#477 CARROLL, MARCUS
Report #3

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PROGRESS REPORT NO. 3

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CNS - EVOKED ARRHYTHMIAS AND CORONARY BLOOD FLOW

A. INTRODUCTION AND GENERAL STATEMENT OF PROGRESS

Since the submission of Progress Report No. 2 (January 1, 1966 through June 30, 1966) on Grant QH-205, considerable research advancements have been achieved despite the temporary setback incurred by changes in personnel* and problems in the procurement of Boxer dogs. The data obtained from our studies may be divided into four major categories. These are:

1. Reconfirmation of neuroanatomical and neurophysiological data in ten animals at each of four frontal levels. (Superior colliculus, posterior commissure, mammillary bodies and anterior hypophysis).

2. Assignment of specific cerebral loci with the production of discrete cardiac arrhythmias.

3. The discovery of loci within the globus pallidus, putamen and caudate nucleus which have jurisdiction over coronary blood flow and other cardiodynamic alterations.

4. The pharmacological evaluation of intravenous nicotine bitartrate 20 to 50 μg/kgm) on spontaneous electrocardiographic activity as well as on CNS-cardiac arrhythmias and other cardiodynamic changes.

B. METHODS OF PROCEDURE

These investigations have been conducted in pure bred Boxer dogs lightly anesthetized with intravenous thiamylal, sodium (Surital) and subsequently maintained on succinylcholine chloride and artificially ventilated. Mean and pulsatile coronary blood flow were monitored by means of a Biotronics BL-410 electromagnetic flowmeter with miniaturized Khouri-Gregg

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* Dr. Kenneth Kahan has replaced Mr. L. Fillisti as Electronics Engineer (part-time). The latter resigned due to illness within the family. Mr. Hodelin René has replaced Mr. R. Byrd as Surgical Research Assistant. Mr. Byrd terminated his affiliation with the project because of increased responsibilities within the Department of Surgery at the Brookdale Hospital Center.

sensor surrounding the left circumflex branch of the coronary artery. Blood flow in the ascending aorta was simultaneously measured with this four-channel unit employing the appropriate sized flow probe for this vessel. Electrocardiographic activity was monitored by means of a standard extremity lead and an esophageal lead. The latter bipolar electrode was fabricated from a size 26 (French) Bardic® catheter and positioned dorsal to the right auricular appendage. Systemic arterial blood pressure was recorded by means of an indwelling polyvinyl catheter appropriately connected to a Statham transducer. Myocardial tension was measured by means of a Brodie strain gauge arch sutured on the left ventricle. All Physiological parameters were recorded on an 8-channel Offner Dynograph. Electrical stimulation was accomplished by means of sine wave stimuli (7 volts, 2 milliamps) delivered through concentric stainless steel electrodes insulated except at the tip and stereotaxically oriented into loci within the cerebellum, thalamus, preoptic and other cerebral areas. Electrode verification was accomplished by the consulting neuroanatomist (Dr. Donald Ford, State University of New York, Downstate Medical Center, Brooklyn, New York).

C. RESULTS

1. Introductory

The data presented in this report are based on studies conducted in 12 Boxer dogs of both sexes and ranging in weight between 18.0 and 25.0 kgm. The animals were carefully selected on the basis of skull topography. Eight of the total experiments were successful. One hundred thirty four of 323 points stimulated in the anatomical areas set forth in Table I evoked changes in coronary blood flow and other cardiodynamic alterations.

2. Spectra of electrocardiographic activity elicited by stimulation of discrete cerebral loci

Fig. 1. Changes in cardiac rate, rhythm and conduction evoked by excitation of the mesencephalic reticular formation.

Fig. 2. E.K.G. abnormalities elicited by stimulation of the entopeduncular nucleus of the thalamus.

Fig. 3. Cardiac arrhythmias evoked by electrical stimulation of the zona incerta of the thalamus.

TABLE I

Anatomical classification of loci from which positive alterations in coronary blood flow and other cardiodynamic changes have been evoked in the unanesthetized Boxer dog

Anatomical Area	Positive points	Negative points	Total points stimulated
Telencephalon	27	155	182
Diencephalon	14	4	18
Mesencephalon	93	30	123
Total	134	189	323

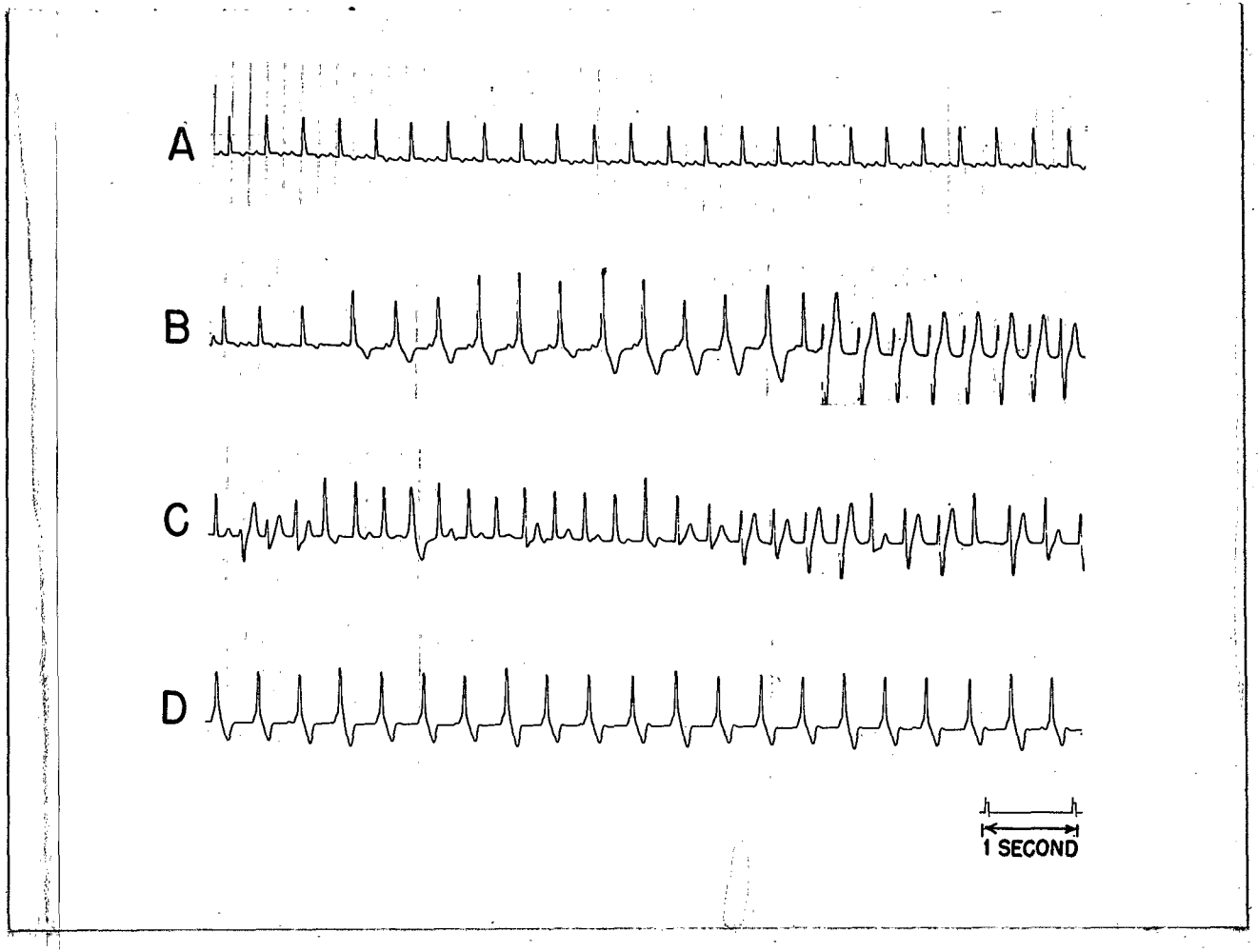

Fig. 1. Changes in cardiac rate, rhythm and conduction evoked by excitation of the mesencephalic reticular formation. A, Control record. B, During stimulation (1 to 10 seconds)- ventricular tachycardia with 9 fusion beats (these simulate the W.P.W. syndrome) followed by ventricular tachycardia from a different focus. C, Post stimulation (0 to 10 seconds)- supraventricular and ventricular beats interspersed with fusion beats. D, Post stimulation (20 to 30 seconds)- ventricular tachycardia which has the same focus as in tracing B.

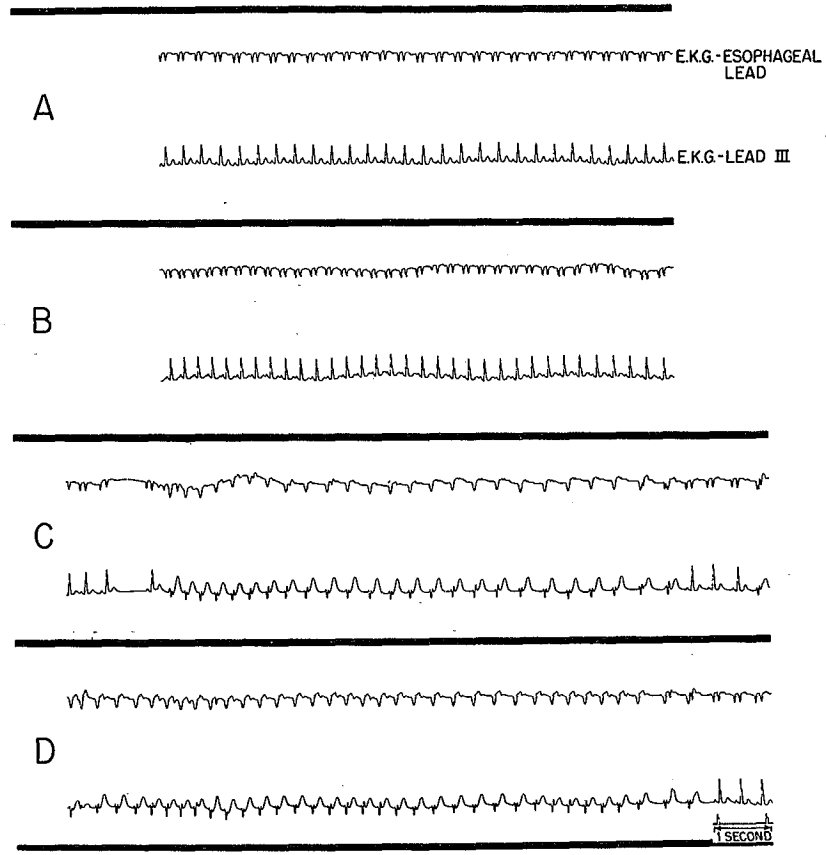

Fig. 2. E.K.G. abnormalities elicited by stimulation of the entopeduncular nucleus. A, Control record. B, During stimulation (10 to 20 seconds)- No significant change over control. C, Post stimulation (1 to 14 seconds)- S-A block followed by nodal tachycardia aberrantly conducted (this terminates in 3 beats of normal sinus rhythm. D, Post stimulation (14 to 28 seconds)- one ventricular extrasystole with continued nodal tachycardia which terminates in normal sinus rhythm.

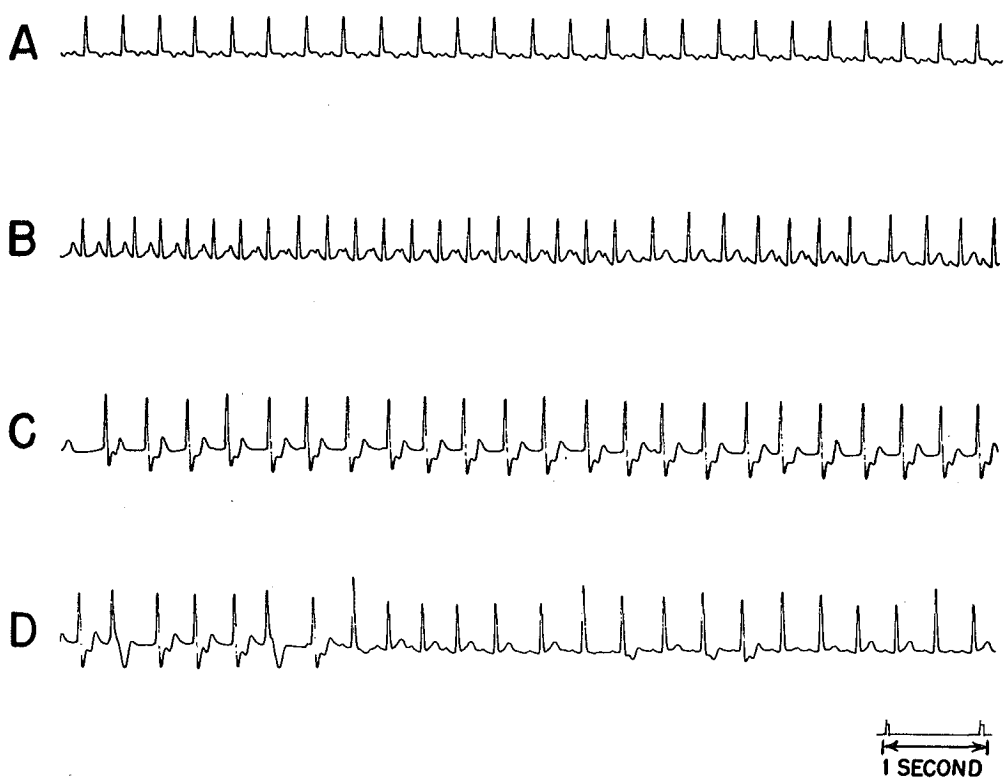

Fig. 3. Cardiac arrhythmias evoked by stimulation of the zona incerta. A, Control tracing. B, During stimulation (10 to 20 seconds)- sinus tachycardia with wandering pacemaker. C, Post stimulation (0 to 10 seconds)- A-V dissociation. D, Post stimulation (10 to 20 seconds)- continued A-V dissociation with occasional premature beats followed by return to normal sinus rhythm (Note the interspersed fusion beats).

3. CNS-evoked changes in coronary blood flow and other cardiodynamic alterations following electrical stimulation of various neuroanatomical loci at the level of the posterior commissure.

Fig. 4. presents a coronal section of the brain of the Boxer dog at the level of the posterior commissure. The data indicate that discrete changes in coronary blood flow have not been observed independent of alterations in one or more of the other cardiovascular parameters monitored. Marked pressor responses (+150/+115 mm. Hg.-systolic/diastolic over control values) as well as increased myocardial tension were elicited from all loci studied with the exception of the median geniculate body. Moderate elevation in both mean coronary and aortic blood flow were only noted following electrical excitation of the median longitudinal fasciculus, posterior commissure and the nucleus of the posterior commissure. A weak to moderate tachycardia was provoked by excitation of the tegmental H fields, the tegmental reticular formation and the red nucleus whereas significant increases in heart beat were observed after stimulation of all other loci.

Regarding classification of cardiac arrhythmias evoked by stimulation of the various neuroanatomical loci at the level of the posterior commissure, discreteness of response, i.e. (auricular vs ventricular disturbance of cariac rate, rhythm and conduction as assigned to specific cerebral loci) appear to be lost. This may undoubtedly be attributed to the fact that more neural pathways converge in the area of the mesencephalon than at higher levels. In addition, numerous internuncial connections are present in the area which may contribute to the excitation of multiple structures. Electrical excitation of all positive loci in the mesencephalon, with the exception of tegmental structures provoked marked sinus tachycardia during stimulation (0 to 20 seconds). Stimulation of tegmental structures produced atrial fibrillation with bouts of chaotic heart action (during stimulation) followed by post stimulatory runs of repetitive multifocal ventricular and/or supraventricular tachycardias with A-V dissociation and S-T segment elevation. It is of interest to note that a complete absence of cardiac arrhythmias was observed on stimulation of the median geniculate body. Moreover, excitation of the habenula and/or habenulointerpeduncular tract evoked a wandering pacemaker (during stimulation) and elevation of the S-T segment (post stimulation).

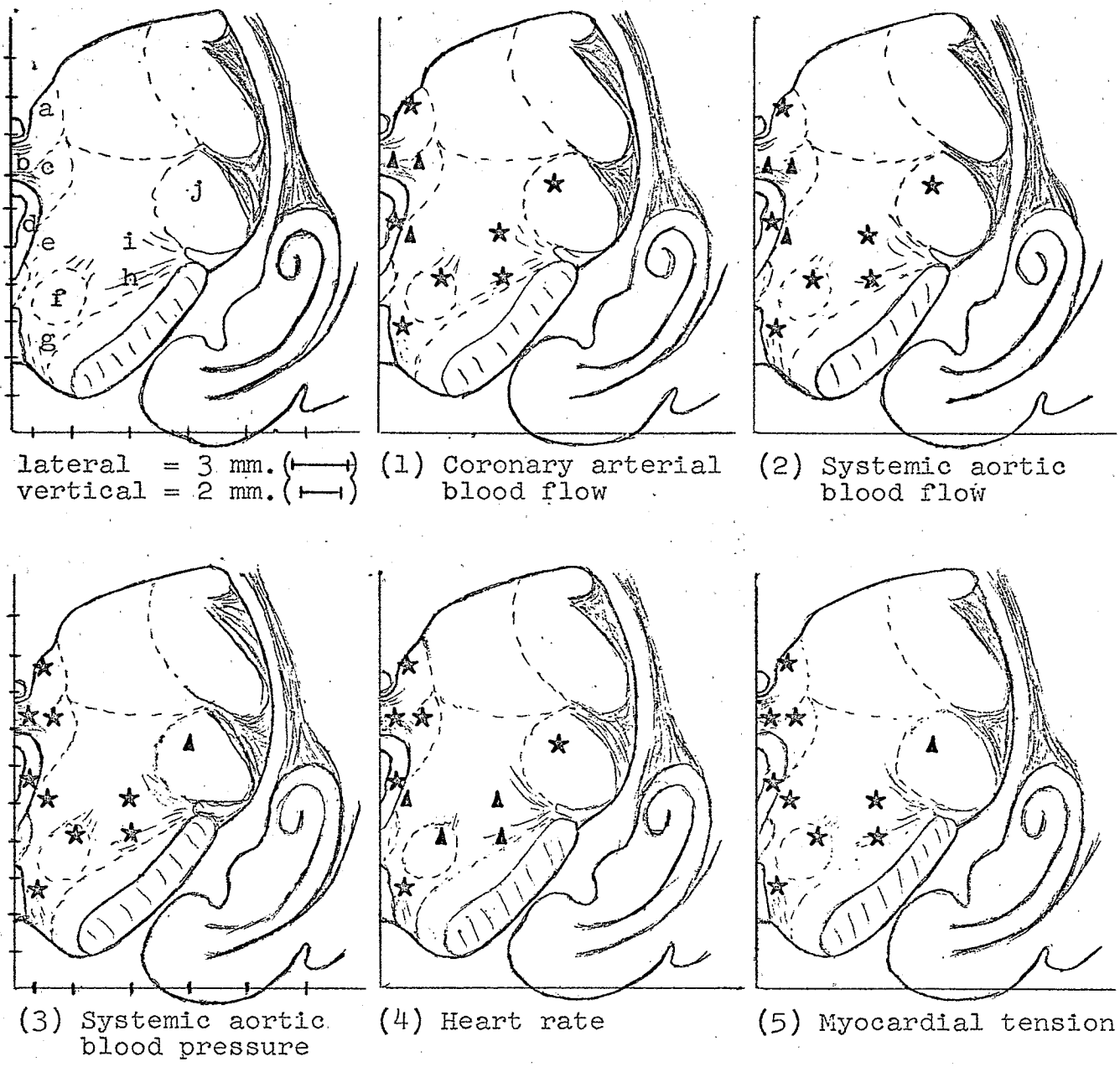

Fig. 4. CNS-evoked alterations in coronary blood flow (1) and other cardiodynamics (2-5) following electrical stimulation of various neuroanatomical loci at the level of the posterior commissure. Anatomical loci: (a) habenula, (b) posterior commissure, (c) nucleus of posterior commissure, (d) central gray, (e) medial longitudinal fasciculus, (f) red nucleus, (g) habenulointerpeduncular tract, (h) tegmental H fields, (i) tegmental reticular formation, (j) medial geniculate body. (Magnification = x3).

SYMBOL CODE

- ▲ Moderate increase
- ▼ Moderate decrease
- ★ Marked increase
- ■ Marked decrease
- △ Biphasic
- ▽ Biphasic
- ○ Triphasic

4. The effects of various doses of intravenous nicotine (bitartrate) on coronary blood flow, aortic blood flow, myocardial tension, heart rate and thoracic aortic blood pressure.

The compound employed in these studies was generously supplied by Dr. Robert C. Hockett, Associate Scientific Director, The Council for Tobacco Research, U.S.A. Nicotine (0.002%) was administered intravenously over twelve minutes. This time interval and percent solution was selected because of the toxic effects of abrupt administration of high concentrations of the compound (e.g. - 70 µg/kgm of 0.2% nicotine, i.v. killed the animal). A dose of 20 µg/kgm had no effect on the cardiovascular parameters monitored. Thirty µg/kgm of the drug produced simultaneous but moderate increases in coronary blood flow, thoracic aortic blood pressure and myocardial tension with minimal change in aortic blood flow.

Intravenous doses of 40 and 50 µg/kgm (See Fig. 5) of nicotine produced simultaneous but marked elevations in aortic blood pressure (+70/+45 systolic/diastolic-mm. Hg over control levels @40 µg/kgm; +175/+105 @50 µg/kgm), myocardial tension (greater than 100% over control values). The initial transient decrease in the responses monitored are rather difficult to explain. Perhaps they may be attributed to the concomitant stimulatory and/or depressant properties of nicotine on both central and peripheral adrenergic or cholinergic receptors.

5. The effects of various doses of intravenous nicotine (bitartrate) on spontaneous heart rate, rhythm and conduction.

Although 20 µg/kgm had little or no effect on heart rate or electrocardiographic activity, doses of greater than 30 µg/kgm, but less than 60 µg/kgm, evoked repetitive multifocal ventricular and/or supraventricular tachycardia (Fig. 5.-seconds 245 to 249) followed by atrial fibrillation with idioventricular beats (Fig. 5.-seconds 251 to 252) which terminated in an A-V nodal conduction defect (Fig. 5.-seconds 256 to 496).

6. The effects of various doses of intravenous nicotine (bitartrate) on CNS-evoked coronary flow changes and other cardiodynamic alterations elicited by stimulation of the red nucleus.

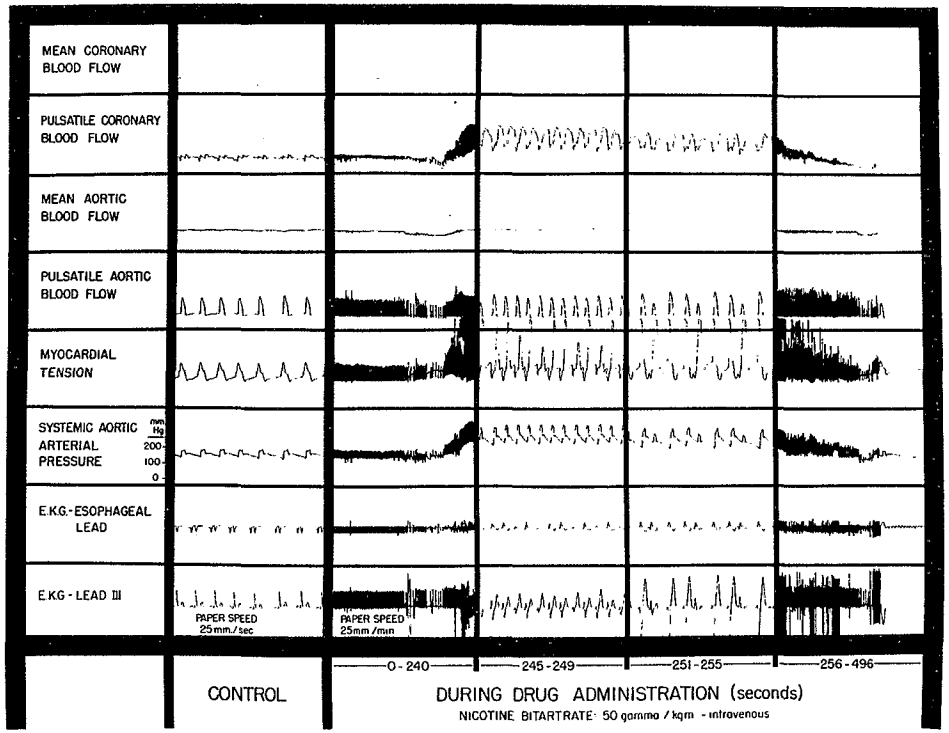

Fig. 5. The effects of intravenous nicotine (bitartrate) on coronary blood flow, aortic blood flow, myocardial tension, heart rate, thoracic aortic blood pressure and cardiac arrhythmias.