might result from operating on irradiated tissue. The proper timing of operation is important; six to eight weeks following the course of radiotherapy is probably the optimum interval. With these precautions no significant difficulties are encountered.

The follow-up of an irradiated lesion is most important. The recurrence of a tumour may be extremely difficult to determine at an early stage because of the presence of post-irradiation inflammation and edema. Considerable experience is necessary before a valid opinion can be given in this regard. Biopsy in these circumstances can be misleading, and clinical judgment is probably more important in deciding when operation for a recurrent lesion should be undertaken. We believe that it is most important to excise recurrences at the earliest possible time before they begin to grow actively.

CONCLUSION

A general classification and discussion of carcinoma of the larynx is presented. Present methods of treatment have been reviewed in the light of a recent study of 419 cases of laryngeal carcinoma treated in the years 1950 to 1960. The importance and feasibility of early diagnosis are stressed. A combination of radiotherapy and surgery is advised for the management of all laryngeal lesions, with provision for close consultation between surgeon and radiotherapist.

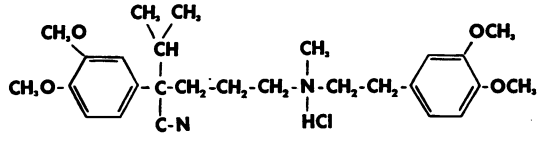
Iproveratril: Experimental Data on Coronary Dilatation and Antiarrhythmic Action

K. I. MELVILLE, M.D., H. E. SHISTER, M.D. and S. HUQ, M.D., *Montreal*

ABSTRACT

Various cardiovascular effects of a new synthetic coronary vasodilator, α-isopropyl-α [(N-methyl - N - homoveratryl)-γ-amino-propyl]-3, 4-dimethoxyphenylacetonitrile HCl (D365, Iproveratril or Isoptin) have been studied. In isolated perfused rabbit hearts the drug exerts a potent coronary vasodilator action, but can depress myocardial contractions and A-V conduction. In anesthetized cats it produces varying degrees of hypotension with bradycardia, and antagonizes ST-T changes induced by ouabain. It can also protect against chloroform-adrenaline and ouabain ventricular fibrillation. On isolated papillary muscle preparations it can lead to adrenergic blockade. It is concluded that in addition to its coronary dilator action, the drug exerts 'quinidine-like' antiarrythmic effects, and appears to deserve further study.

A NEW synthetic compound, α-isopropyl-α[(N-methyl-N-homoveratryl)-γ-amino-propyl]-3, 4-dimethoxyphenylacetonitrile hydrochloride (D365, Iproveratril or Isoptin), has been reported by Haas and Härtfelder,[1] in Germany, to exert marked coronary dilator action in both dogs and rabbits. The chemical structure of this agent, given by these authors, is as follows:



From their studies on the isolated rabbit heart it was concluded that the compound was 100 times more effective than papaverine; that is, it required a 100 times higher concentration of papaverine than of this drug to produce a similar coronary dilator action. Haas and Härtfelder[1] also found that the drug increased the oxygen content of the coronary sinus blood and reduced the coronary arteriovenous oxygen difference; cardiac oxygen uptake was reduced in most cases. Schlepper and Witzleb,[2] however, reported definite increase in myocardial oxygen consumption but concluded that the coronary dilator action was not due to changes in cardiac metabolism. Gerlach and Deuticke[3] also observed that, unlike dipyridamole (Persantin), the drug did not lead to accumulation of adenosine in the myocardium. One clinical report in the German literature[4] also suggests that the drug might be a useful therapeutic agent for patients with coronary insufficiency.

In view of the reported marked coronary dilator potency of the drug and its potential clinical usefulness for patients with coronary insufficiency, it appeared of interest to investigate further its cardiovascular effects. It was also hoped that these studies might throw further light upon its mecha-

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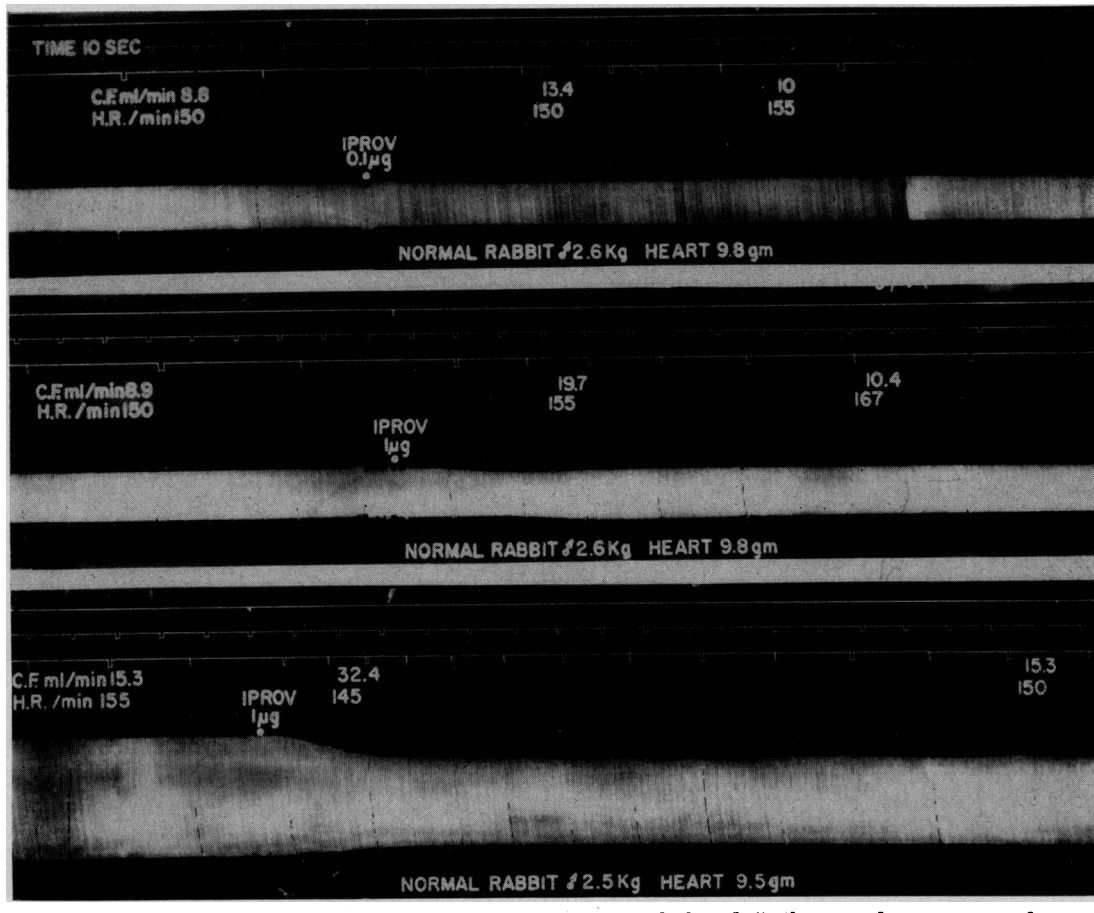

Fig. 1.—In this and the succeeding figures (Figs. 2, 3 and 4) the records are arranged from above downward as follows: I. Signal line showing time of the injections. II. Time-intervals of 10 seconds. III. Coronary inflow line—a volume of 4.2 ml. of perfusing fluid entered the coronary vessels during the interval between each successive mark on the line—calculated coronary flows (C.F. ml./min.) and associated heart rates as recorded on the electrocardiograms (H.R./min.) are also given. IV. Heart contractions recorded with a lever attached to the apex of the heart—systole above, diastole below. *Upper records* show effects of 0.1 µg. of Iproveratril (Iprov.); *middle and lower records,* effects of 1.0 µg, as marked.

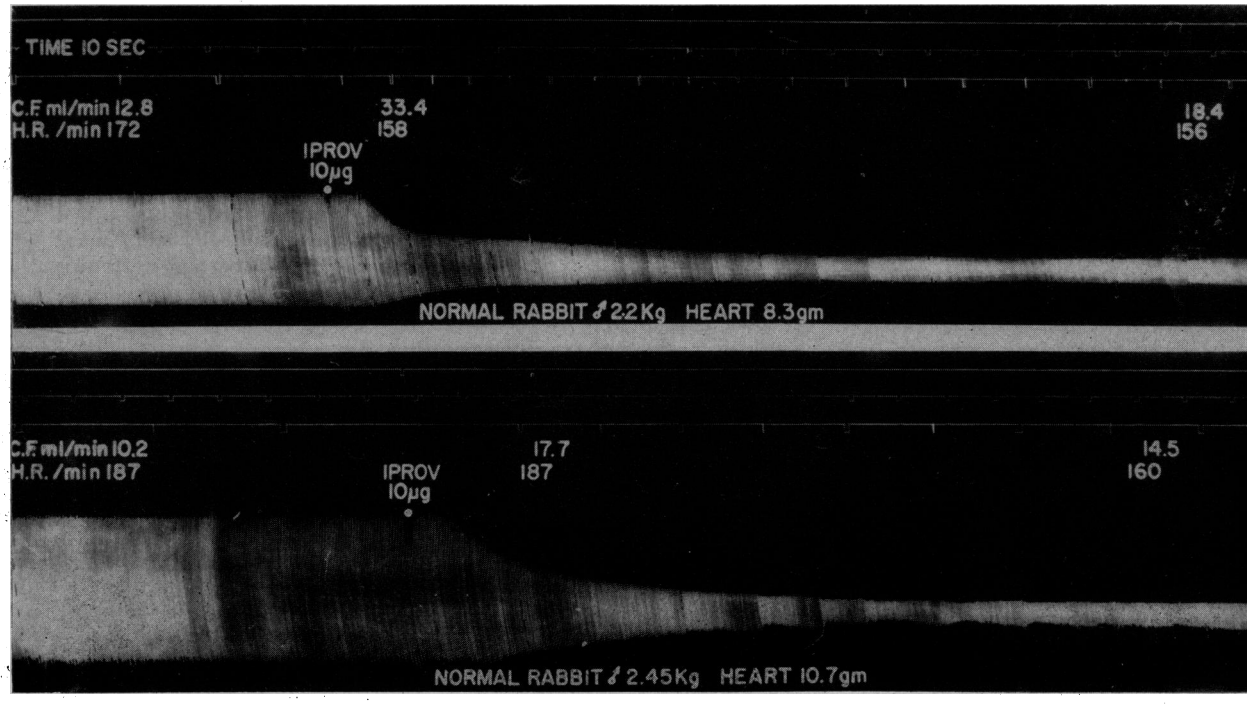

Fig. 2.—Effects of doses of 10 µg. of Iproveratril (Iprov.) on coronary flow and heart contractions in two experiments (see legend of Fig. 1).

nism of action. The object of this report is to present some preliminary results of these studies.

METHODS

In the first series of experiments concomitant coronary inflow and heart contraction changes were recorded in the isolated rabbit heart perfused by a modified Langendorff technique, as previously described by Lu and Melville[5] and Melville and Mazurkiewicz.[6] The perfusing fluid employed in these studies was McEwen solution[7] of the following composition: NaCl 0.71%, KCl 0.042%, $CaCl_2$ 0.024%, NaH_2PO_4 0.0163%, $NaHCO_3$ 0.21%, dextrose 0.2% and sucrose 0.45%, freshly prepared and aerated with a mixture of 95% oxygen and 5% carbon dioxide. Electrocardiograms were also recorded as previously described by Melville and Korol,[8] and the heart rates were calculated from these records. All injections were made close to the heart through rubber tubing connecting the perfusing cannula with the apparatus.

In order further to assess the effects of the drug upon the myocardial contractions without concomitant alterations in coronary flow, the isolated frog heart perfused with Clark solution was also used, and the changes in contraction were recorded on a kymograph in the usual manner.

In other experiments simultaneous changes in blood pressure and electrocardiogram (lead II) were recorded using a Sanborn Twin-Viso apparatus. Cats anesthetized with chloralose or pentobarbitone sodium and under artificial respiration were used. In all of these experiments the cats were placed in a prone position with the head elevated and in a suitable head-holder; the blood pressure was recorded from a femoral artery, and all injections were made through a polyethylene tube inserted into a femoral vein.

For assessment of antiarrhythmic action, the effects of the drug were also studied (a) on chloroform-adrenaline arrhythmias in chloralosed cats, employing the method earlier described,[9] and (b) on ouabain toxicity in pentobarbitalized cats.

The drug Iproveratril used in these experiments was supplied in the form of a powder, through the courtesy of Knoll Pharmaceutical Company, Orange, New Jersey, and freshly prepared solutions were always employed.

RESULTS

Effects on Coronary Flow and Heart Contractions in the Isolated Rabbit Heart

It was observed that following injections of small doses (0.1 μg.) there was a prompt and definite increase in the coronary inflow rate (averaging 72% above the control in five experiments) without any consistent or significant change in the amplitude of the heart contractions or heart rate. A typical example of this type of response is shown in Fig. 1 (upper record). As can be seen, following the administration of the drug there was a rapid increase in coronary inflow from 8.8 to 13.4 ml. per min. occurring within 40 sec., the rate returning to the control level within two minutes. There was also no change in the heart contractions.

It is noteworthy that in comparable experiments with papaverine hydrochloride, as previously reported,[5] the minimal effective coronary dilator dose under similar conditions was approximately 3 μg. On the basis of this comparison, Iproveratril would appear to be about 30 times more effective than papaverine, dose for dose. These findings confirm in a general way the earlier described results of Haas and Härtfelder[1] and leave no doubt that the drug is a more potent coronary dilator agent than papaverine, dose for dose.

Following injection of a dose of 1 μg., the average maximal increase in coronary flow recorded was 104% (four experiments). However, the associated changes in heart contraction and rate were rather variable with this dose, and while in some experiments there was no significant change (Fig. 1, middle record), in others there was a definite depression in the amplitude of contractions and slowing of the heart rate (Fig. 1, lower record). There is some possibility that this difference in response might be dependent on the control rate of inflow in the particular experiment. Thus presumably, when this rate is high (lower record) the heart would be exposed more rapidly to a higher concentration of the drug than when the control inflow rate is slower (middle record). In any event, it is evident that even with this relatively low dose (1 μg.) in some experiments the drug can induce a depressant effect on the myocardium with slowing of the heart rate.

When doses of 10 and 100 μg. were studied (Figs. 2 and 3), the intensity of the coronary dilator response was more marked, but there was also more marked depression of the heart contractions. After a dose of 10 μg. the average maximum increase in coronary flow was 120% over the controls (four experiments). However, invariably there was a concomitant depression of the myocardium, associated with slowing of the heart rate. These effects on the amplitude of contraction and on rate were also prolonged, and recovery only ensued after 10 to 15 min.

Following injection of doses of 100 μg. (Fig. 3), concomitant with the increase in coronary inflow the intensity of cardiac depression was further accentuated, and the maximum average increase in coronary flow was 225% over the controls (four experiments). The depression of the heart contractions was, however, extremely marked, leading to irreversible cardiac arrest. As can be seen from Fig. 3, in each experiment shown, although the mechanical records of contraction are barely discernible, the heart rates could still be clearly determined from the electrocardiograms.

Fig. 4 shows the results of a similar experiment with a superimposed section of the electrocardiograms, as recorded at the time of the maximum in-

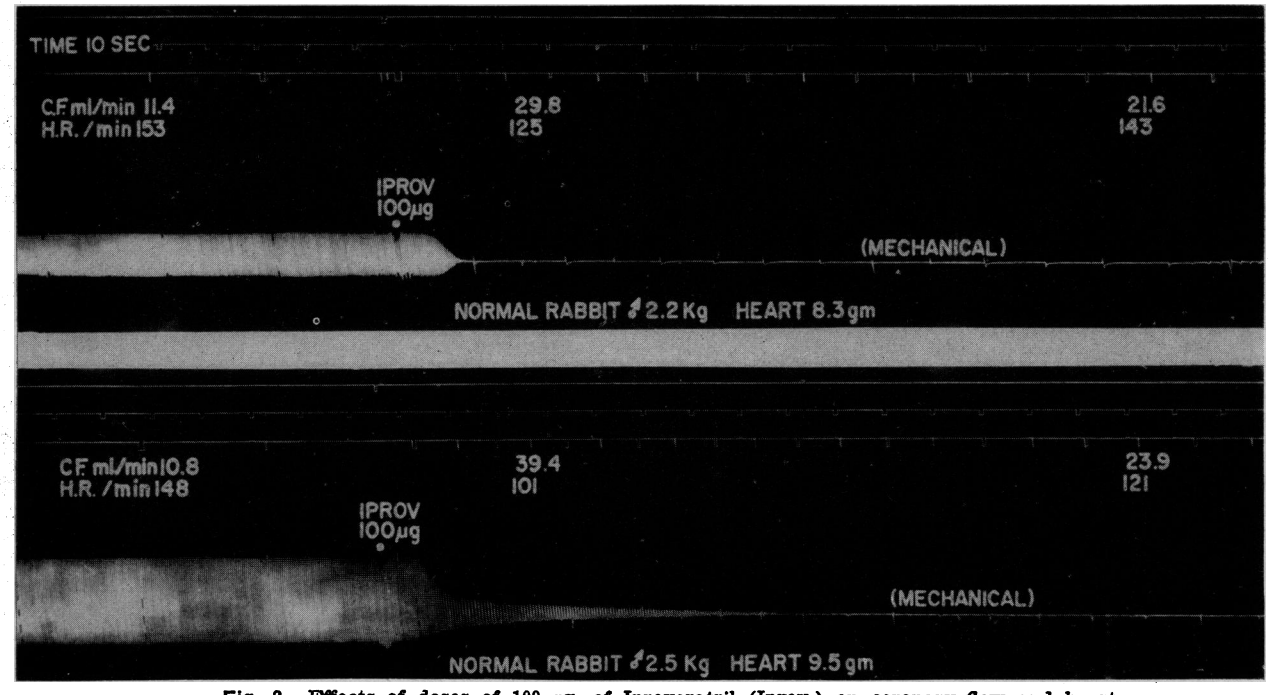

Fig. 3.—Effects of doses of 100 µg. of Iproveratril (Iprov.) on coronary flow and heart contractions in two experiments (see legend of Fig. 1).

crease in coronary inflow (55 ml./min.) following an injection of 100 µg. of Iproveratril. Again, there is a marked and sustained increase in coronary inflow, associated with intense depression and slowing of the heart contractions. As is evident from the electrocardiograms, there was also a marked sustained A-V block (complete heart block) and the ventricular rates recorded were only 43 and 39 beats per minute. It must be concluded therefore that although Iproveratril is a potent coronary vasodilator agent, it is also a potent depressant of the myocardium and the conducting system in the rabbit heart.

EFFECTS ON THE ISOLATED FROG HEART

Using the perfused frog-heart preparation, it was observed that with increasing concentrations there were increasing degrees of myocardial depression and slowing associated with A-V dissociation (Fig. 5). Thus, with a concentration of 0.1 µg. per ml. (upper record) there was only a progressive depression of heart contractions, but no change in rate. This effect, however, persisted for several minutes after the perfusion was changed back to normal Clark solution, although complete or almost complete recovery ensued in most experiments within 10 minutes.

With a perfusing concentration of 1 µg. per ml. (middle records), the immediate depression was more marked and although perfusion of the drug was continued for only 60 sec., recovery ensued much more slowly. Finally, with a perfusing concentration of 10 µg. per ml. (lower records) complete cardiac arrest ensued within 60 sec. and recovery did not occur after changing back to Clark's solution. The above findings confirm the observations on the rabbit heart and show clearly that Iproveratril also exerts a marked depressant action

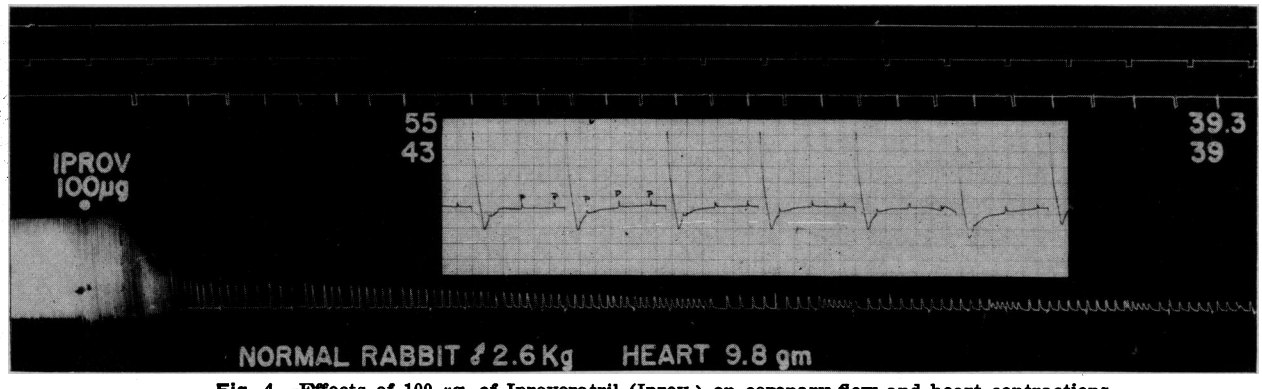

Fig. 4.—Effects of 100 µg. of Iproveratril (Iprov.) on coronary flow and heart contractions (see legend of Fig. 1). The section of the electrocardiograms reproduced was taken at the time of the maximum increase in coronary flow (55 ml./min.) when the ventricular rate was 43/min., as marked.

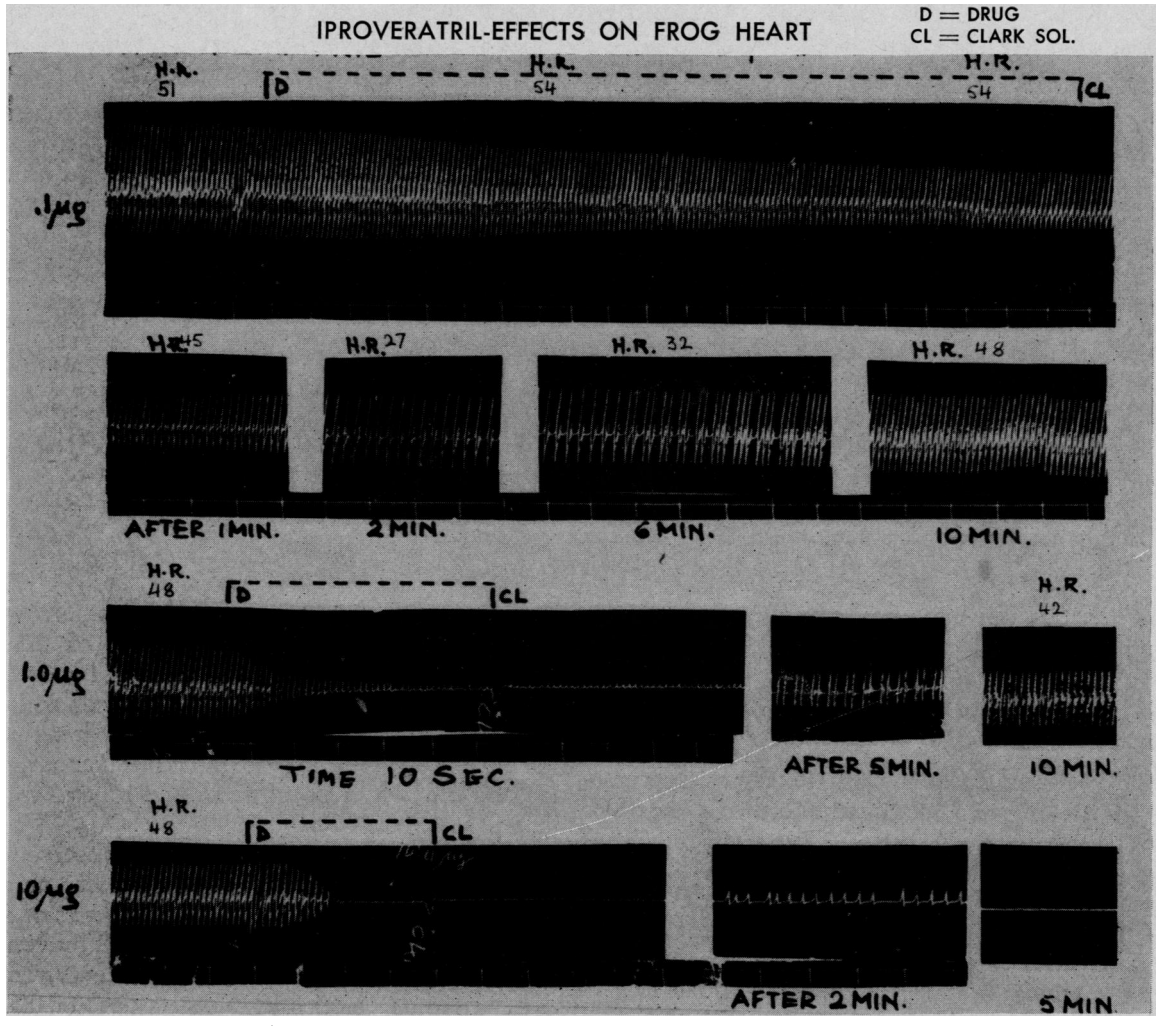

Fig. 5.—Effects of Iproveratril on the contractions (systoles above, diastoles below) of the perfused frog heart. The heart rates per min. (H.R.) as shown were calculated from the electrocardiograms. The letter "D" followed by a broken line to "Cl" indicates the duration of perfusion with Iproveratril. The concentrations used are marked at the left of the records, that is, 0.1 µg., 1.0 µg., and 10 µg. per ml. in each case. The time scale is 10 sec.

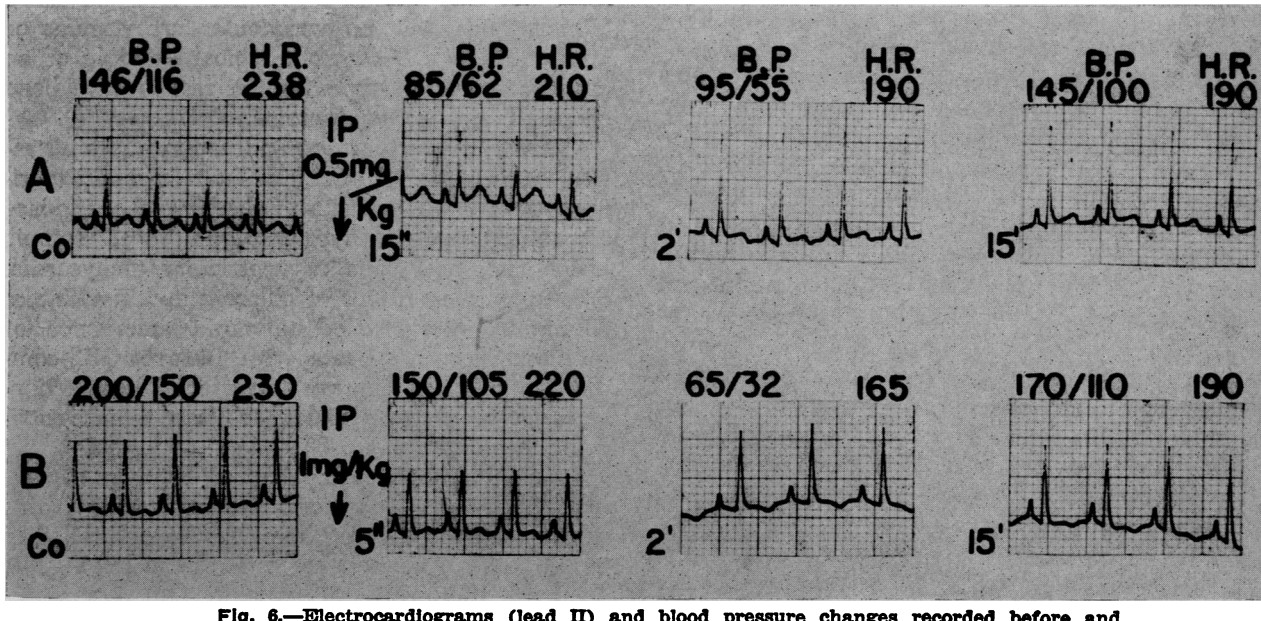

Fig. 6.—Electrocardiograms (lead II) and blood pressure changes recorded before and after intravenous injection of doses of 0.5 mg./kg. (A) and 1.0 mg./kg. (B) of Iproveratril in a chloralosed cat. An interval of 30 minutes elapsed between the upper and lower records (see "Methods").

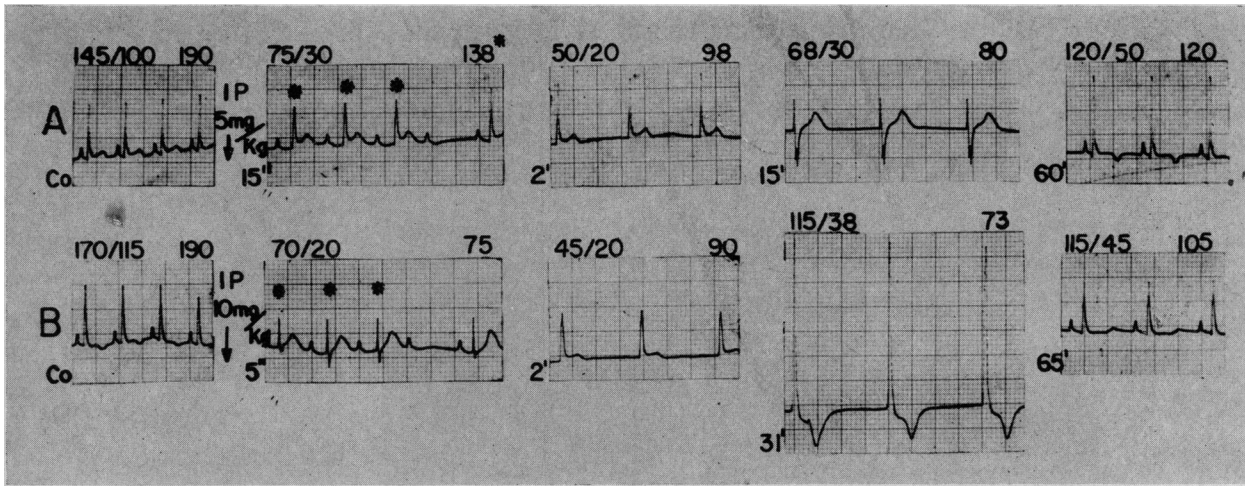

Fig. 7.—Electrocardiograms (lead II) and blood pressure changes recorded before and after intravenous injection of doses of 5 mg./kg. (A—Exp. 14E) and 10 mg/kg. (B—Exp. 15E) of Iproveratril in chloralosed cats (see "Methods").

on the myocardium and conducting system in this preparation.

EFFECTS ON BLOOD PRESSURE AND ELECTROCARDIOGRAM

When increasing doses were injected intravenously in cats under chloralose anesthesia, it was observed that amounts up to 0.1 mg./kg. produced no significant change in blood pressure or electrocardiogram (three experiments). Doses of 0.5 mg. and 1 mg./kg., however, invariably (seven experiments) led to prompt fall in blood pressure associated with sinus bradycardia and minimal ECG changes (diphasic or inverted T waves). Some examples of these responses are shown in Fig. 6. With these doses, recovery also ensued within 15 to 30 minutes.

With higher doses (5 and 10 mg./kg.), both the depressor response and cardiac depression were more marked (five experiments). Some examples of these changes are shown in Fig. 7.

As can be seen, there was again a prompt and marked depressor response associated with early sinus bradycardia followed by marked ECG changes (P-R prolongation, sagging of the P-R, A-V block, and nodal rhythm). However, with doses of 5 mg./kg. recovery ensued within 50 to 60 minutes. On the other hand, with the higher doses (10 mg./kg.) associated with the more intense depressor response, the ECG also showed idioventricular rhythm with sharply inverted T waves and very tall R waves. Recovery was also still more delayed in such experiments and irreversible cardiac arrest ensued in some. There was no evidence of ventricular extrasystoles or fibrillation in any of these experiments.

EFFECTS ON CHLOROFORM-ADRENALINE ARRHYTHMIAS

In view of the potent coronary dilator and myocardial depressant actions of Iproveratril, it was of interest to investigate its possible antiarrhythmic actions. In these experiments doses of 0.5 to 1 mg./kg. of the drug were injected two minutes after chloroform inhalation was started, and three minutes later a challenging dose of adrenaline bitartrate (100 μg./kg.) was given intravenously. The chloroform was discontinued one to two minutes later.

In control experiments it was observed that under these conditions adrenaline induced a prompt rise in blood pressure with early outbursts of multifocal ventricular extrasystoles followed by ventricular tachycardia, and in some experiments ventricular fibrillation. After injection of a dose of 0.5 mg./kg. of Iproveratril during chloroform inhalation, there was also a prompt fall in blood pressure and distinct inversion of the T waves. Following subsequent (three minutes later) injection of adrenaline, there was a marked rise in blood pressure associated with sinus tachycardia and persisting T negativity, but no ventricular arrhythmias or fibrillation. Fig. 8 shows a typical example of an experiment of this type. Similar results have been obtained in three experiments.

When similar chloroform-adrenaline administration was repeated 30 minutes later in such experiments, there was again a marked pressor response associated with tachycardia, multifocal ectopic beats and short runs of ventricular tachycardia. Subsequent repetitions of chloroform-adrenaline at 30-minute intervals led to rapid emergence of multifocal ectopic beats with bizarre QRS-complexes indicating aberrant ventricular conduction, and followed by ventricular tachycardia and ventricular fibrillation (Fig. 8).

When a dose of 1 mg./kg. of Iproveratril was injected during chloroform administration (three experiments) as above, there was a marked fall in blood pressure associated with the usual T-wave changes. Following subsequent (three minutes later) injections of adrenaline, there was the usual rise in blood pressure associated with a slight sinus

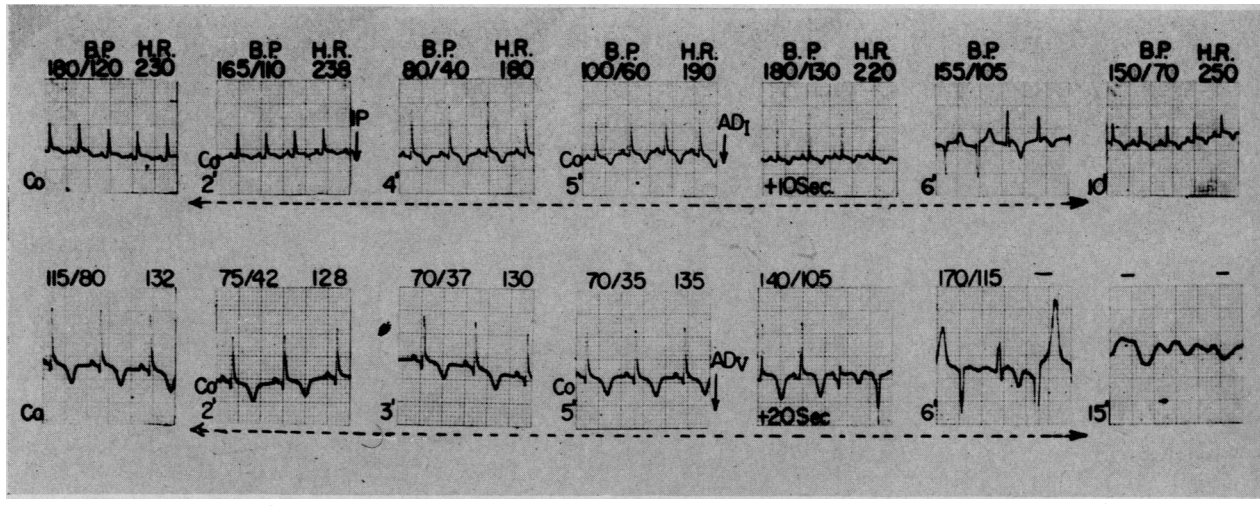

Fig. 8.—Electrocardiographic and blood pressure changes recorded before (Co) and after intravenous injection of Iproveratril (IP—0.5 mg./kg.), followed by adrenaline (AD 1—100 μg./kg.) during chloroform administration (upper records—broken line with arrows). Similar chloroform-adrenaline administration was repeated at 30-minute intervals. The lower records show the results observed during the fifth such repetition (see "Methods").

tachycardia but the form of the electrocardiogram was essentially normal. A typical example of this type of experiment is shown in Fig. 9.

Subsequent repetitions of chloroform-adrenaline at 30-minute intervals again showed the progressive development of increasing degrees of arrhythmias (extrasystoles, ventricular tachycardia) and finally ventricular fibrillation ensued. Similar results were obtained in three experiments.

It is therefore concluded that Iproveratril in doses of 0.5 and 1 mg./kg. can protect chloralosed cats against the ventricular arrhythmias induced by adrenaline during chloroform administration.

In the course of the above experiments, several unsuccessful attempts were made to reverse established ventricular fibrillation by either intracardiac or intravenous injections of the drug with associated cardiac massage and intravenous saline infusions. It would therefore appear that the drug cannot reverse established ventricular fibrillation.

It was also observed in two experiments that when excessive quantities of chloroform were administered, so that a definite fall (25 to 45 mm. Hg) in the blood pressure ensued, the myocardial depression and depressor responses to Iproveratril (0.5 and 1 mg./kg.) were greatly potentiated. In-

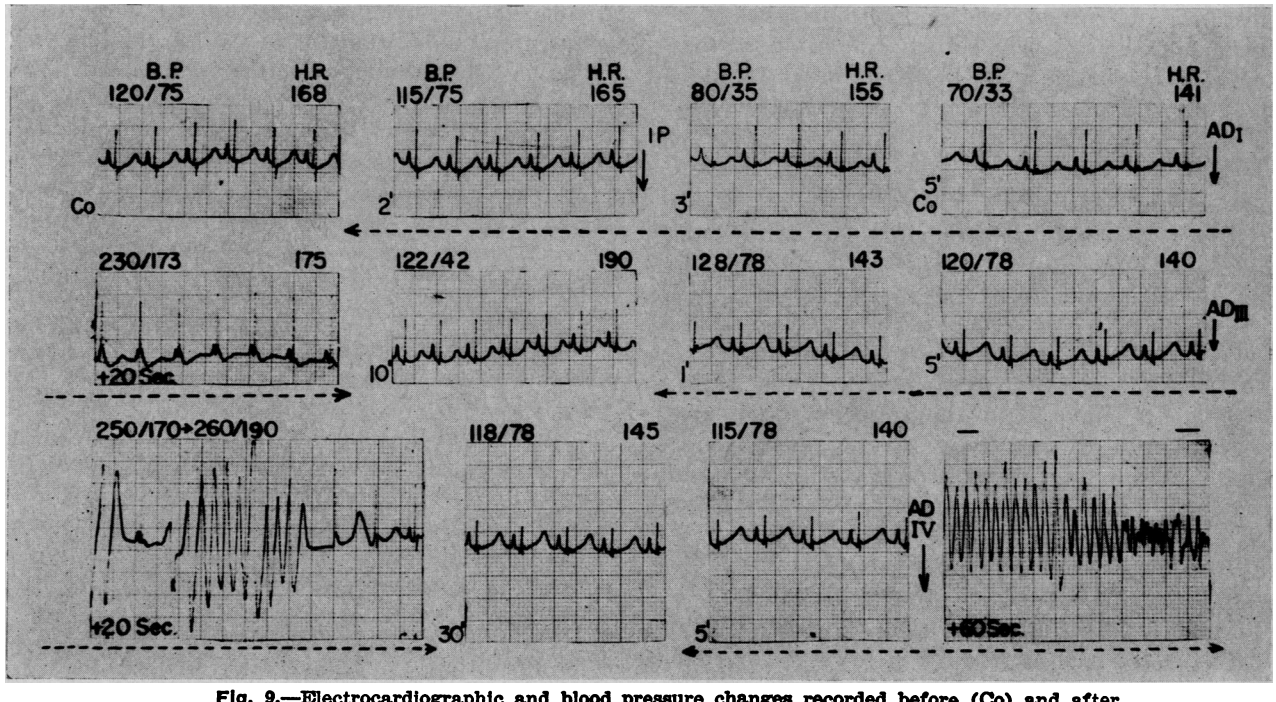

Fig. 9.—Electrocardiographic and blood pressure changes recorded before (Co) and after intravenous injection of Iproveratril (IP—1.0 mg./kg.) followed by adrenaline (AD 1—100 μg./kg.) during chloroform administration (broken line with arrows—upper and first section of middle records). The effects of the second (AD2) and fourth (AD IV) injections of similar doses of adrenaline during similar repetitions of chloroform at 30-minute intervals are also shown.

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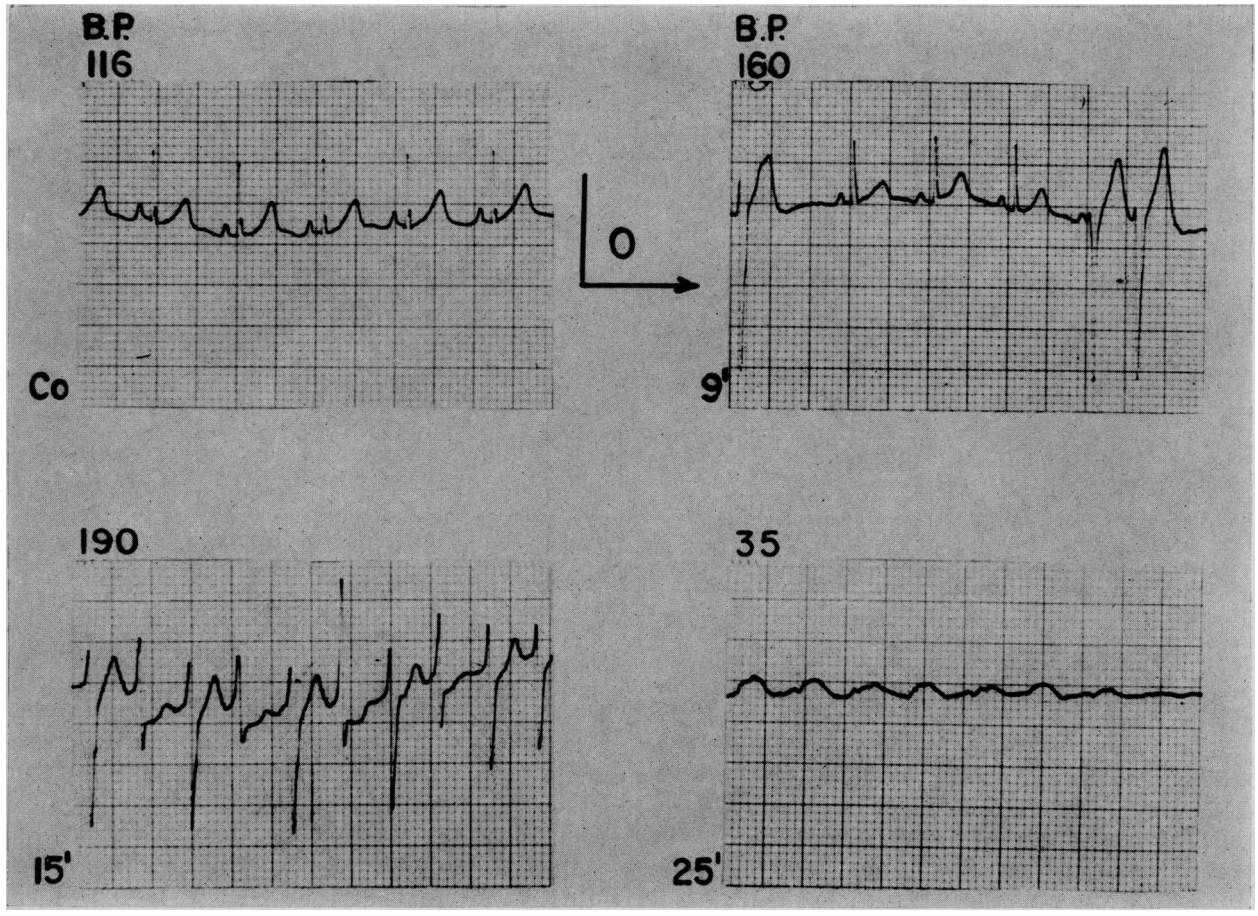

Fig. 10.—Electrocardiographic and blood pressure changes before (Co) and during a continuous infusion of ouabain (5 μg./kg./min.) throughout (⌊0 start). Sections of the records obtained at 9, 15 and 25 minutes are shown.

deed, in both such experiments, injection of adrenaline did not induce the usual pressor response, and death rapidly ensued (within two to three minutes) from cardiac arrest. The cardiac effects of Iproveratril therefore appear to be potentiated by deep chloroform depression when the responses to adrenaline are also antagonized.

EFFECTS ON OUABAIN ARRHYTHMIAS

It was observed that with continuous intravenous infusions of ouabain in a dose of 0.005 mg./kg./min. in cats under pentobarbital anesthesia, there was a progressive increase in blood pressure associated within nine to 10 minutes with T-wave depression and marked arrhythmias (ventricular ectopic beats). With continued ouabain administration, these latter were intensified and progressively multifocal ectopic rhythms, ventricular tachycardia and ventricular fibrillation developed. A typical illustration of this type of response is shown in Fig. 10.

In three similar control experiments ventricular fibrillation developed in 24, 28 and 25 minutes, respectively. In contrast, in three other experiments in which Iproveratril in a dose of 0.5 mg./kg. was injected repeatedly at intervals of five minutes during similar continuous ouabain infusions, it was observed (a) that there was a striking delay in the onset of T-wave changes, which, during the initial 15 minutes of infusion, were either completely absent or slight; (b) that occasional ventricular ectopic beats were recorded but the more frequent manifestations were nodal rhythm—A-V block; (c) that although transient ventricular fibrillation ensued in two experiments, despite continued ouabain infusions for as long as 50 to 60 minutes, the fibrillation spontaneously reverted and was replaced by idioventricular rhythms with ventricular tachycardia; and (d) that irreversible ventricular fibrillation only ensued after 54, 55 and 68 minutes, respectively, in this group. Some examples of these experiments are shown in Figs. 11 and 12.

When a similar dose (0.5 mg./kg.) of Iproveratril alone was injected at five-minute intervals into four animals it was observed that death ensued in 55, 55, 89 and 95 minutes, respectively. However, in each instance this was associated with a progressive fall in blood pressure, bradycardia, A-V dissociation and nodal rhythm with final cardiac arrest. These changes were similar to those already described when single large doses (10 mg./kg.) of the drug were used.

In three of the above experiments there was no evidence of the occurrence of ventricular fibrillation, although in the animal which survived for 95 minutes, terminal ventricular fibrillation ensued. It is difficult to determine whether this effect was due

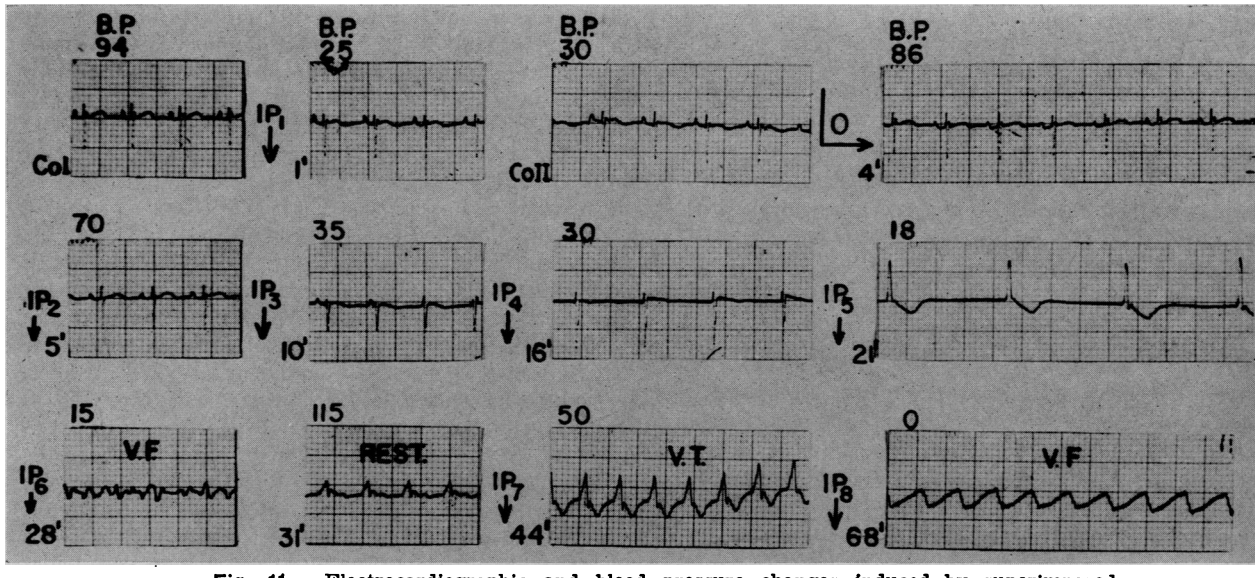

Fig. 11. — Electrocardiographic and blood pressure changes induced by superimposed repeated injections of Iproveratril (IP—0.5 mg./kg. at 5-min. intervals) before (Co) and during continuous infusions of ouabain (5 μg./kg./min.) throughout (| 0 start). Sections of the records obtained at 4, 5, 10, 16, 21, 28, 31, 44 and 68 minutes are shown. ⟶

to the Iproveratril or was only secondary to the prolonged myocardial hypoxia resulting from the sustained low blood pressure and depression of the heart which persisted in this experiment. It is nevertheless apparent that with these high doses of Iproveratril, the antagonism to ouabain toxicity might have been complicated by the intense cardiac action of the drug.

It was therefore of interest to test the effect of smaller doses upon the responses to ouabain. Thus, in five experiments in which doses of 0.25 mg./kg. of Iproveratril were injected at five-minute intervals during similar continuous ouabain infusions, it was observed that ventricular fibrillation ensued in 40, 41, 42, 51 and 52 minutes, respectively, i.e. in an average of 45.3 minutes, as compared with an average of 25.6 minutes (three experiments) when ouabain alone was infused (see above). It is therefore evident that this dose of Iproveratril protected against the development of ouabain ventricular fibrillation, and hence delayed the onset of ouabain toxicity. However, as in the case of chloroform-adrenaline ventricular fibrillation, subsequent injections of the drug alone could not be shown to reverse established ouabain ventricular fibrillation in this group of experiments.

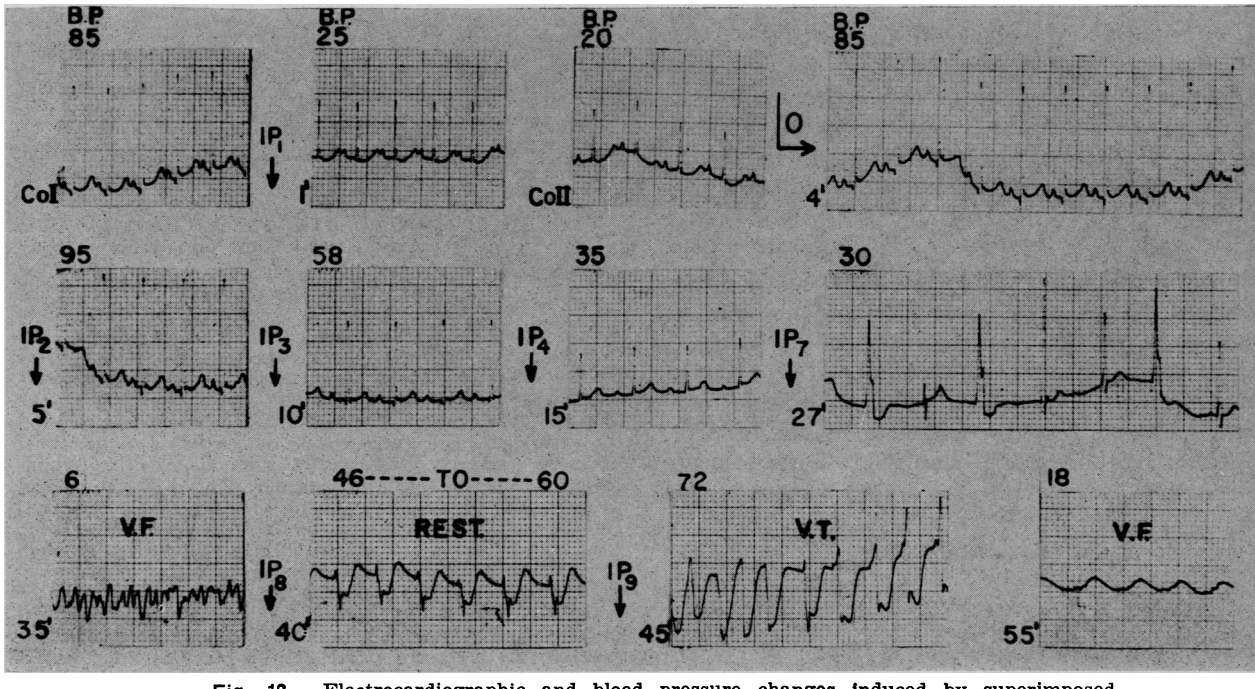

Fig. 12. — Electrocardiographic and blood pressure changes induced by superimposed repeated injections of Iproveratril (IP—500 μg./kg. at 5-min. intervals) before (Co) and during continuous infusions of ouabain (5 μg./kg./min.) throughout (| 0 start). Sections of the records obtained at 4, 5, 10, 15, 27, 35, 40, 45 and 55 minutes are shown. ⟶

DISCUSSION

The above findings show clearly that Iproveratril is a potent coronary vasodilator agent in the isolated rabbit heart, but that it also leads to associated depression of the myocardium and the conducting system. In anesthetized cats the drug produces a fall in blood pressure associated with bradycardia, ST-T changes and depression in A-V conduction. It has, however, not been established to what extent the drug affects peripheral vasodilatation, and the question arises whether or not the observed depressor response is due only to its intense myocardial depressant action. Iproveratril can also protect to some extent against ventricular arrhythmias induced both by injections of adrenaline during light chloroform anesthesia and by ouabain infusions. However, the mechanism of these actions is still unknown.

It was earlier suggested by Haas[10] in Germany that Iproveratril might exert its favourable action in angina pectoris by blocking β-adrenergic receptor mechanisms. In this connection, as has already been pointed out, during deep chloroform depression of the cardiovascular system, the cardiac depressant actions of Iproveratril are potentiated and the cardiac responses to adrenaline also antagonized. In addition, it has been observed, in other experiments on the isolated perfused rabbit heart, that prior injection of a small dose (10 μg.) of Iproveratril decreases significantly both the amplitude of the heart contractions and the tachycardia following injections of high doses (100 μg.) of both adrenaline and noradrenaline. Finally, using the isolated papillary muscle preparation and recording the contractions during constant rate electrical stimulation, as described by Benfey and Varma,[11] it has been observed that in the presence of a low concentration (1 μg./ml.) of Iproveratril, the positive inotropic action of noradrenaline can be blocked without reducing the responsiveness of the preparation to calcium.[12] It would therefore appear that Iproveratril may exert its effect on the heart by blocking β-receptor adrenergic (sympathetic) mechanisms. This aspect of the problem is being further studied.

The electrocardiographic findings leave little doubt that Iproveratril exerts a striking antagonism to the early T-wave changes induced by ouabain, and on that basis appears to influence repolarization. However, the basic mechanism for the antiarrhythmic actions of the drug is unknown. Indeed, the electrocardiographic changes following large doses of the drug would also suggest that it might exert a "quinidine-like" action. The drug therefore appears deserving of further study.

SUMMARY

It has been shown that the new synthetic compound, α-isopropyl-α [(N-methyl-N-homoveratryl)-γ-amino-propyl]-3,4 - dimethoxyphenylacetonitrile hydrochloride (D365, Iproveratril or Isoptin), is a potent coronary dilator agent in the isolated perfused rabbit heart; doses of 0.1 and 1 μg. increase coronary flow without significant changes in heart contraction or rate, but with higher doses (10 and 100 μg.) cardiac depression, bradycardia and A-V dissociation ensue.

In the perfused frog heart, concentrations ranging from 0.1 to 10 μg./ml. induce increasing degrees of myocardial depression and slowing.

In chloralosed cats, doses of 0.5 and 1 mg./kg. intravenously produce a fall in blood pressure with only slight bradycardia and can protect against chloroform-adrenaline ventricular arrhythmias; higher doses (5 and 10 mg./kg.) lead to more marked depressor effects with more marked bradycardia, ST-T changes, A-V dissociation and nodal rhythms; with doses of 10 mg./kg., ultimate cardiac standstill ensued in some cases.

In pentobarbitalized cats, doses of 0.25 and 0.5 mg./kg. injected intravenously at five-minute intervals reverse the early ST-T changes induced by ouabain and significantly delay the onset of ouabain ventricular fibrillation.

In addition to its coronary dilator action Iproveratril therefore appears (a) to block β-adrenergic receptor mechanisms in the heart, (b) to influence repolarization of the myocardium, and (c) to exert a quinidine-like action. This drug appears, therefore, to warrant further study.

We are grateful to Messrs. Leo Cullen and Bruno Klingner for their technical assistance with these experiments.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

WHAT WILL BE THE END?

In his report for the year 1913, Dr. J. V. Anglin, the superintendent of the Provincial Hospital, Saint John, New Brunswick, comments on the increasing numbers of mentally afflicted or defective persons who seek admission to the hospital. The provision of suitable accommodation and the maintenance of such persons is becoming a heavy tax upon the province. What will be the end? Are the asylums to be enlarged year by year as the number of patients increases? The results of treatment offer little encouragement and, in the majority of cases, the most that can be expected is a more or less permanent restoration. However, although the subject is somewhat shrouded in gloom, a more hopeful attitude of mind comes with the reflection that increased knowledge may teach us more of the nature, causes, and possible means of prevention. Dr. Anglin refers also to the necessity for a trained pathologist in every asylum, "whose sole duty it should be to study insanity in all its aspects and communicate the results of all his investigations to the people at large."—Editorial comment, *Canad. Med. Ass. J.*, 4: 317, 1914.