Leeds and London during placebo and after 40 mg oral oxprenolol.
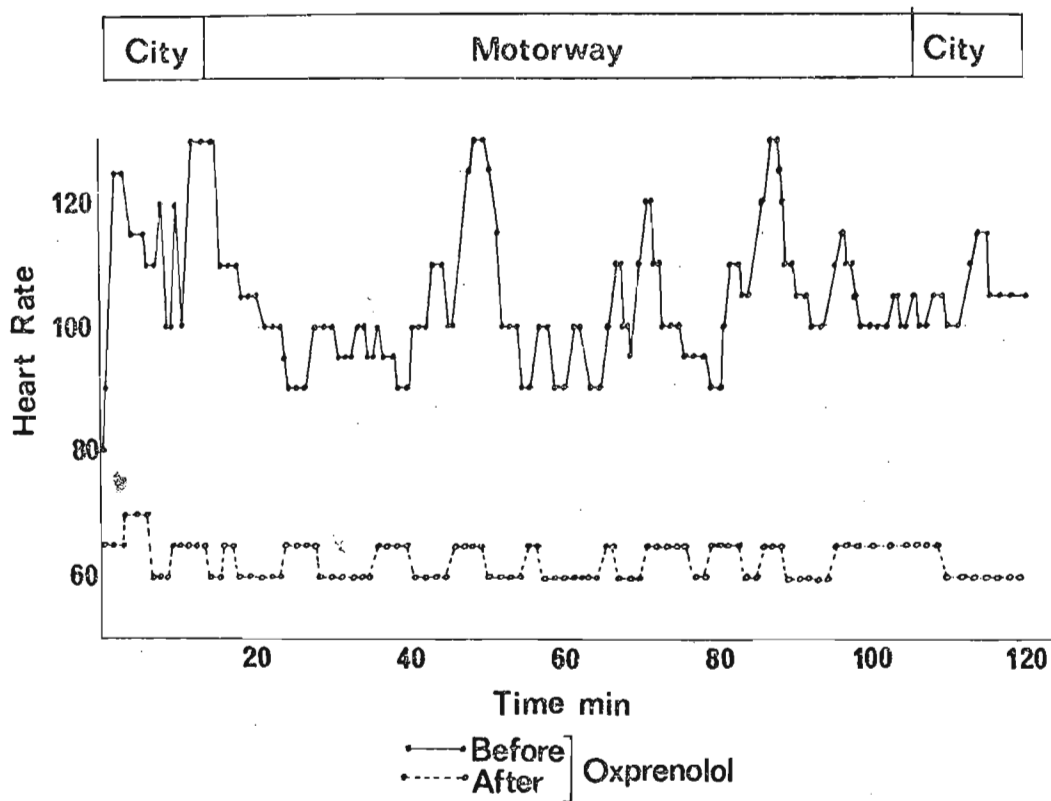
FIGURE 74

Record of the heart rate in a passenger with ischaemic heart disease between Leeds and London, during placebo and after 40 mg oral oxprenolol.
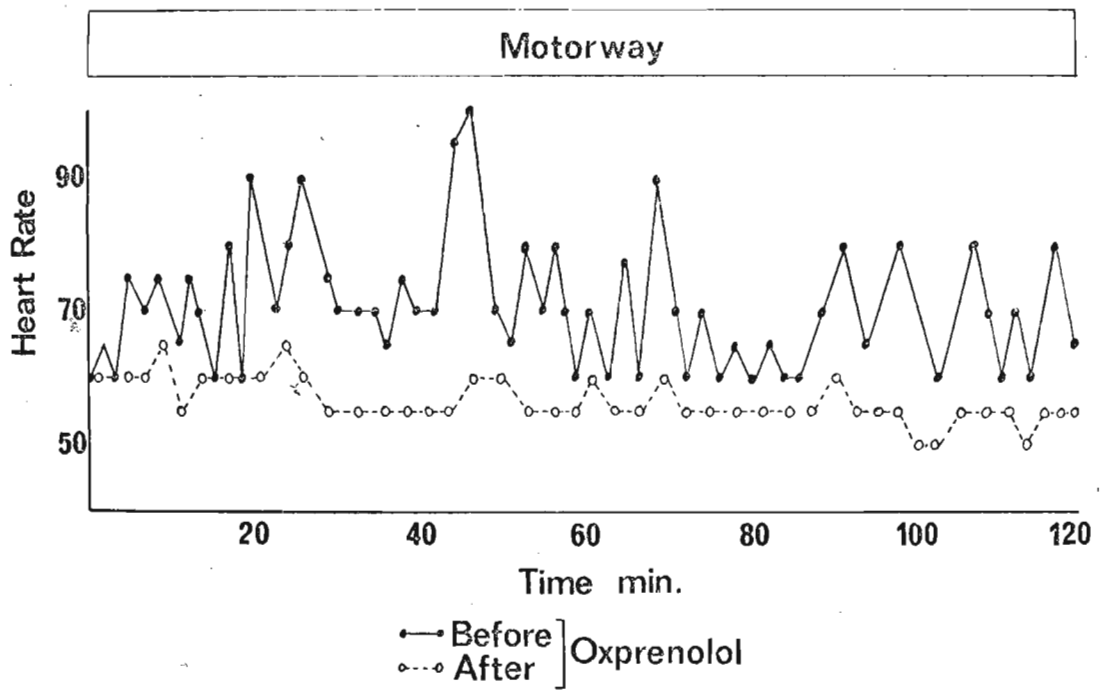
FIGURE 75

Record of the heart rate in a passenger with ischaemic heart disease between Leeds and London, during placebo and after 40 mg oral oxprenolol.
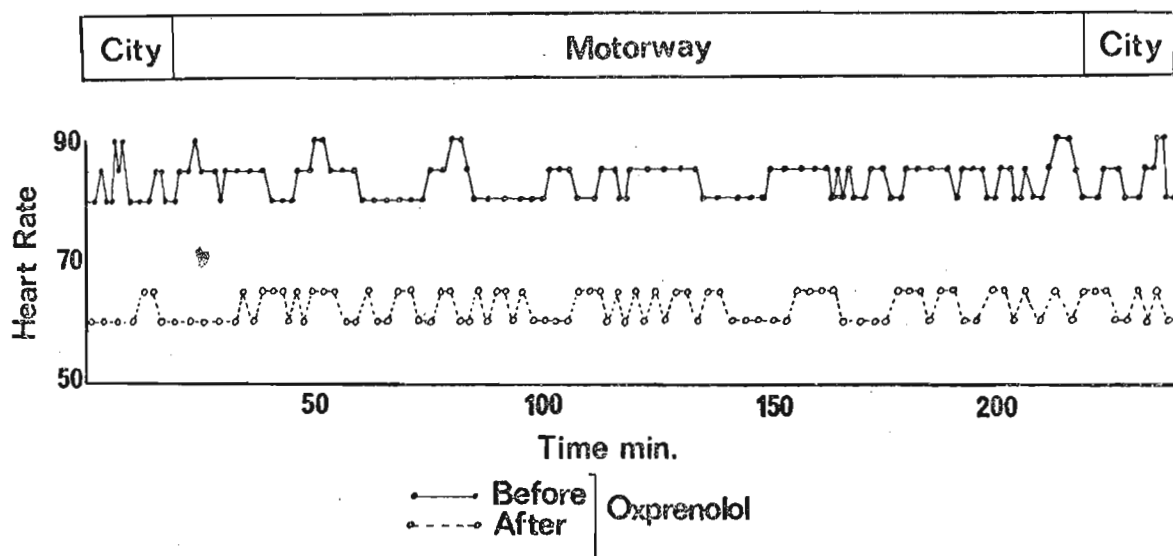
FIGURE 76

Record of the heart rate in a passenger with ischaemic heart
disease between Leeds and London, during placebo and after 40 mg
oral oxprenolol.
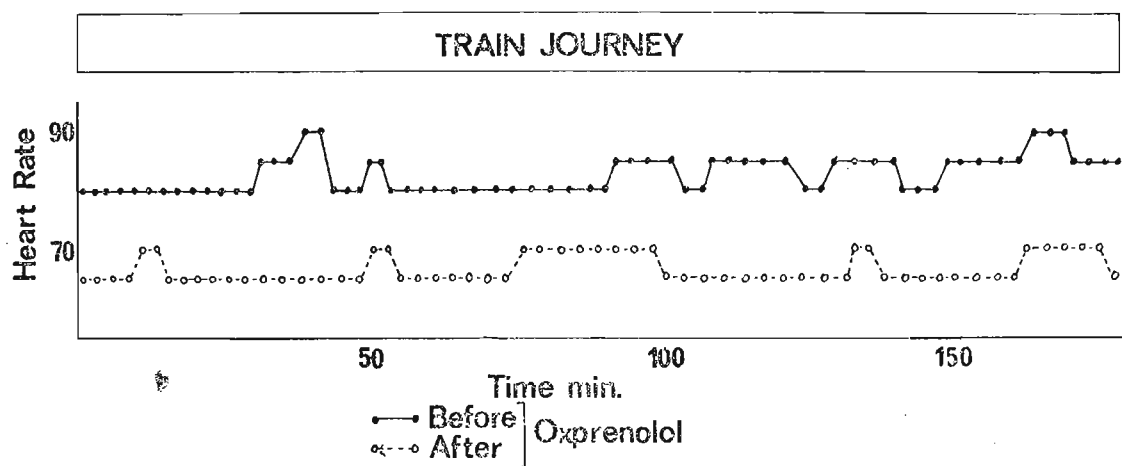
FIGURE 77

Record of the heart rate in a normal subject travelling by
rail between Leeds and London before and after 40 mg oral oxprenolol.
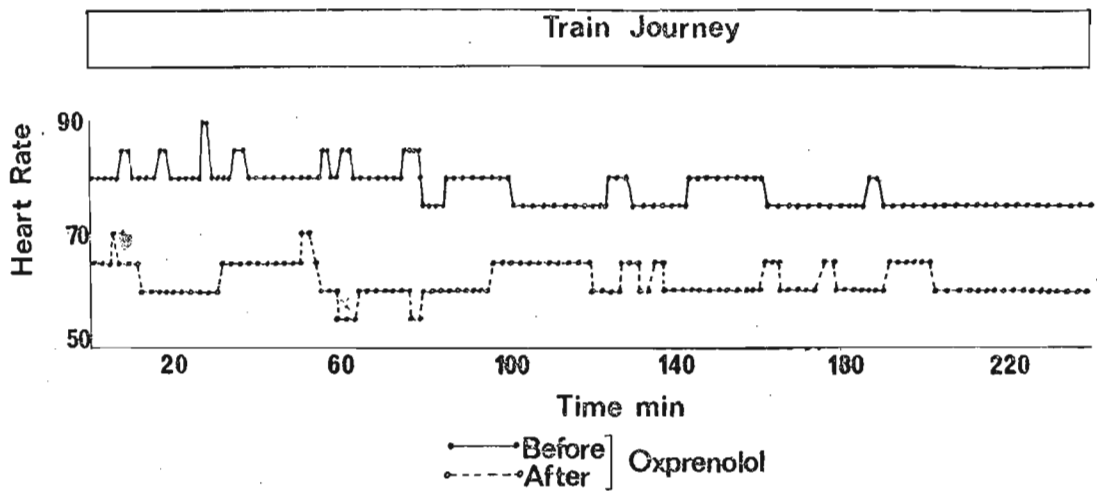
FIGURE 78

Record of the heart rate in a normal subject travelling by rail
between Leeds and London before and after 40 mg oral oxprenolol.
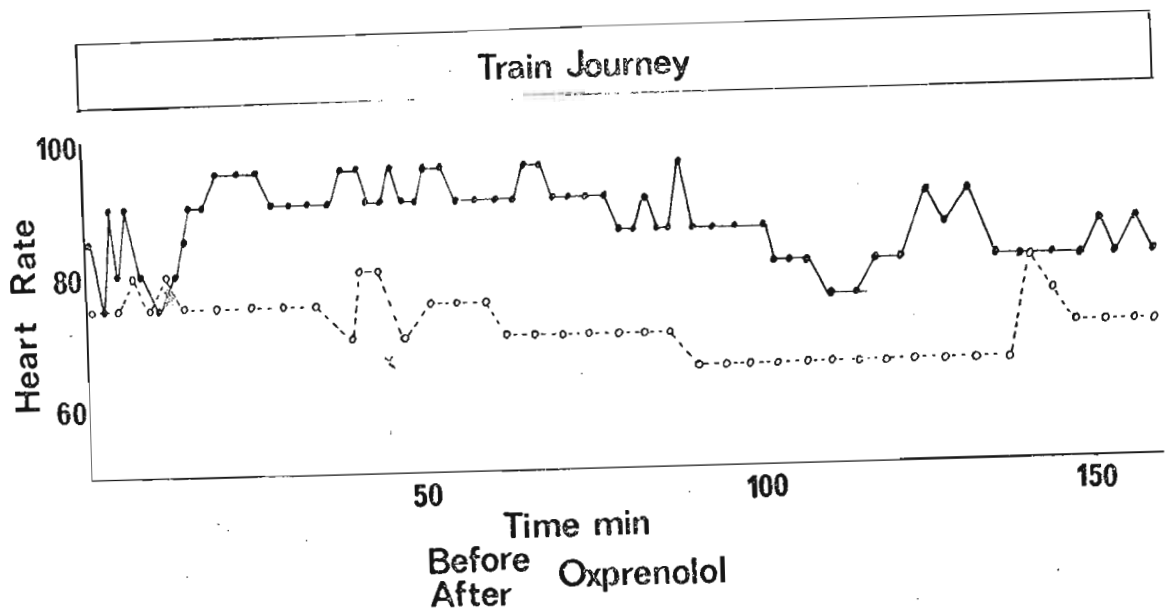
FIGURE 79

Record of the heart rate in a normal subject travelling by
rail between Leeds and London before and after 40 mg oral α prenolol.
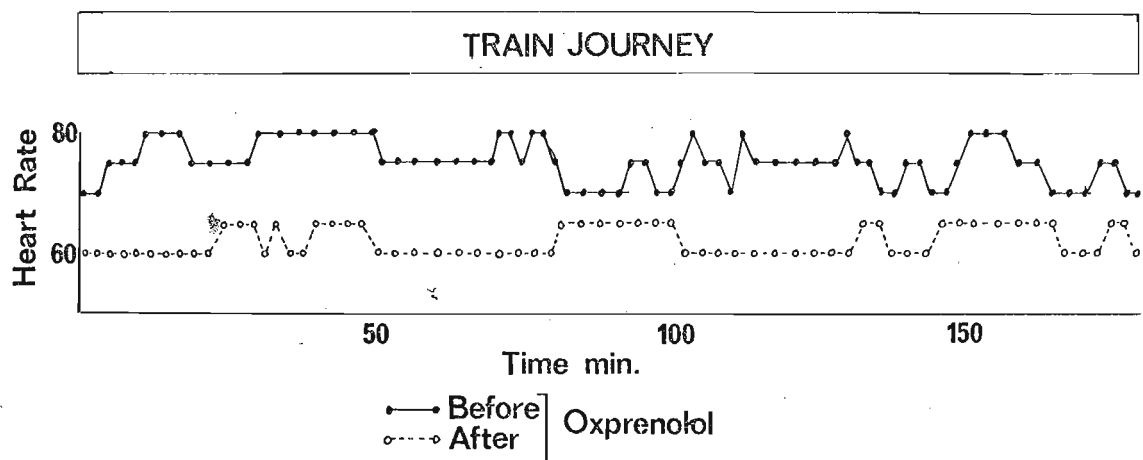
FIGURE 80

Record of the heart rate in a subject with ischaemic heart disease travelling by rail between Leeds and London during placebo and after 40 mg oral oxprenolol.
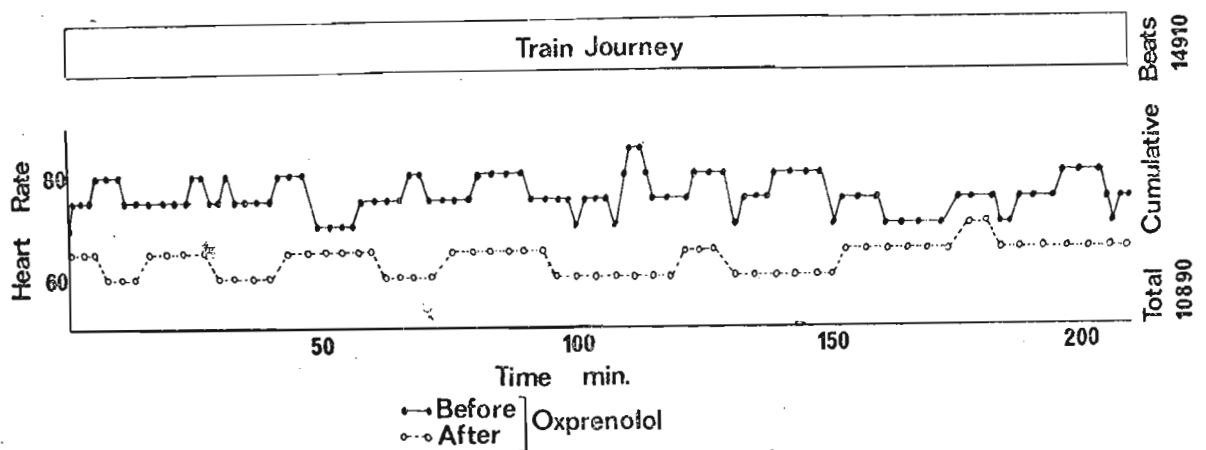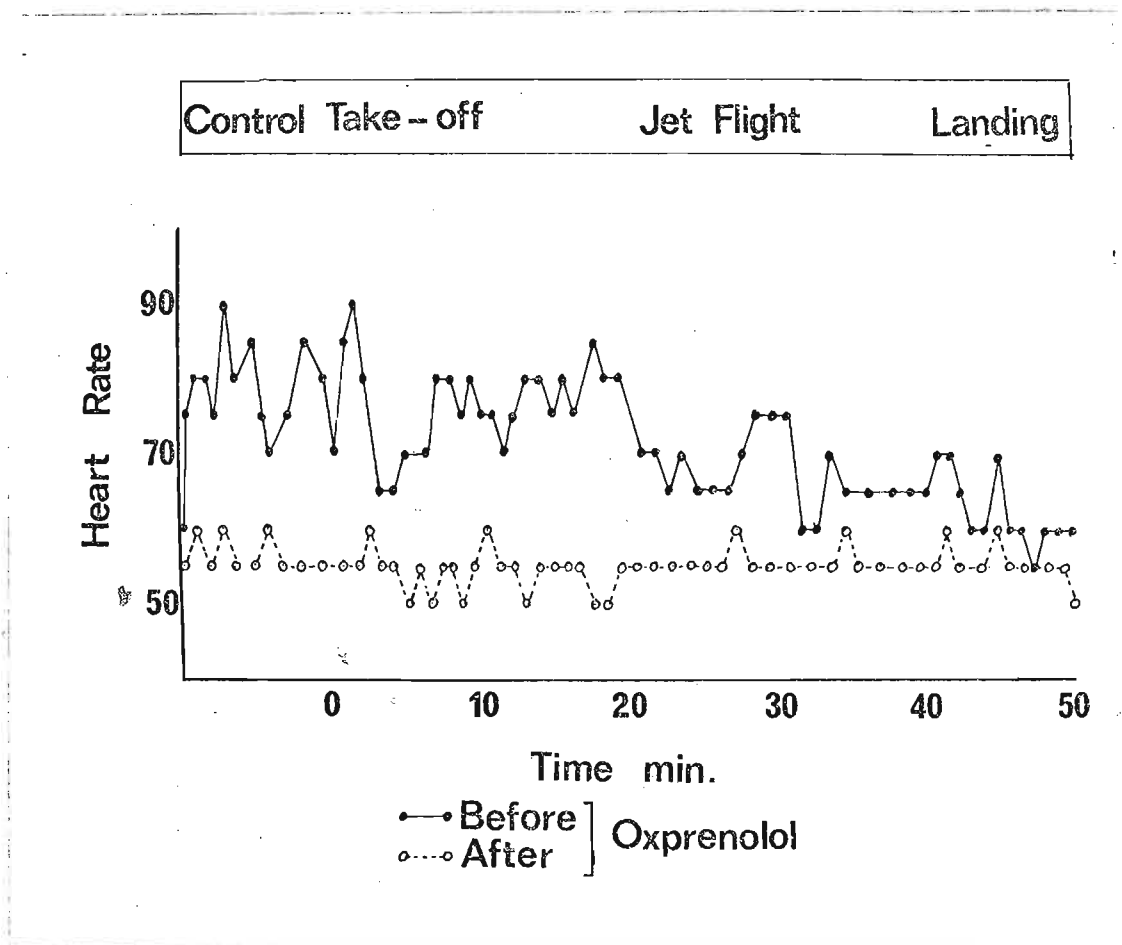
FIGURE 81

Record of the heart rate in a subject with ischaemic heart disease travelling by rail between Leeds and London during placebo and after 40 mg oral oxprenolol.
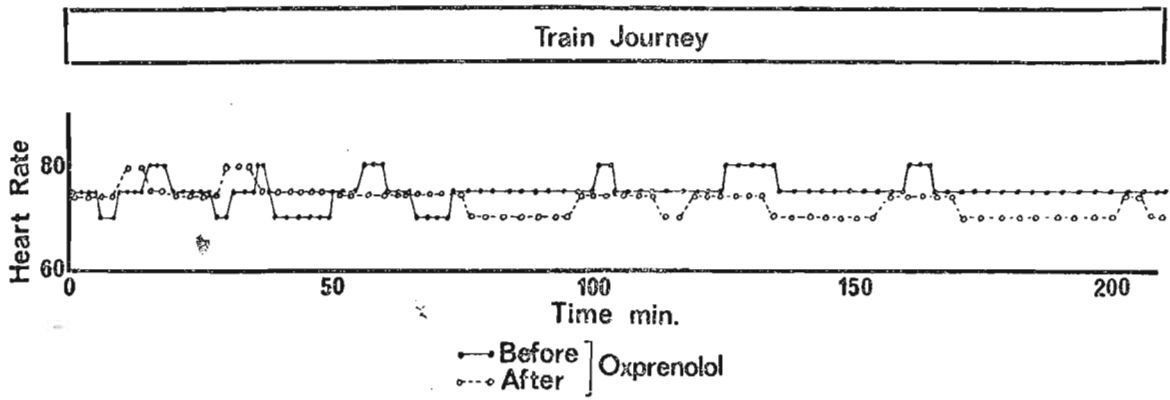
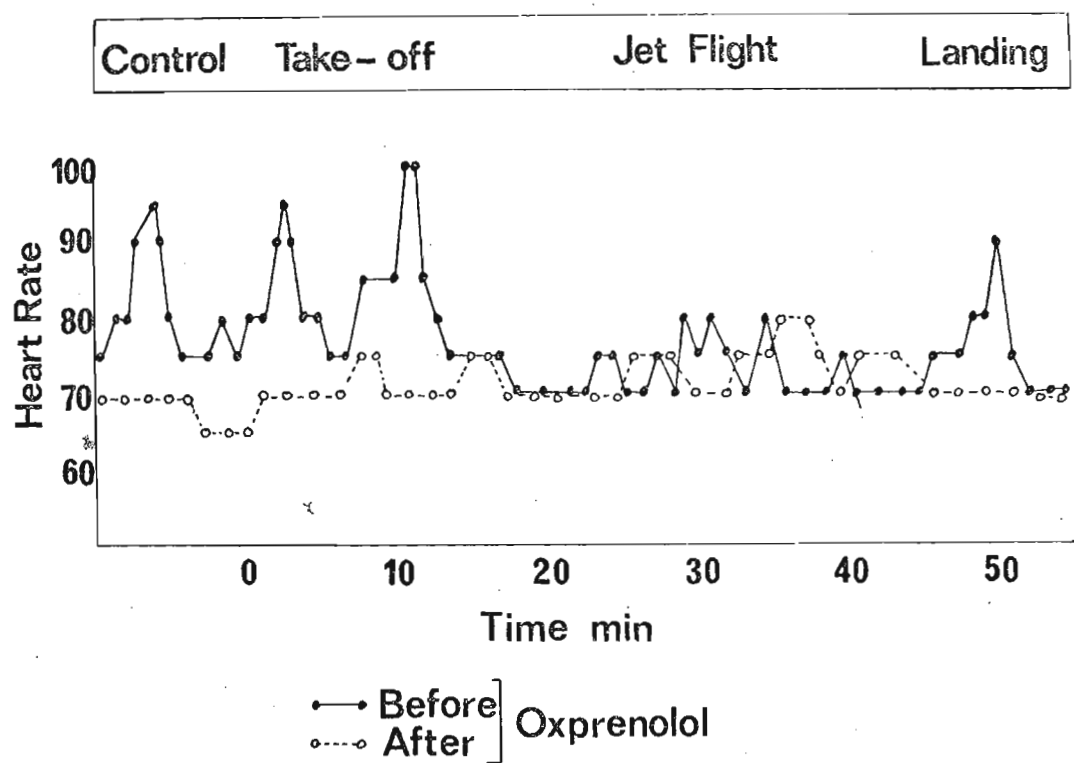**FIGURE 82**

Record of the heart rate in a subject with ischaemic heart
disease travelling by rail between Leeds and London during placebo
and after 40 mg oral oxprenolol.
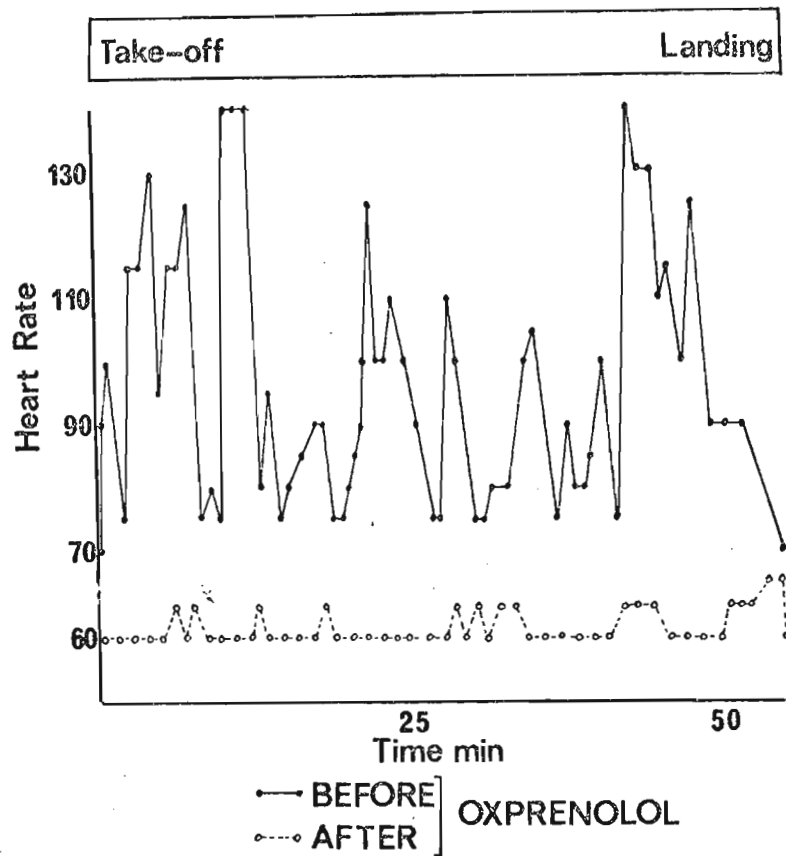
FIGURE 83

Record of the heart rate in a normal subject travelling by
passenger turbo-propeller aircraft between Leeds and London and
the modulation of the response by 40 mg oral oxprenolol taken one
hour before the flight.
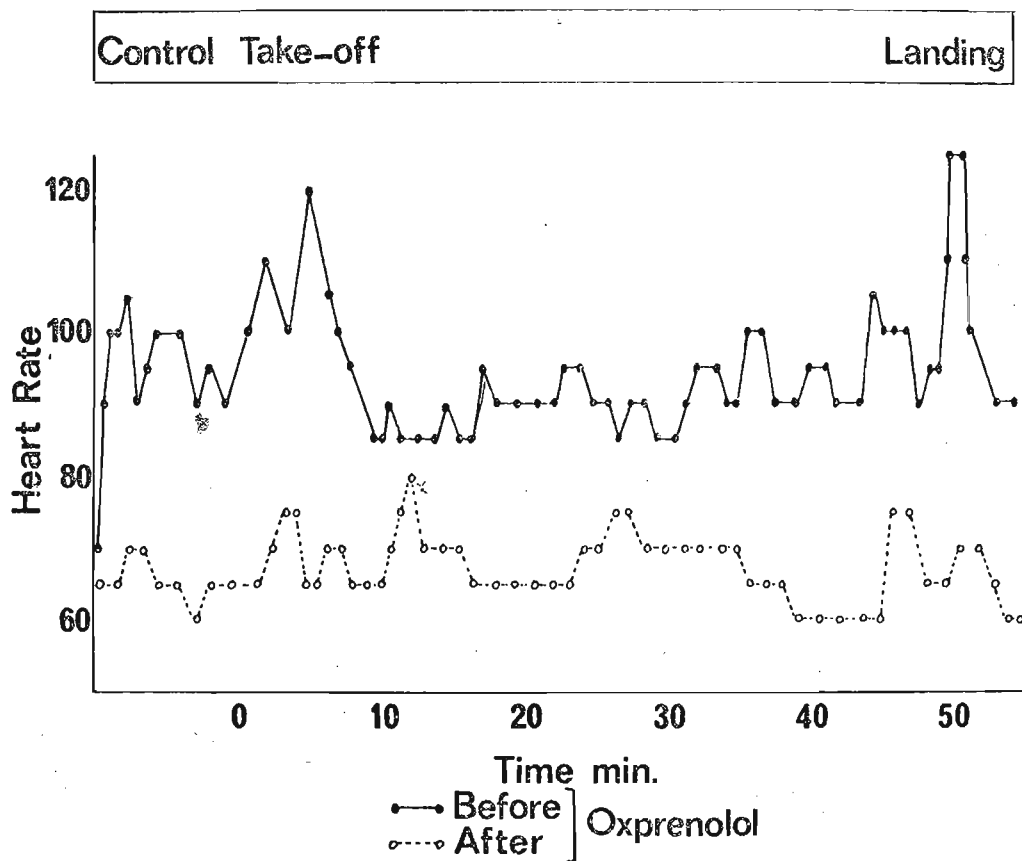
FIGURE   84

Record of the heart rate in a normal subject travelling by passenger turbo-propeller aircraft between Leeds and London and the modulation of the response by 40 mg oral oxprenolol taken one hour before the flight.
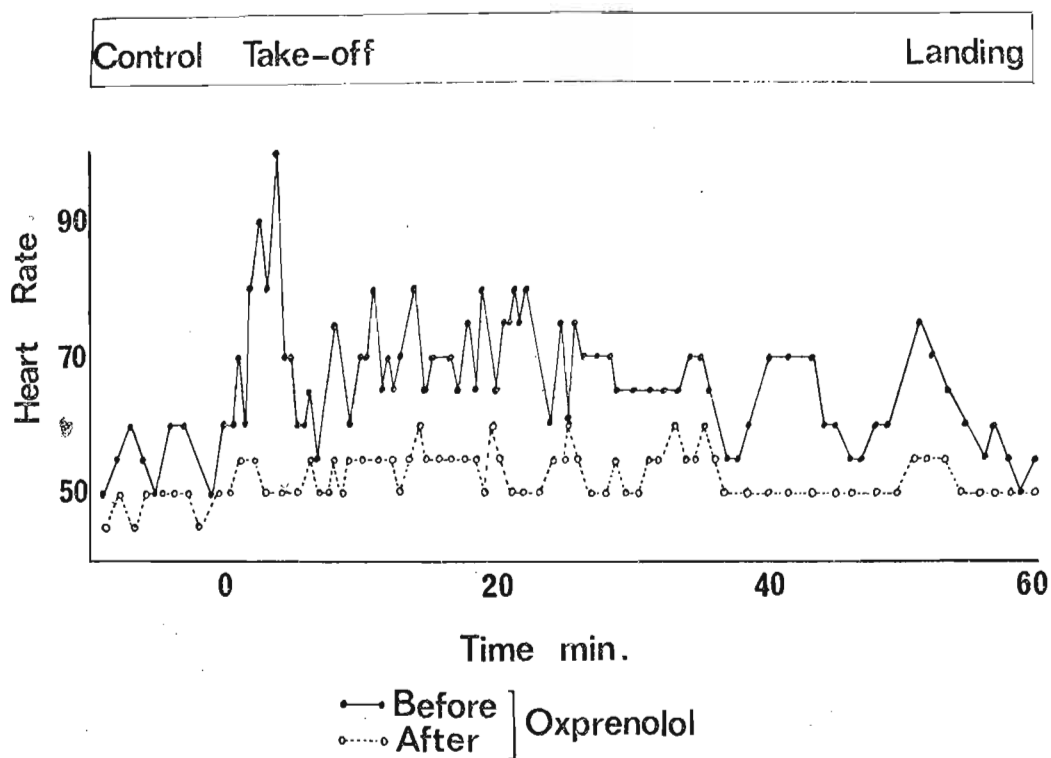
FIGURE 85

Record of the heart rate in a normal subject travelling by
passenger turbo-propeller aircraft between Leeds and London and
the modulation of the response by 40 mg oral oxprenolol taken one
hour before the flight.
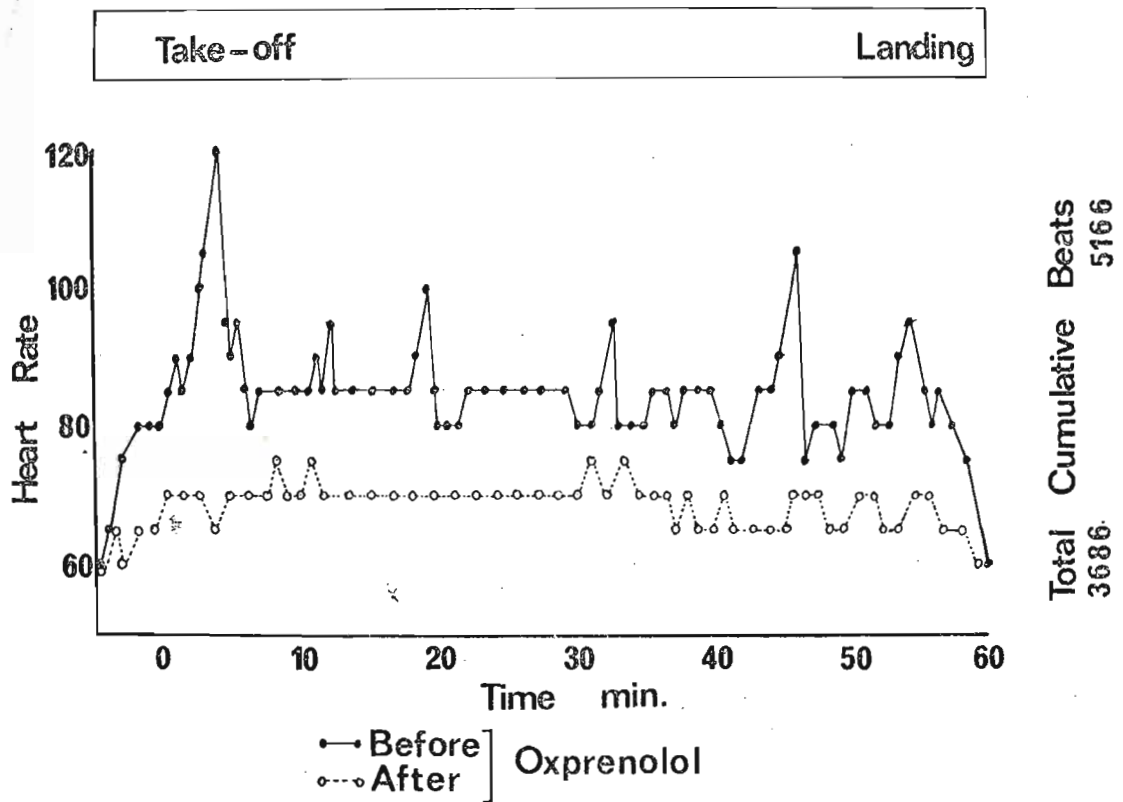
FIGURE 86

Record of the heart rate in a patient with ischaemic heart
disease travelling by turbo-propeller aircraft between Leeds and
London during placebo and one hour after 40 mg oral oxprenolol.
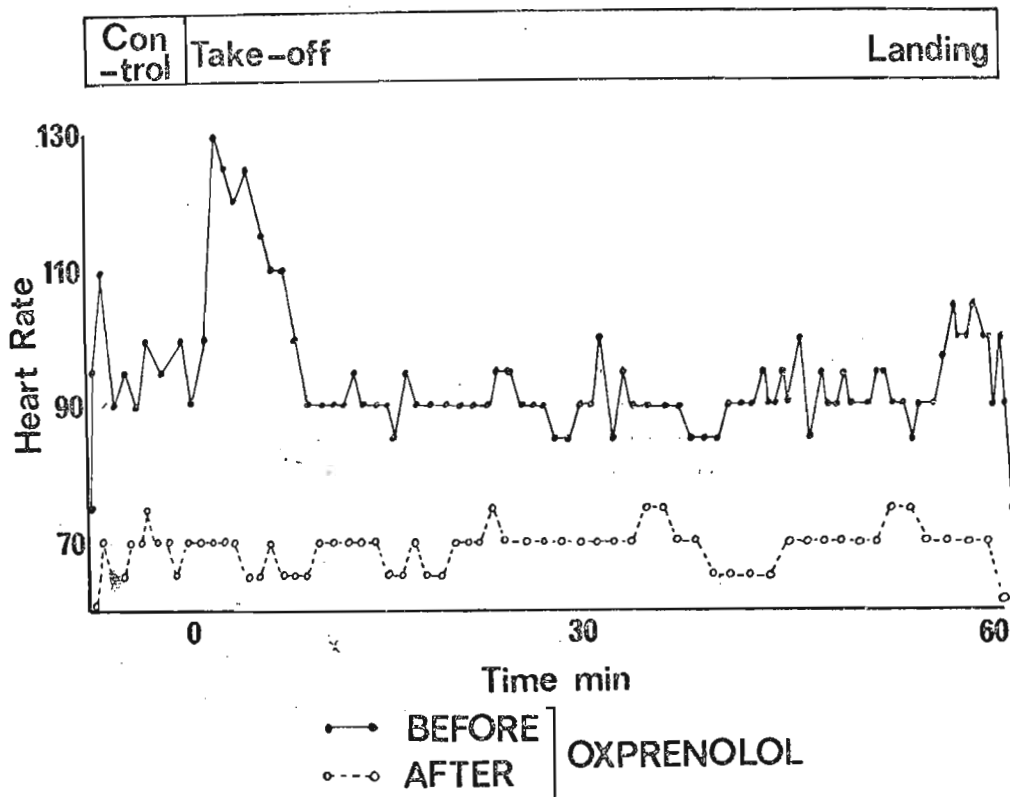
FIGURE 87

Record of the heart rate in a patient with ischaemic heart disease travelling by turbo-propeller aircraft between Leeds and London during placebo and one hour after 40 mg oral oxprenolol.
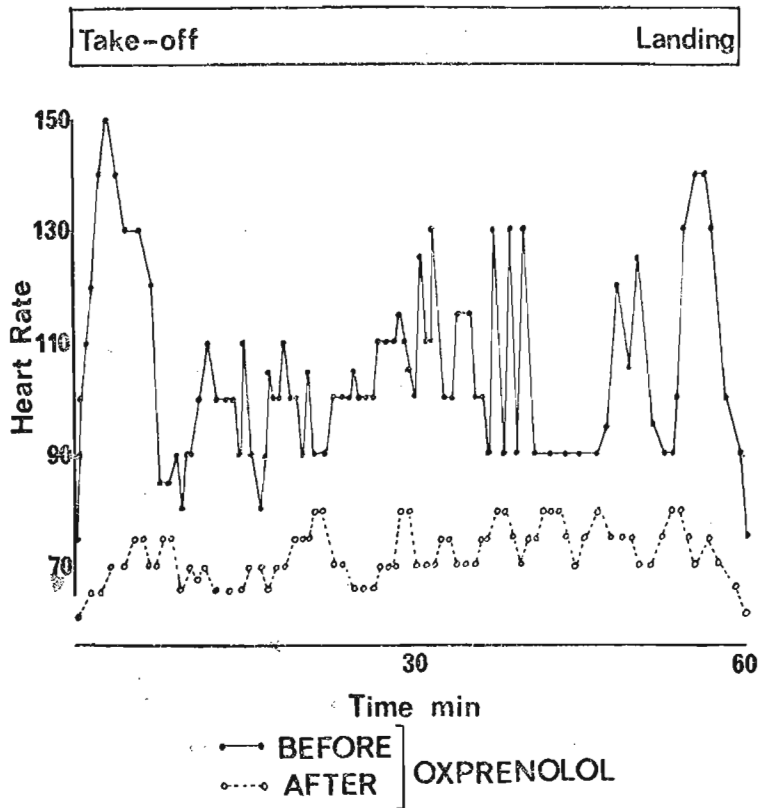
FIGURE 88

Record of the heart rate in a patient with ischaemic heart disease travelling by turbo-propeller aircraft between Leeds and London during placebo and one hour after 40 mg oral oxprenolol.
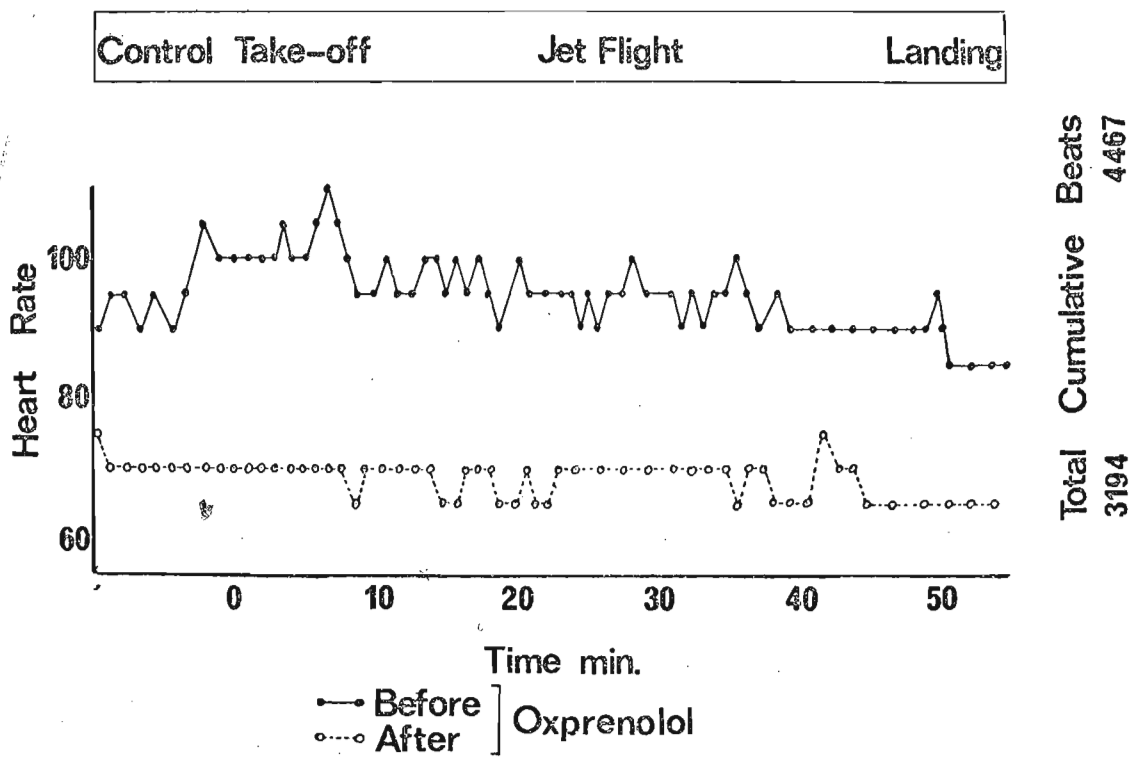
FIGURE 89

Record of the heart rate in a normal subject travelling by jet aircraft between Newcastle and London and the modulation of the response by 40 mg oral oxprenolol taken one hour before the flight.
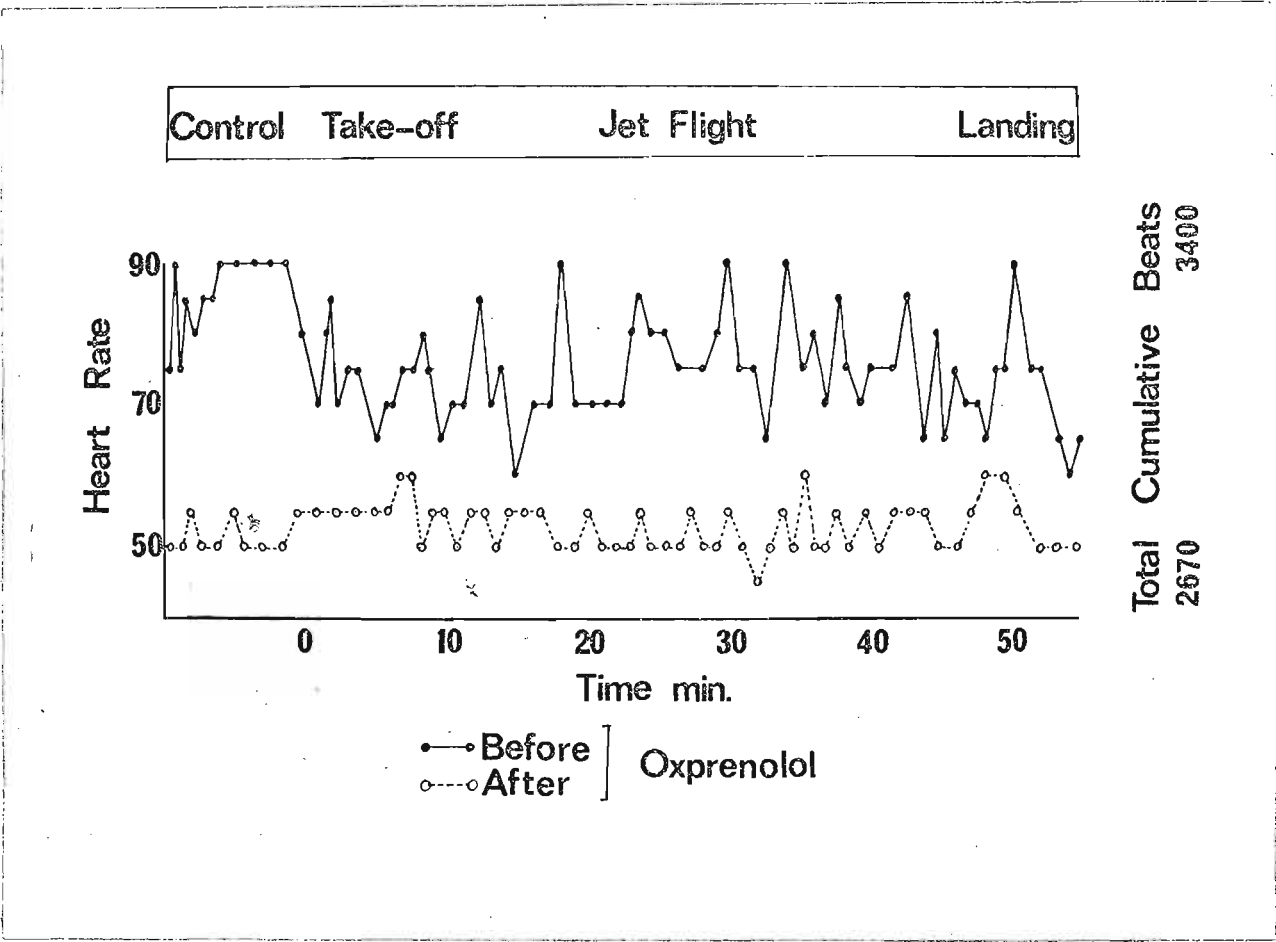
FIGURE 90

Record of the heart rate in a normal subject travelling by
jet aircraft between Newcastle and London and the modulation of the
response by 40 mg oral oxprenolol taken one hour before the flight.

FIGURE 91

Record of the heart rate in a patient with ischaemic heart disease travelling by jet aircraft between Newcastle and London during placebo and one hour after 40 mg oral oxprenolol.

FIGURE 92

Record of the heart rate in a patient with ischaemic heart
disease travelling by jet aircraft between Newcastle and London
during placebo and one hour after 40 mg oral oxprenolol.
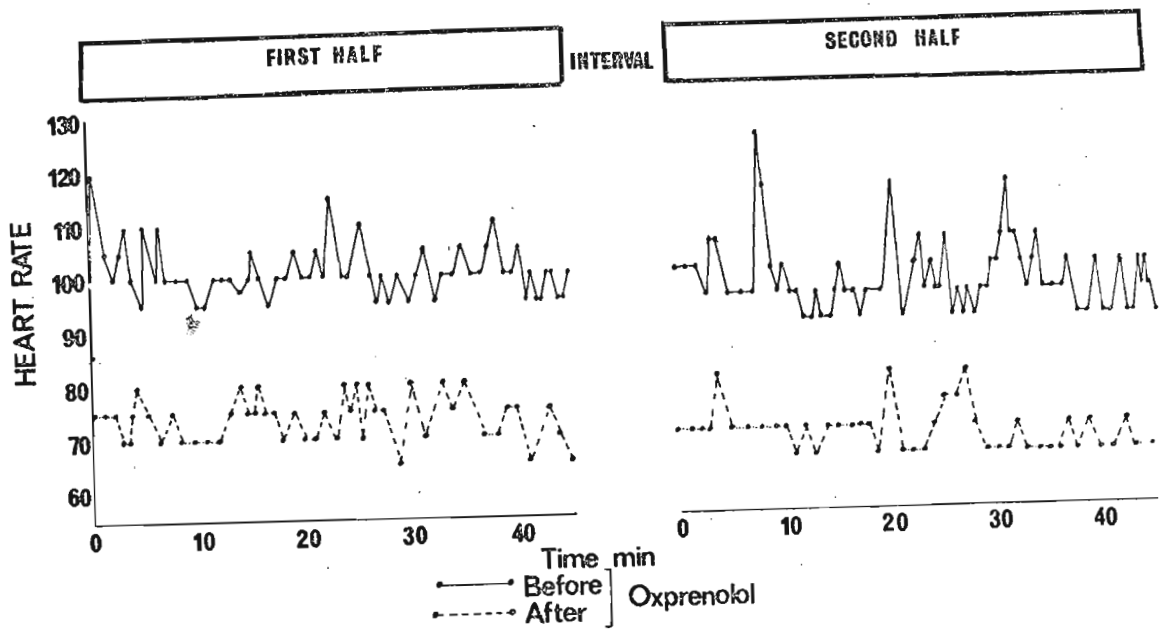
FIGURE   93

Record of the heart rate in a normal subject watching a soccer
match after the ingestion of placebo and the modulation of the response
produced by 40 mg oral oxprenolol taken one hour before a similar
match.
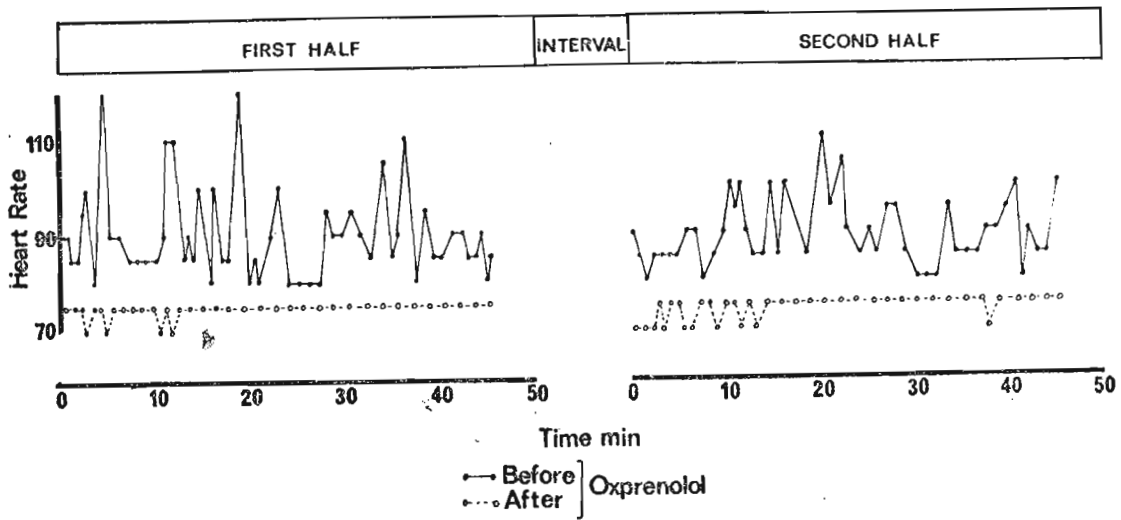
FIGURE 94

Record of the heart rate in a normal subject watching a soccer
match after the ingestion of placebo and the modulation of the response
produced by 40 mg oral oxprenolol taken one hour before a similar match.
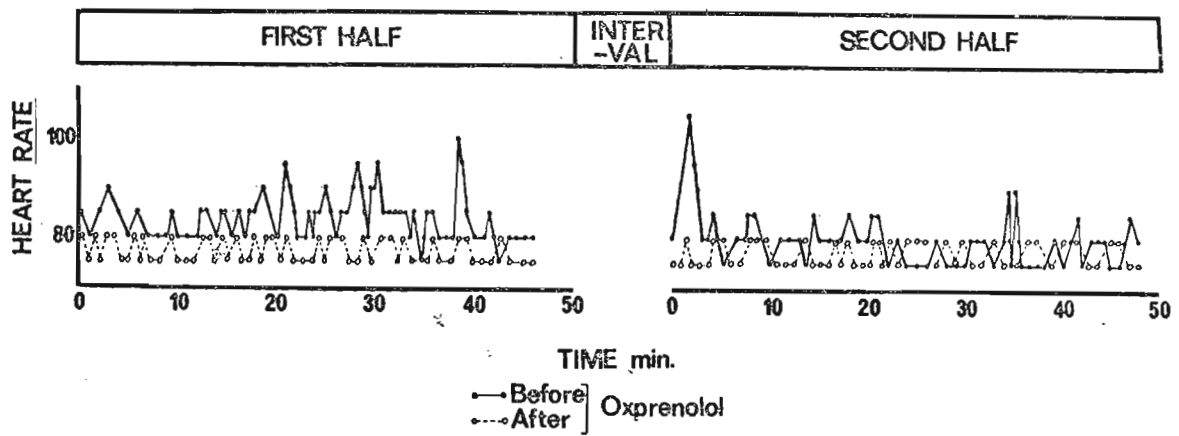
FIGURE 95

Record of the heart rate in a normal subject watching a soccer match after the ingestion of placebo and the modulation of the response produced by 40 mg oral oxprenolol taken one hour before a similar match.
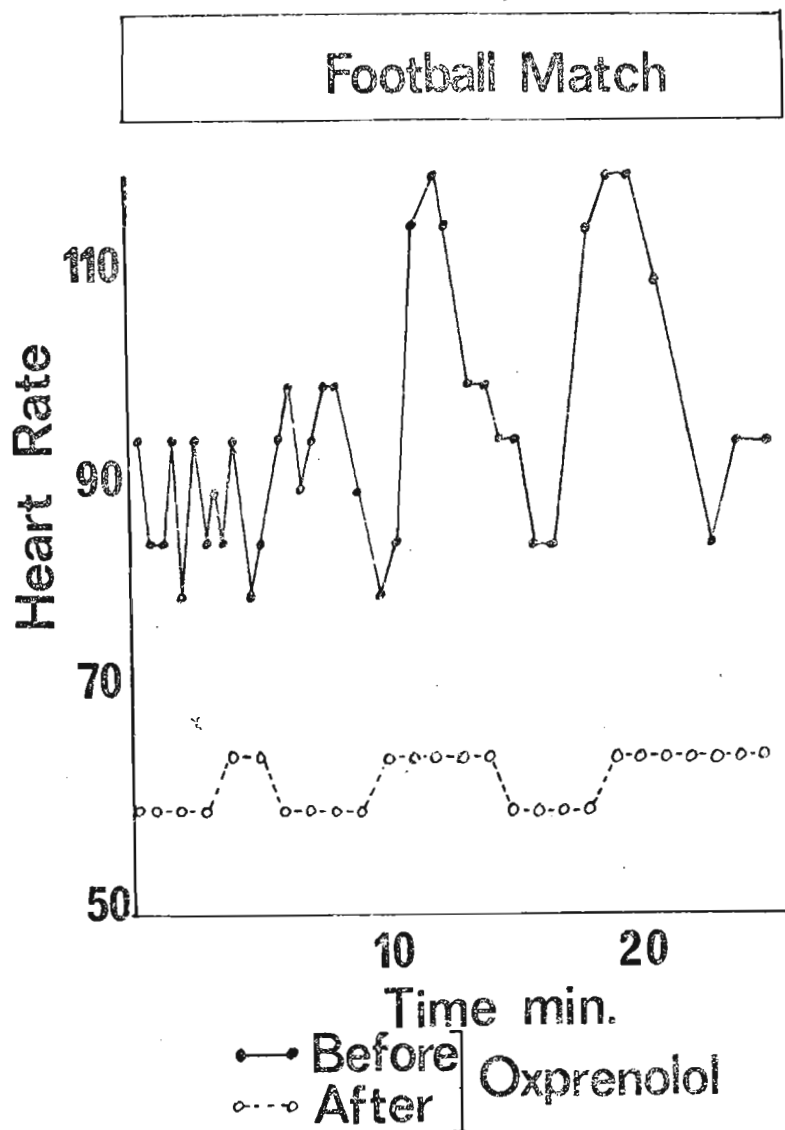
FIGURE 96

Record of the heart rate in a normal subject watching a televised live football match and the effect of 40 mg oral oxprenolol taken 30 minutes after the start of the match.
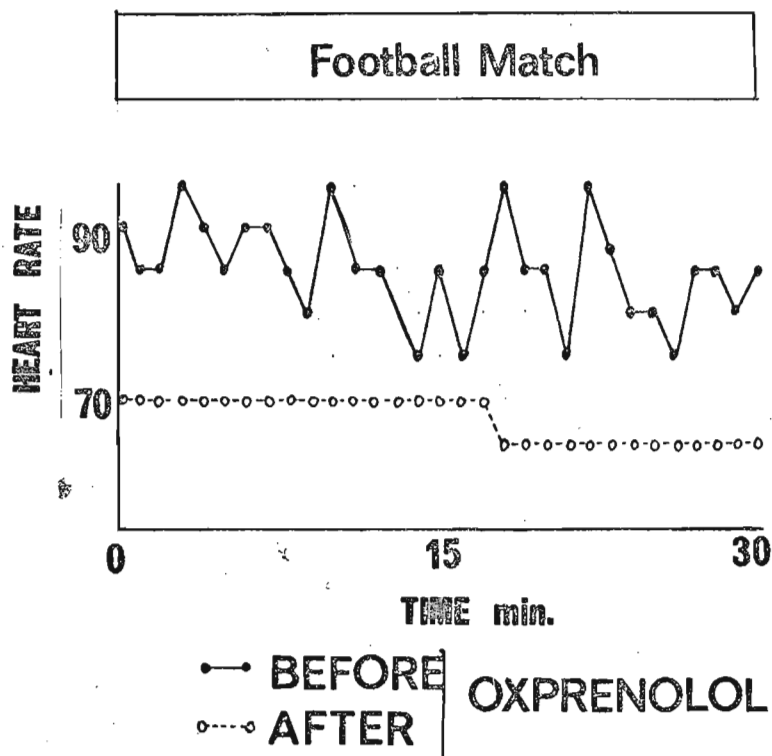
FIGURE 97

Record of the heart rate in a normal subject watching a televised live football match and the effect of 40 mg oral oxprenolol taken 30 minutes after the start of the match.
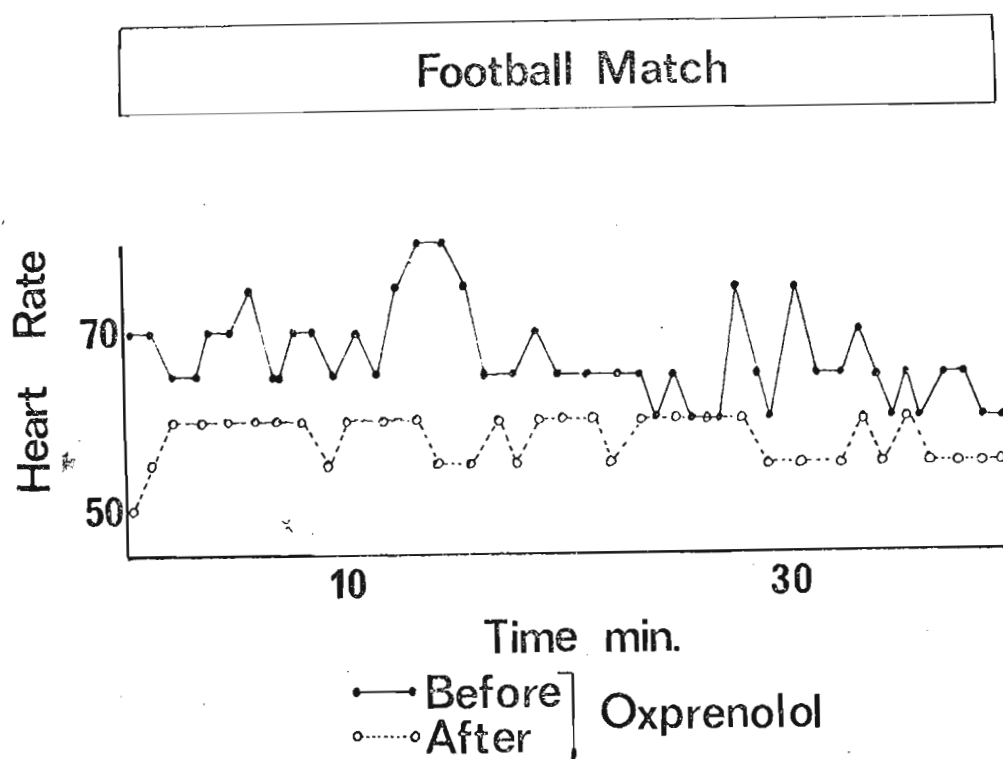
FIGURE 98

Record of the heart rate in a patient with ischaemic heart disease watching a soccer match and the modulation of the response by 40 mg oral oxprenolol taken 30 minutes after the start of the match.
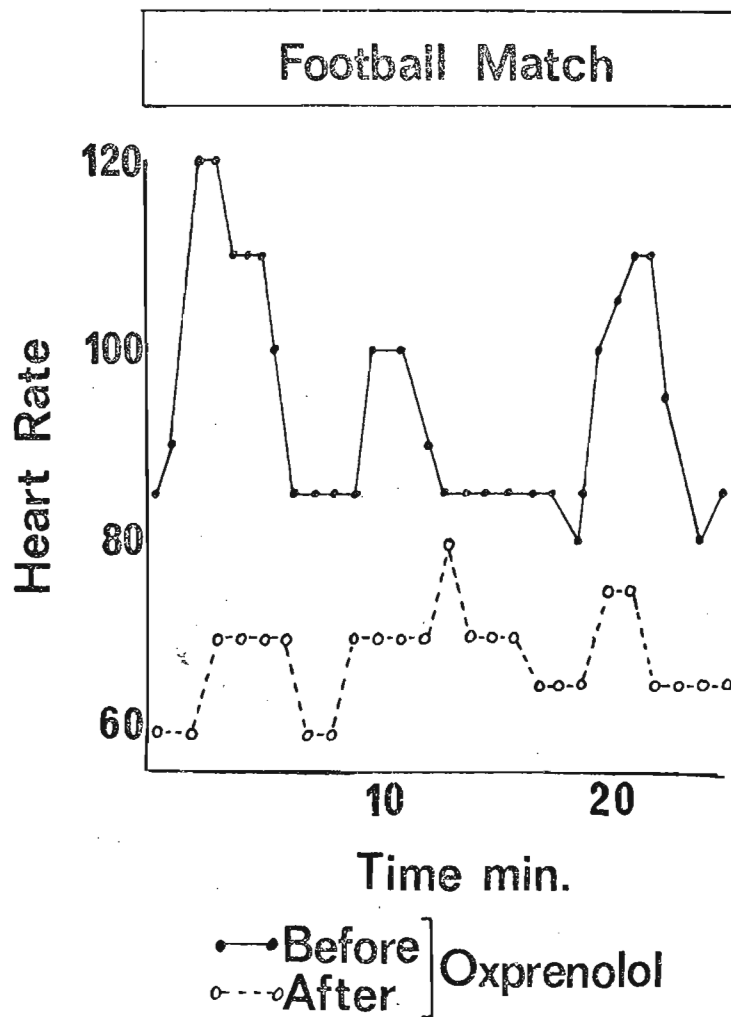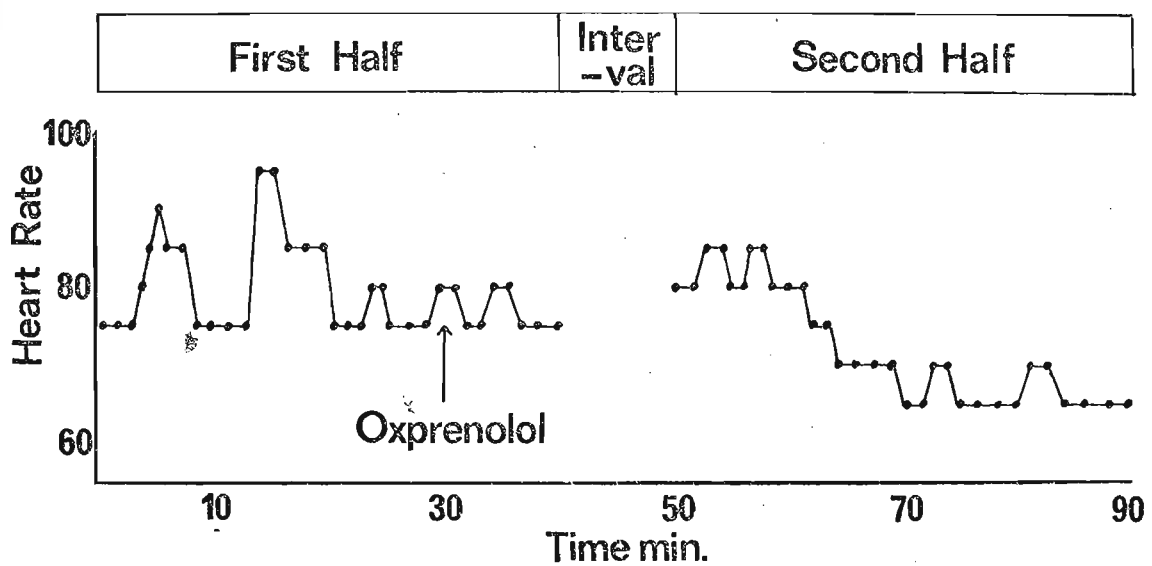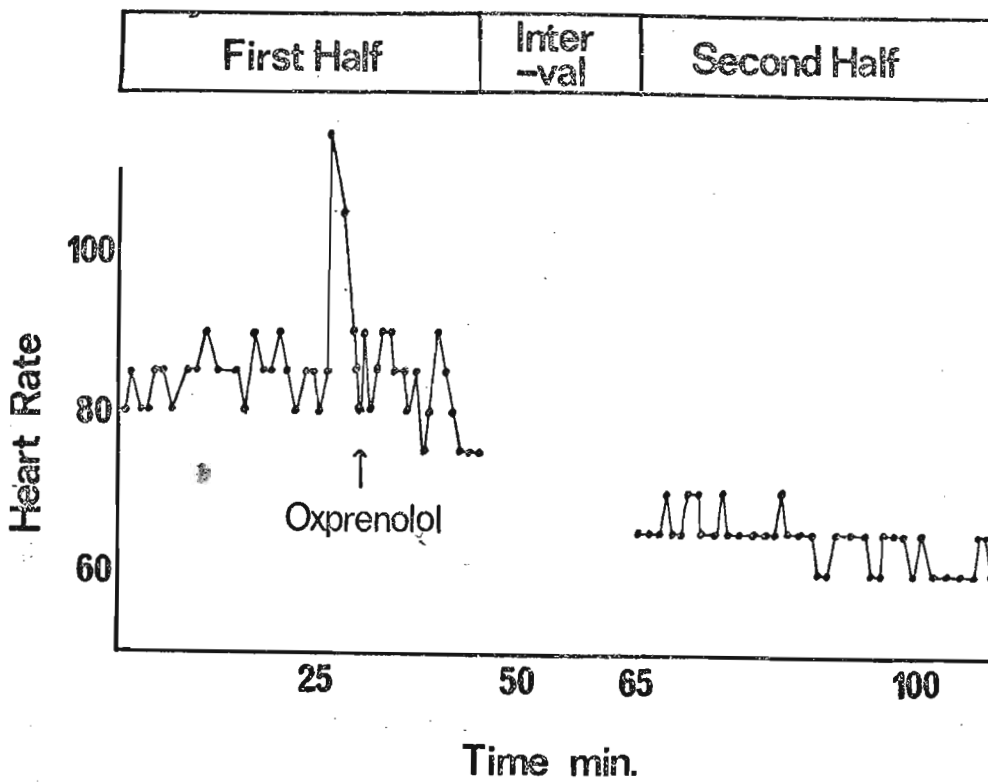
FIGURE 99

Record of the heart rate in a patient with ischaemic heart disease watching a soccer match and the modulation of the response by 40 mg oral oxprenolol taken 30 minutes after the start of the match.
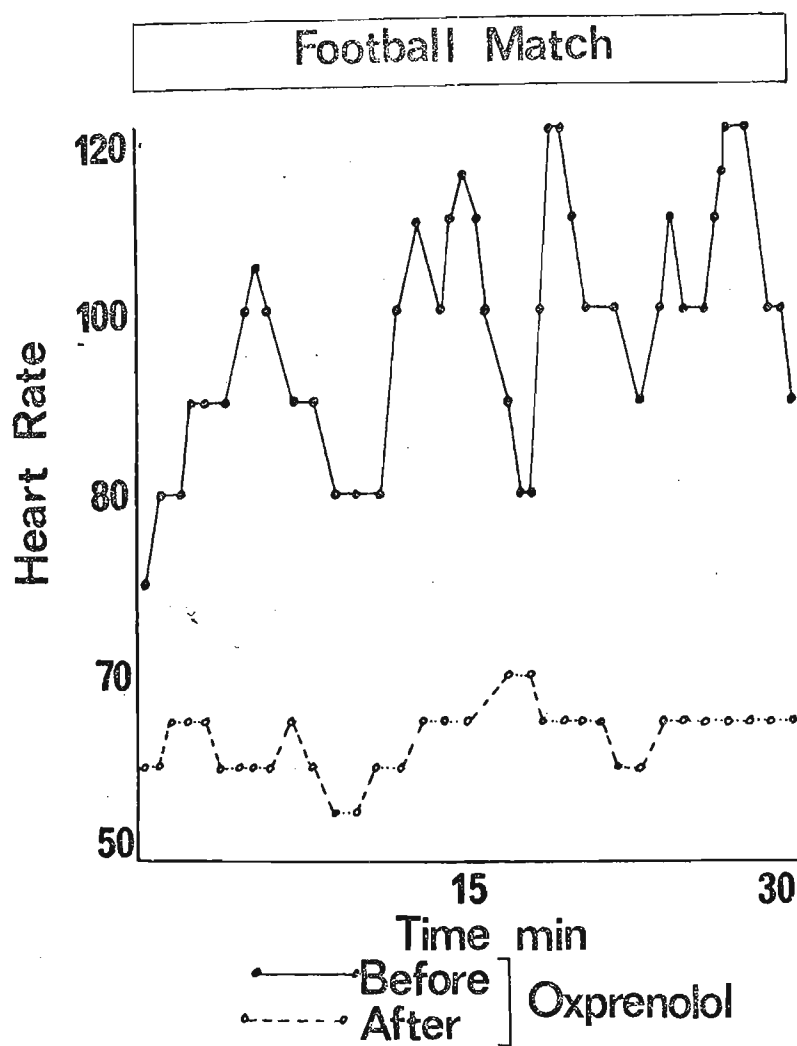
FIGURE 100

Record of the heart rate in a patient with ischaemic heart disease
watching a soccer match and the modulation of the response by 40 mg
oral oxprenolol taken 30 minutes after the start of the match.

FIGURE 101

Record of the heart rate in a patient with ischaemic heart disease watching a televised live football match and the effect of 40 mg oral oxprenolol taken 30 minutes after the commencement of the match.

FIGURE 102.

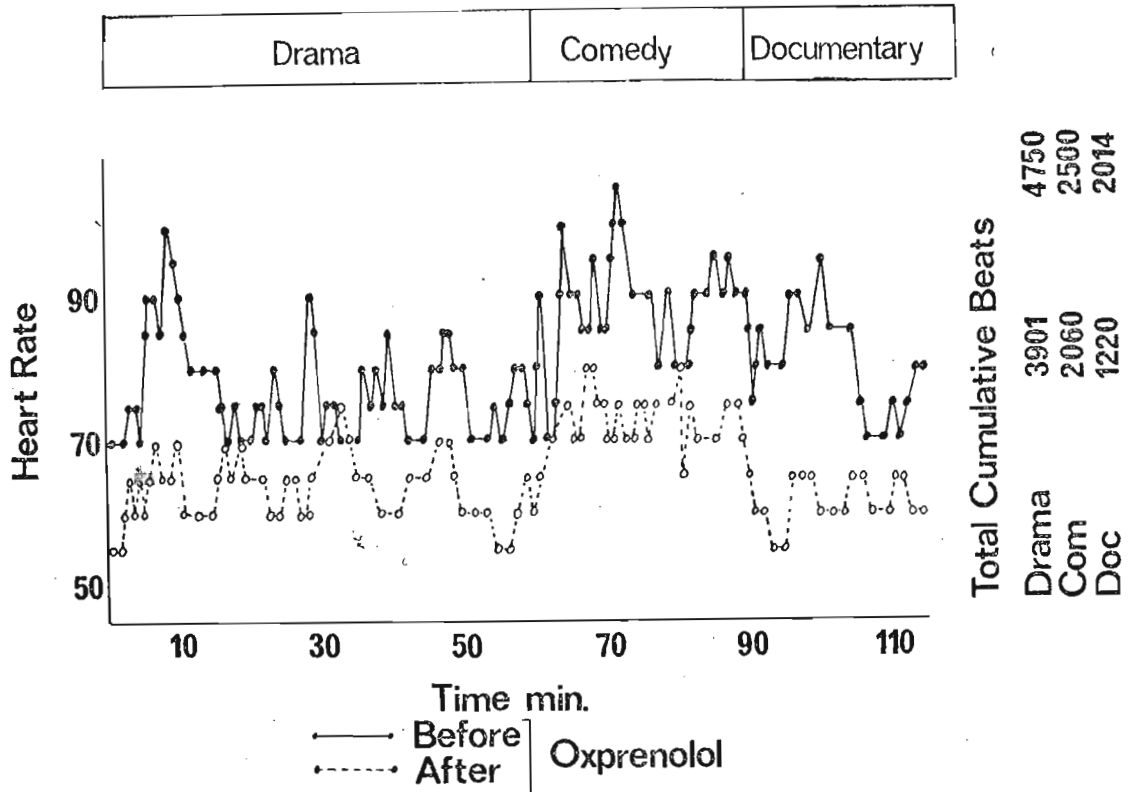Record of the heart rate in a patient with ischaemic heart disease watching a televised live football match and the effect of 40 mg oral oxprenolol taken 30 minutes after the commencement of the match.
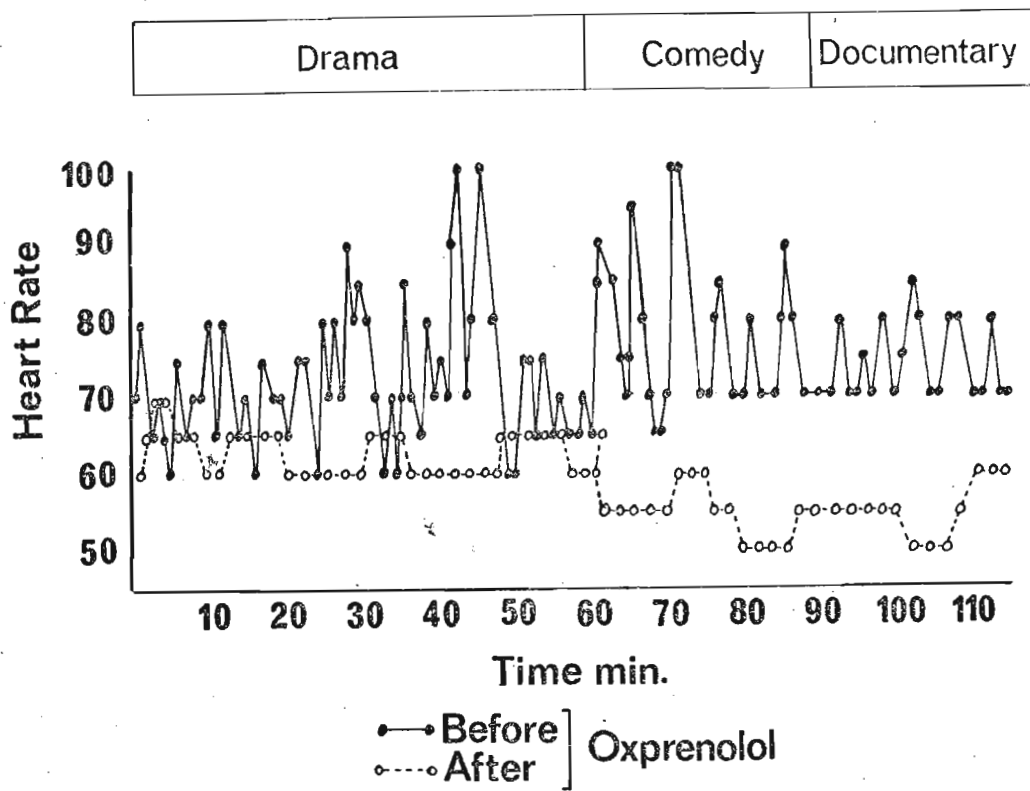
FIGURE 103

Record of the heart rate in a normal subject watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.
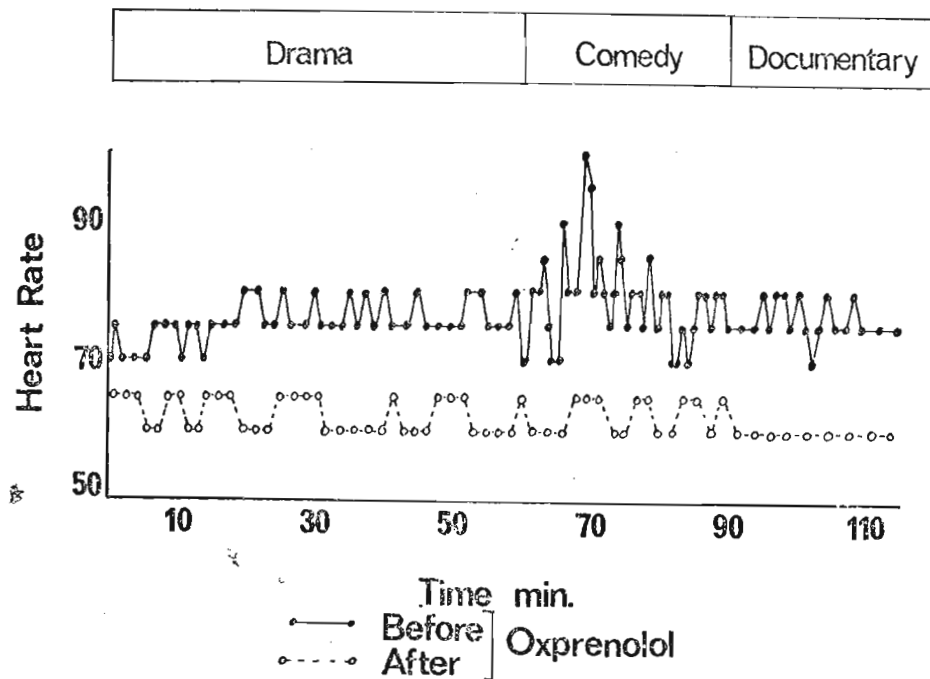
FIGURE 104

Record of the heart rate in a normal subject watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.

FIGURE   105

Record of the heart rate in a normal subject watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.
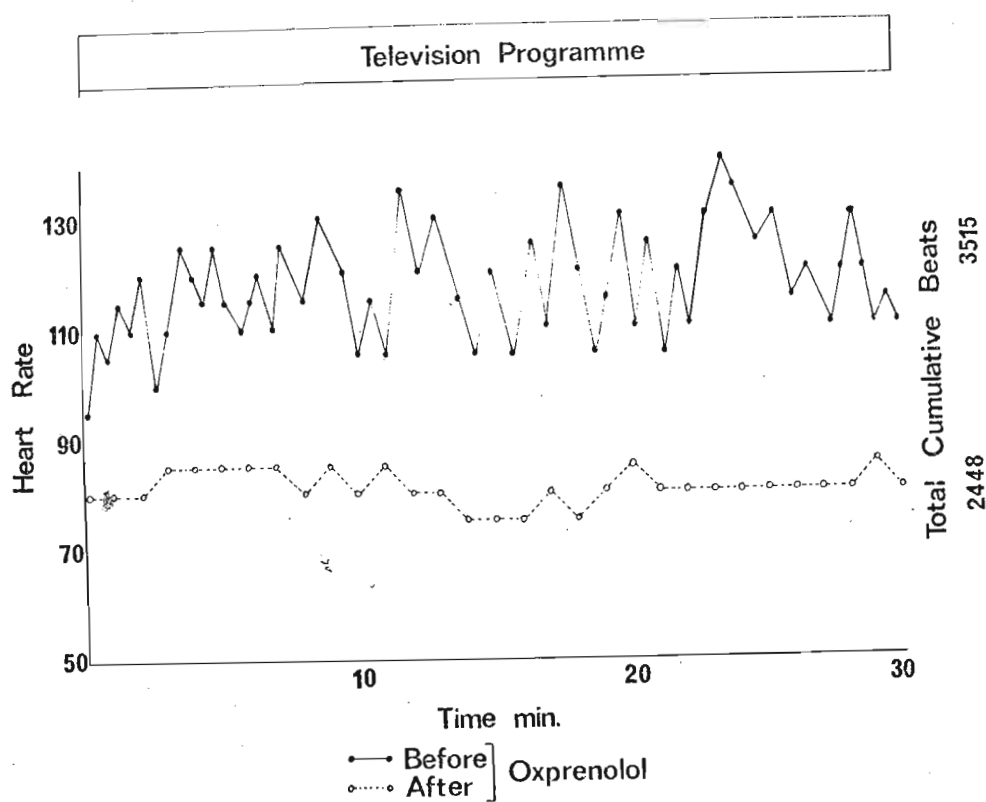
FIGURE 106

Record of heart rate in a sensitive subject watching a television
thriller film and the modulation of the response by 40 mg oral oxprenolol
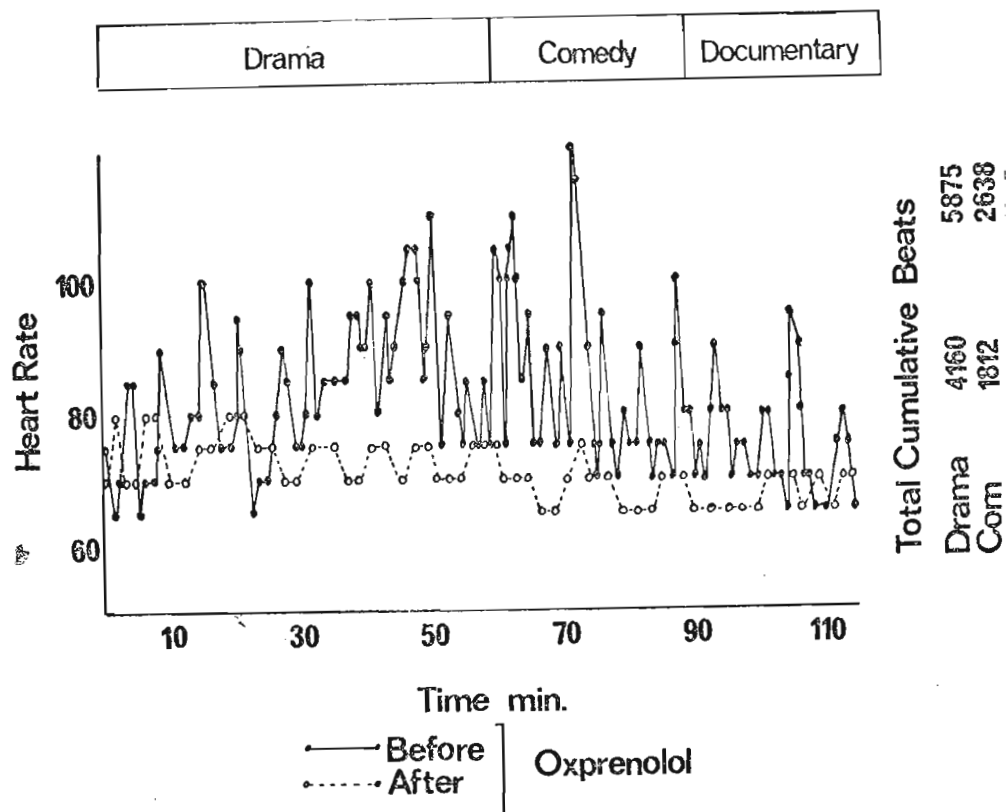taken one hour before a similar programme.

FIGURE 107

Record of the heart in a patient with ischaemic heart disease
watching programmes of Drama, Comedy and Documentary on television
during placebo and the modification of the response by 40 mg oral
oxprenolol taken one hour before the programme.

FIGURE 108

Record of the heart rate in a patient with ischaemic heart disease watching programmes of Drama, Comedy and Documentary on television during placebo and the modification of the response by 40 mg oral oxprenolol taken one hour before the programme.
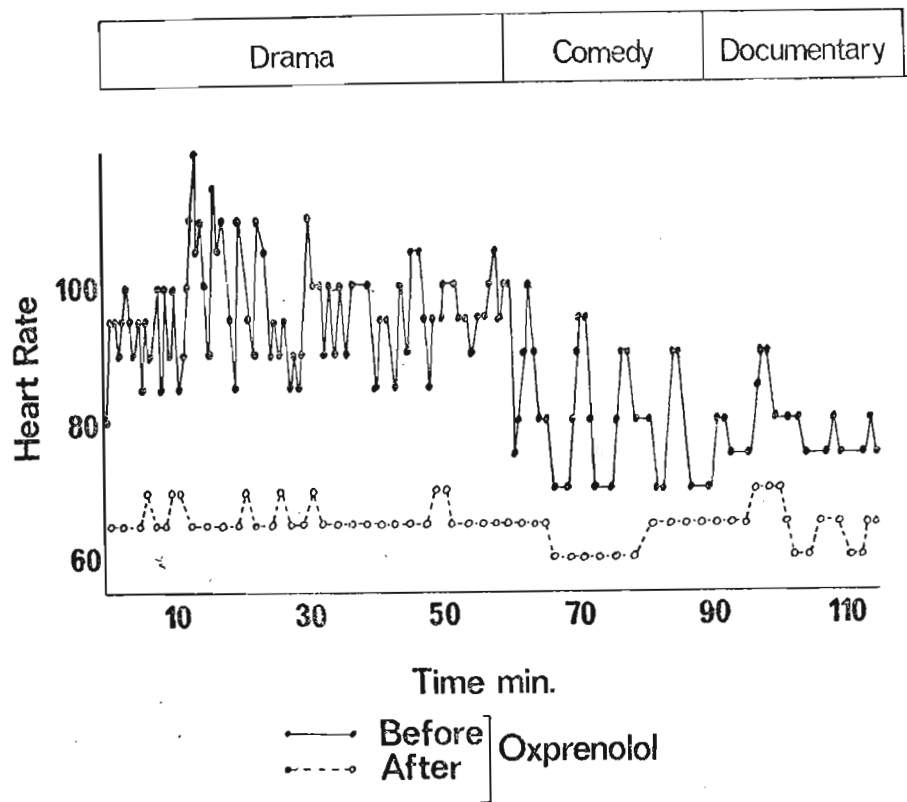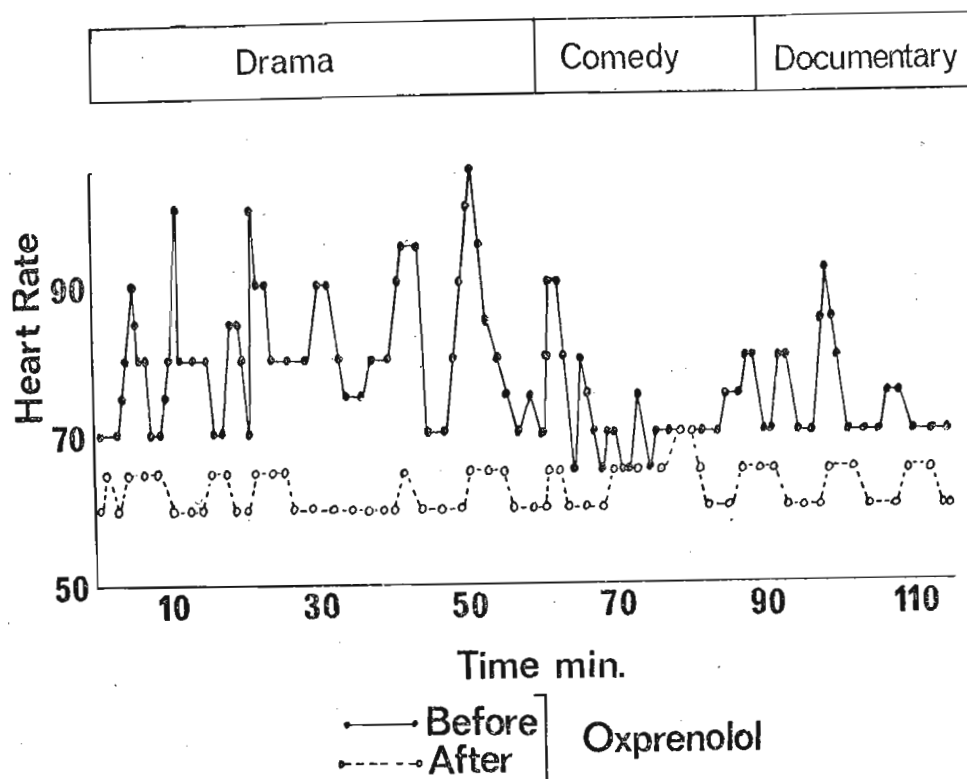
FIGURE 109

Record of the heart rate in a patient with ischaemic heart disease
watching programmes of Drama, Comedy and Documentary on television
during placebo and the modification of the response by 40 mg oral
oxprenolol taken one hour before the programme.

EXCURSION BUS DRIVER
360 MILES

FIGURE 110

Record of heart rate during long distance bus driving.

FIGURE 111

Record of heart rate during long distance bus driving.

EXCURSION BUS DRIVER
480 MILES

FIGURE 112

Record of heart rate during long distance bus driving.

EXCURSION BUS DRIVER
360 MILES

FIGURE 113

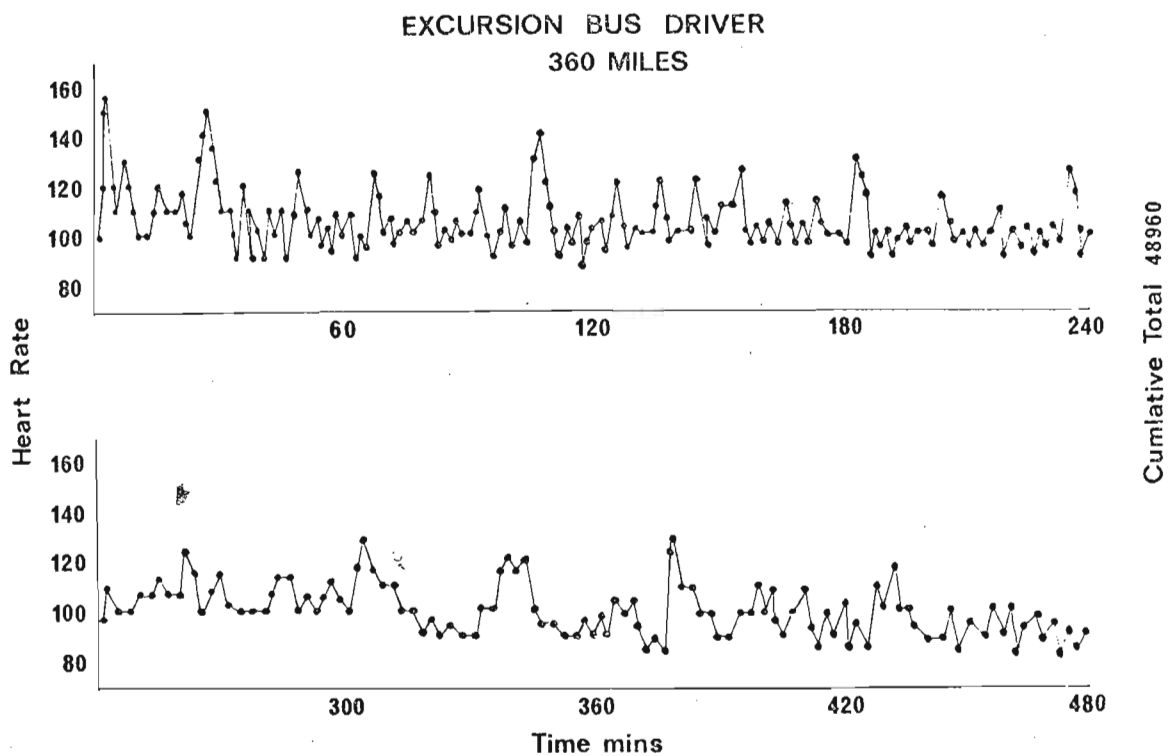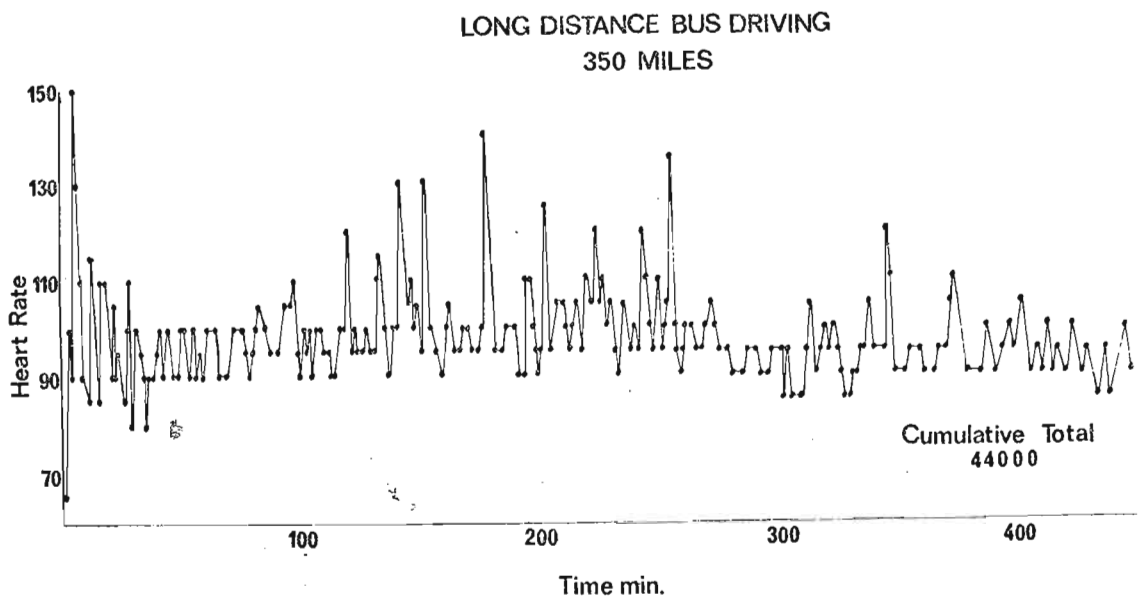Record of heart rate during long distance bus driving.

FIGURE 114

Record of heart rate during long distance bus driving.

LONG DISTANCE DRIVER
480 MILES
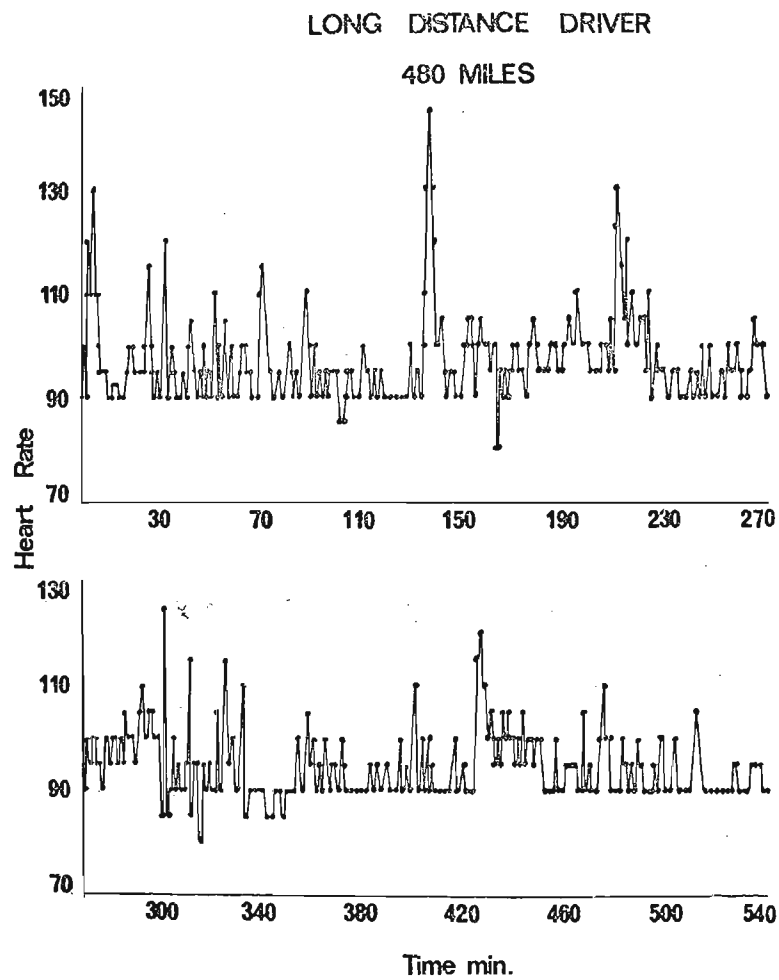
FIGURE 115

Record of heart rate during long distance bus driving.

FIGURE 116

Record of heart rate during bus-driving in London.
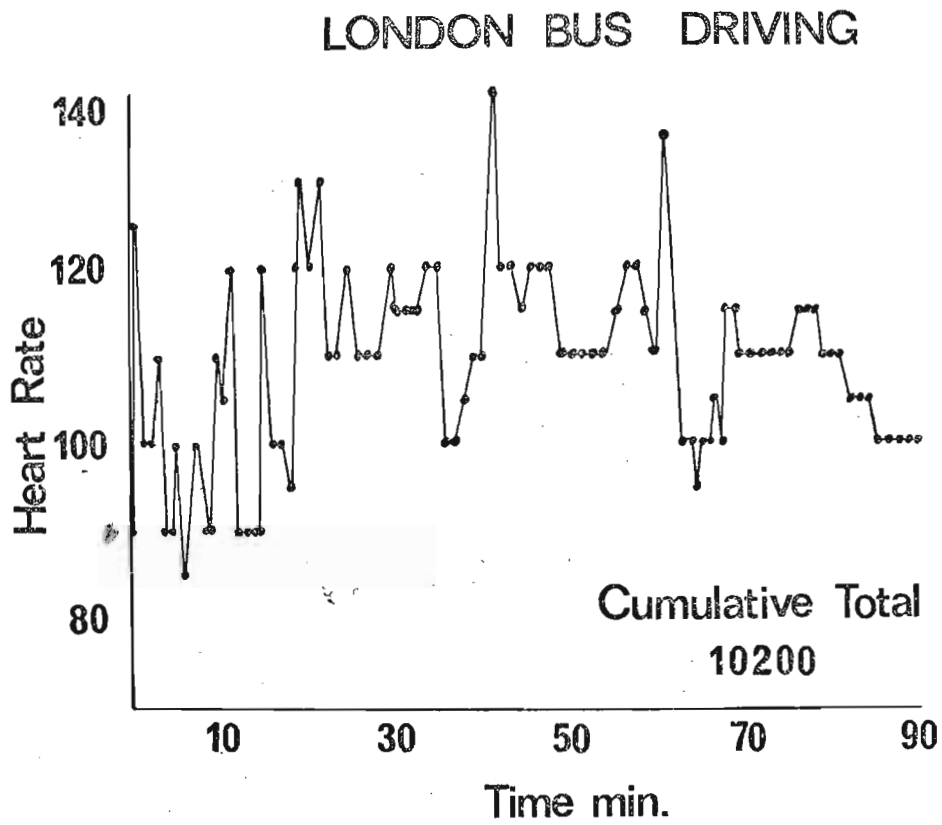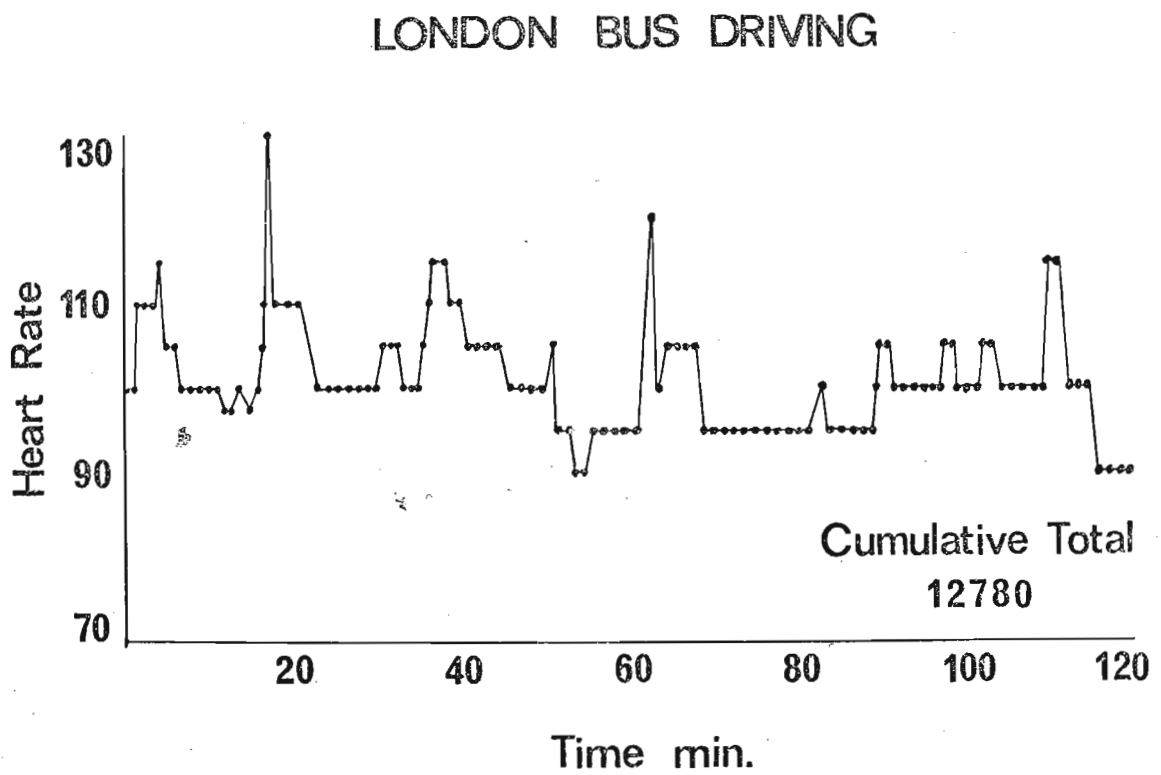
FIGURE 117

Record of heart rate during bus-driving in London.

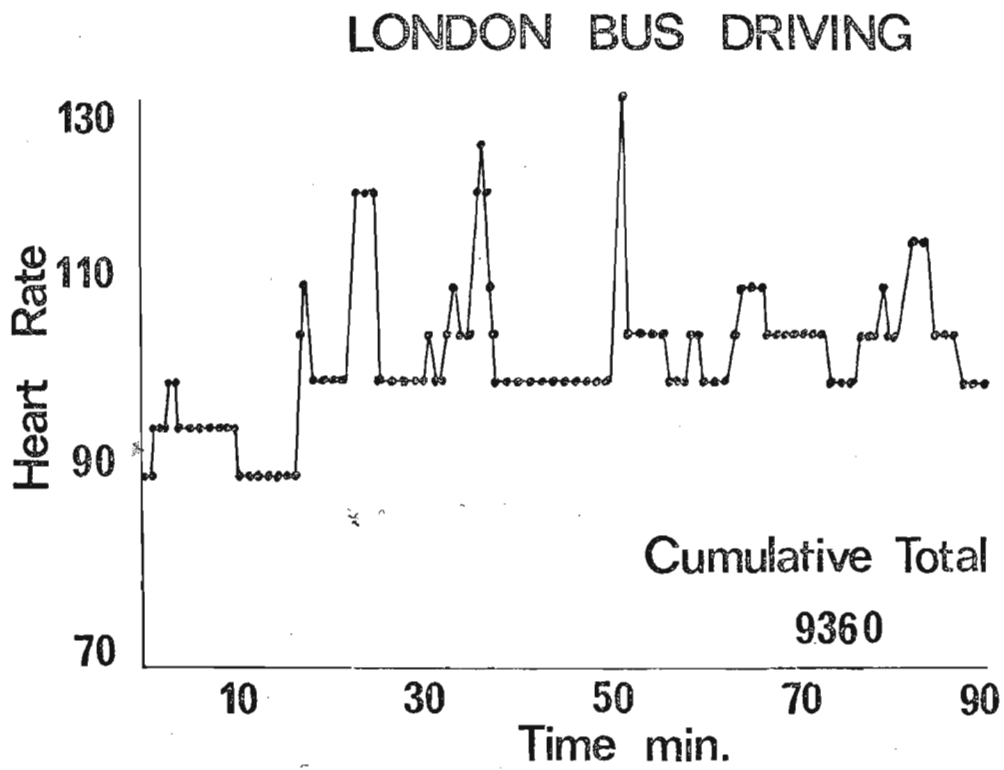**FIGURE 118**

Record of heart rate during bus-driving in London.
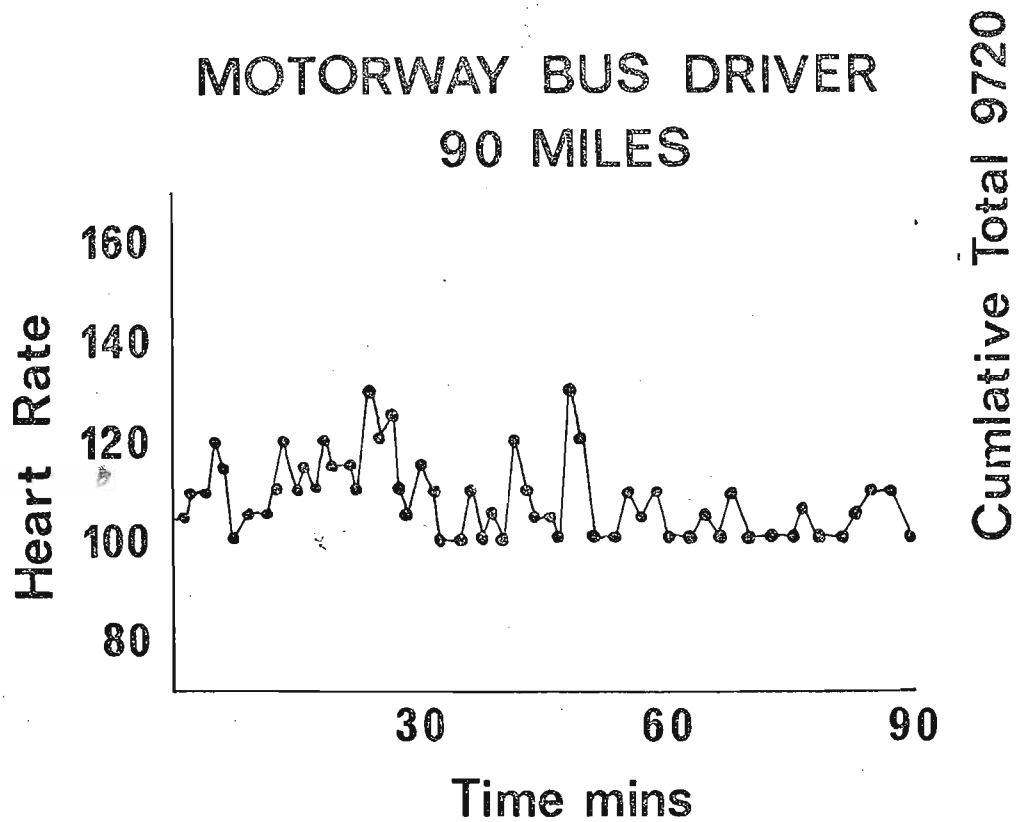
FIGURE 119

Heart rate records of experienced bus drivers during motorway driving between Leeds and London.
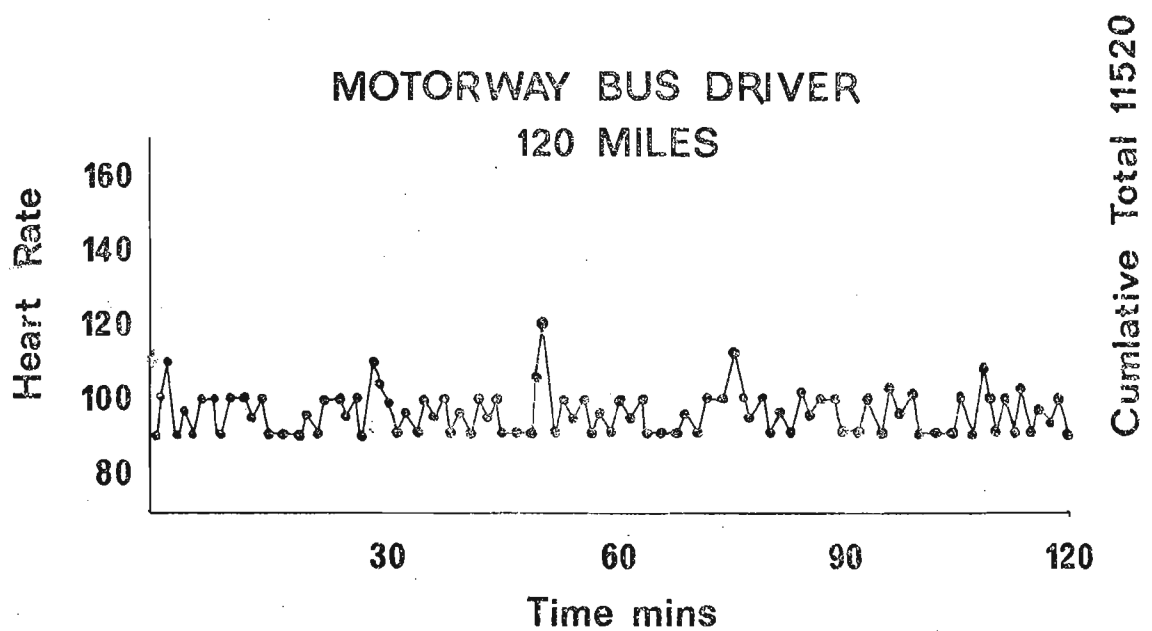
FIGURE 120

Heart rate records of experienced bus drivers during motorway driving between Leeds and London.

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