THE EFFECT OF ADENOSINE TRIPHOSPHATE ON THE ELECTROCARDIOGRAM OF MAN AND ANIMALS

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The increasing importance of adenosine triphosphate (*ATP*) in the field of biochemistry demands a close study of its pharmacological properties. Earlier work on the lower nucleotides and nucleosides derived from *ATP* showed that these compounds have important effects on the cardiovascular system. Now that large amounts of the higher derivatives, such as *ATP*, have become available, it has been shown that the action of these substances is not confined to the cardiovascular system but affects all the organs of the body (Green and Stoner, 1949). Although the effect of these compounds on the heart has been studied in some detail by Drury and his school (1936), their electrocardiographic observations were almost entirely confined to the lower members of the series. In the present paper we propose to describe the effects of *ATP* on the electrocardiogram of man and animals. The cardiographic method is the only satisfactory one available for the study of changes in cardiac rhythm in man. We have also applied this method to the study of the cardiac effects of *ATP* in animals in order to determine the effects of doses higher than those that would have been justifiable in man and also to analyse these actions by procedures impracticable clinically. The observations in animals will be reported first, then those in the human subjects, and finally the conclusions arrived at from the combined study.

I. ANIMAL EXPERIMENTS

Early work on the effect of adenosine and its derivatives on the electrocardiogram has been well reviewed by Drury (1936). It has been shown that these substances affect the conducting system, causing sinus slowing and A-V block. In most animals the main effect is upon the S–A node but in the guinea pig the A-V node seems more sensitive

to their action. It will be seen that the action of *ATP* is on the whole similar to that of the lower compounds. The further actions of *ATP* on the cardiovascular system have been described by us elsewhere (Green and Stoner, 1949).

Methods. Experiments were performed on 10 cats and 11 guinea pigs under pentobarbitone sodium (nembutal) anæsthesia. The electrocardiogram was recorded with a Sanborn Viso-cardiette. In the cat the pressure in the carotid artery was determined with a mercury manometer and respiration recorded by a tambour attached to a tracheal cannula. Artificial respiration was used in the majority of the guinea pig experiments. All injections were given into the external jugular vein and washed in with 1·5 ml. 0·9 per cent sodium chloride from a burette. The time of the injection was 1 sec. Both the sodium and magnesium salts of *ATP* were used in the animal experiments, the solutions being prepared from *BaATP* (Boots) as described elsewhere (Green and Stoner, 1949). In the observations on man the magnesium salt was used. The purity of the *ATP* was checked by chemical analysis and found to be not less than 98 per cent. The adenosine used was obtained from British Drug Houses Ltd.

RESULTS

Guinea Pig. The effect of *ATP* on the conducting system of the guinea pig heart was followed in leads I and II. Two dosage levels were used— 0·5 mg. and 1·0 mg. *MgATP* per kg. body weight. With the smaller dose the effect on the heart commenced almost immediately after the injection and lasted about 21 seconds, reaching a maximum in 6 to 9 seconds. The first effects were on the sinus rate and the P–R interval. The sinus rate was reduced by about 18 per cent and the P–R interval
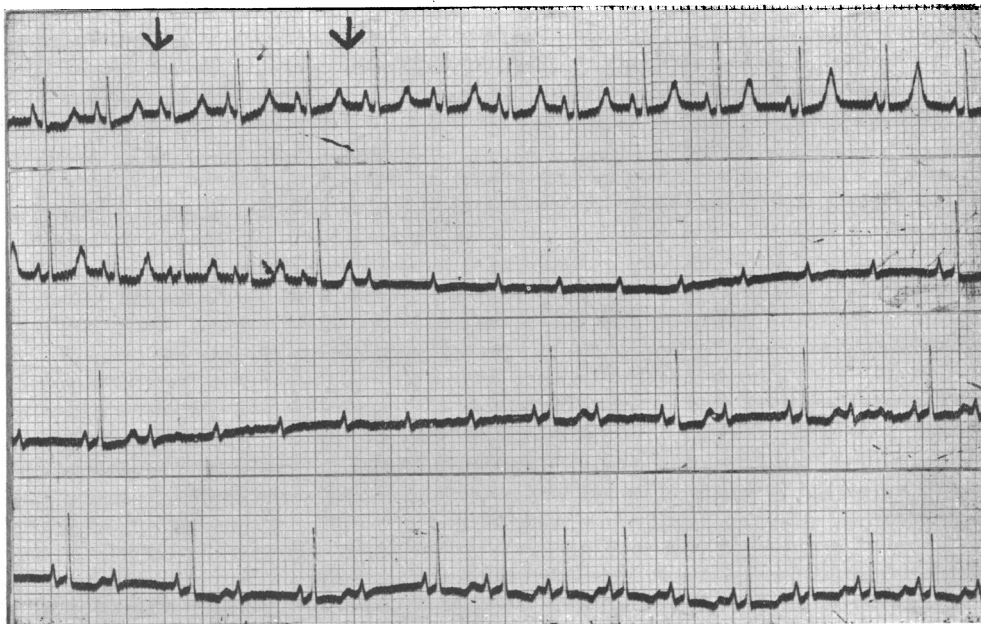
FIG. 1.—To be read from left to right and from above downwards. The effect of 0·5 mg. *MgATP* per kg. body wt., given intravenously, on the electrocardiogram (lead II) of the guinea pig under pentobarbitone (nembutal) anæsthesia. The beginning and end of the injection indicated with arrows. Shows sinus slowing followed by ventricular arrest and 2:1 A-V block.

1 mV=1·6 cm.   1 sec.=2·5 cm.

was increased from an average control value of 0·06 to between 0·09 and 0·12 second. At the height of the effect *ATP* exerted a much greater action on the A-V node than on the S-A node and the ventricular beat was completely suppressed for periods of up to 3 seconds. Ventricular beating then returned with 2:1 heart block progressing to normal rhythm (Fig. 1).

Despite these marked changes in rhythm the form of the complexes showed little change. The only constant alterations seen were some depression of the P-Q interval giving a spiky appearance to the P waves and increased amplitude of the T waves.

After the larger dose of *ATP* the effect attained a maximum at about the same time after the injection and persisted for about 30 seconds. The sequence of events was as before but both the sinus slowing and prolongation of the P-R interval were more marked. The sinus rate was reduced by a maximum of about 36 per cent and the P-R interval was prolonged until at the height of the effect the ventricular beat was suppressed for 6 to 9 seconds. On occasions this was accompanied by atrial asystole. Recovery occurred as before with varying grades of heart block.

Changes in the configuration of the complexes were commoner after the larger dose of *ATP*. Increased amplitude of the T wave was evident and low voltage QRS complexes and extrasystoles were also seen. These extrasystoles arose from a focus close to, but below, the A-V node. Occasional abnormalities which were seen, usually during the recovery period, were inversion of the P wave, auricular fibrillation, nodal rhythm, and displacement of the S-T segment.

When adenosine was given in equimolecular amounts it had the same effect on cardiac rhythm as *ATP*. Section of the vagi in the neck did not alter the response to *ATP* or adenosine.

Cat. The effect of *ATP* on the electrocardiogram (lead II) of the cat was studied after the intravenous injection of 1·0 mg. and 2·0 mg. *MgATP* (0·3–0·5 and 0·7–1·0 mg. per kg. body weight). The effects observed differed somewhat from those in the guinea-pig and more closely resembled those to be described in man.

The main effects after the smaller dose of *ATP* were sinus bradycardia and lengthening of the P–R interval. The degree of sinus slowing varied but at the height of the effect, about 10 seconds after

injection, the sinus rate was usually decreased by about 50 per cent. The effect persisted for a further 10 to 20 seconds by which time the rate had returned to normal. The P–R interval increased from 0·06 to 0·09 second at the height of the effect. The P–Q interval was depressed and changes constantly occurred in the T wave. In the majority of experiments the T wave was increased in amplitude during the first 10 seconds after the injection. Sometimes this change persisted for as long as 42 seconds and was accompanied by alterations in the level of the S–T segment (Fig. 2). In other experiments, during the later stages of the *ATP* action, the T waves were depressed and then inverted.
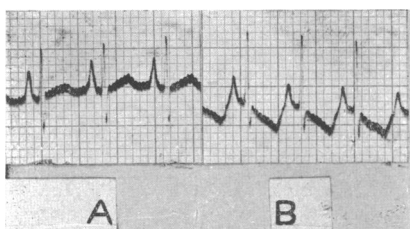

FIG. 2.—Segments of the electrocardiogram (lead II) record immediately before (A), and 15 sec. after (B), the intravenous injection of 2·0 mg. *MgATP* into a cat (3·0 kg. body wt.) under pentobarbitone (nembutal) anæsthesia, showing the depression of the S–T segment.

1 mV=1·6 cm.   1 sec.=2·5 cm.

Similar but more marked changes occurred after the larger dose (Fig. 3). Here the P–R interval was increased from an average control value of 0·07 to 0·11 second. Sinus bradycardia, which was still the main effect, was more pronounced sometimes leading to complete asystole; in one experiment there was complete asystole for 6 seconds with ventricular asystole for 11 seconds. The maximum effect occurred about 10 seconds after the injection and was characteristically heralded by a run of about four extrasystoles (Fig. 4) arising from a focus close to, but below, the A-V node. The T wave changes were of the same type as before but were more evident after these larger doses.

Previous work has shown that the vagus is concerned in the cardiovascular response to *ATP* in the cat (Bielchowsky, Green, and Stoner, 1946). In this animal section of the vagi in the neck or atropinization diminished the effect of *ATP* on both the blood pressure and the heart, but the blood pressure changes were much less affected than one would have expected from the changes in the cardiac response (Fig. 5). For instance, in one experiment

where the depressor response to 2·0 mg. *MgATP* was 35 mm. Hg. before vagal section, the P–R interval was prolonged from 0·06 to 0·10 second, and the sinus rate slowed from 180 to 60 beats a minute with complete A-V dissociation for 3 seconds. After vagal section the same dose only prolonged the P–R interval very slightly, from 0·06 to 0·08 second, and slowed the sinus rate only from 160 to 140 beats a minute without dissociation; nevertheless the blood pressure fell by as much as 22 mm. Hg. Although inactivation of the vagi greatly reduced the effect of *ATP* on cardiac rhythm it did not alter its action on the configuration of the complexes nor prevent the appearance of extrasystoles.

Prostigmine had the opposite effect to vagal section and greatly potentiated the action of *ATP* on cardiac rhythm in the cat (Fig. 6). In a normal cat 2·0 mg. *MgATP*, injected intravenously, lengthened the P–R interval from 0·08 to 0·12 second, and produced complete asystole for 3 seconds. In the same cat, after intravenous injection of 0·125 mg. prostigmine, the same dose of *MgATP* lengthened the P–R interval from 0·11 to 0·14 second and produced complete asystole for 18 seconds followed by a slow return to normal beating. At the same time the depressor response was increased. This effect of prostigmine could be prevented by vagal section.

In the cat the rate changes produced by *ATP* were not reproduced by equimolecular amounts of adenosine until after section of the vagi when the effects were similar.

Effect of Magnesium. The influence of intravenous magnesium sulphate on the response to *ATP* was tested in both guinea pig and the cat in view of previous work on the effect of this ion on nucleotide action (Green and Stoner, 1944; Bielchowsky, Green, and Stoner, 1946). The alteration in the response after Mg was more easily interpreted in the guinea pig since the vagus is not implicated in that animal. As shown in Table I, the effect of intravenous magnesium sulphate was to increase the effect of *ATP* on the cardiac rhythm. Mg^{++} had a similar influence on the action of *ATP* on the cardiac rhythm of the cat but in that animal the effect was complicated by the anæsthetic action of Mg^{++} on the vagus. Small doses of Mg^{++}, however, increased the effect of *ATP* on the P–R interval and the duration of the effect. The prolongation of the action of *ATP* on cardiac rhythm was not the only effect of Mg^{++} on the *ATP* response, since it also prevented the appearance of extrasystoles.

Effect of Antimalarial Drugs. Raventós (1948) has recently postulated that there is an antagonism between adenosine and the antimalarial group of
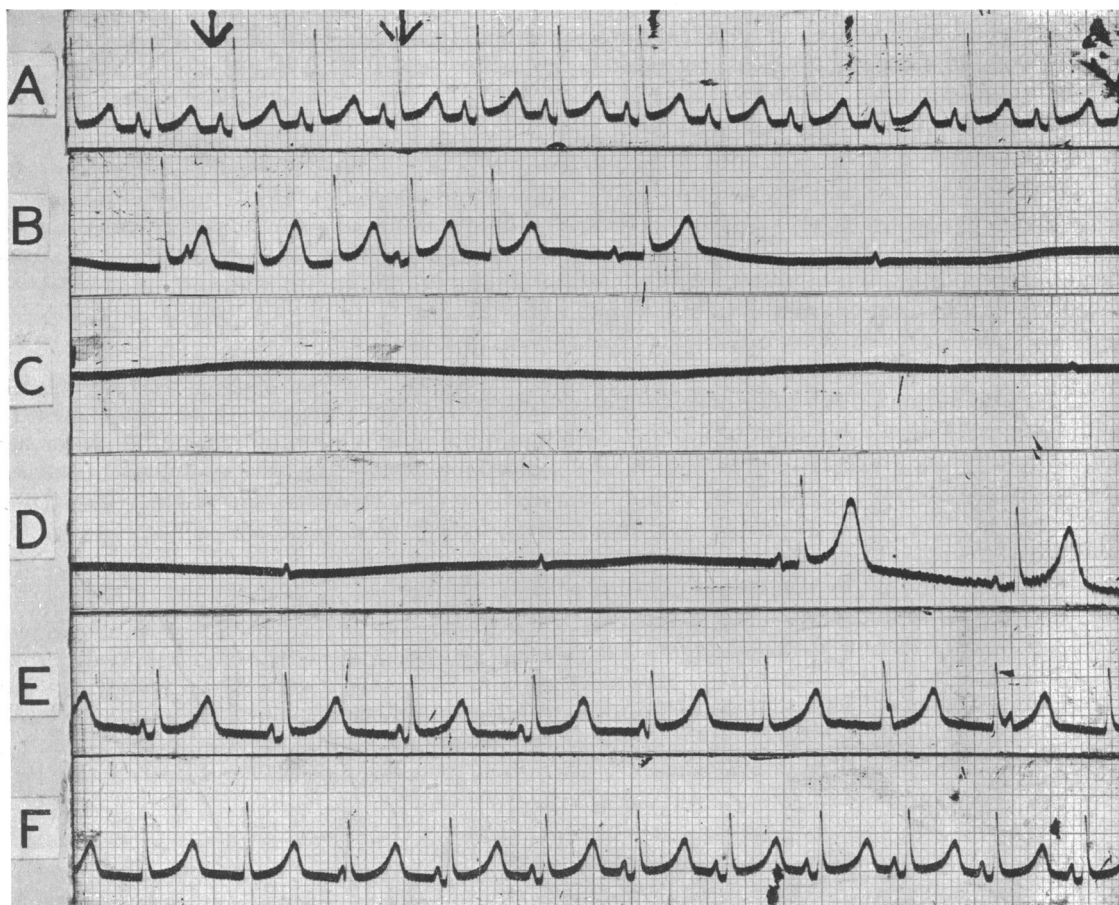
FIG. 3.—To be read from left to right and from above downwards. The effect of 2·0 mg. *MgATP* given intravenously on the electrocardiogram (lead II) of the cat (2·9 kg. body wt.) under pentobarbitone anæsthesia. The beginning and end of the injection is indicated with arrows. Shows sinus slowing, ventricular asystole and complete asystole with nodal rhythm during the recovery period.

(A)	0–5 sec.	(D)	22–27 sec.
(B)	11–16 sec.	(E)	45–50 sec.
(C)	16–22 sec.	(F)	55–60 sec.

1 mV=1·6 cm.   1 sec.=2·5 cm.

drugs since he found that the cardiac effects of adenosine were less after the previous administration of quinine, mepacrine, pamaquin, and paludrine. In the guinea pig heart lung preparation he found that paludrine, added directly to the circulating blood, did not antagonize the action of adenosine but that the blood of guinea pigs treated with paludrine did have this effect.

In part we have been able to confirm these findings. In the cat, the intravenous or intramuscular injection of quinine sulphate (25 mg. per kg. body weight) does decrease the effect of *ATP* on the heart and blood pressure. In the guinea pig also, quinine sulphate (15 mg. per kg. body weight) decreases the effects of adenosine and *ATP* on the heart. In our hands paludrine hydrochloride has behaved differently and when doses in the therapeutic range have been given intravenously over a period of half an hour no change was observed in the electrocardiographic response to *ATP* in the cat or guinea pig. It was only when the dose was raised to the limits of tolerance (60 mg. per kg. body weight) that any alteration in the response was observed and then the changes were only slight and equivocal.
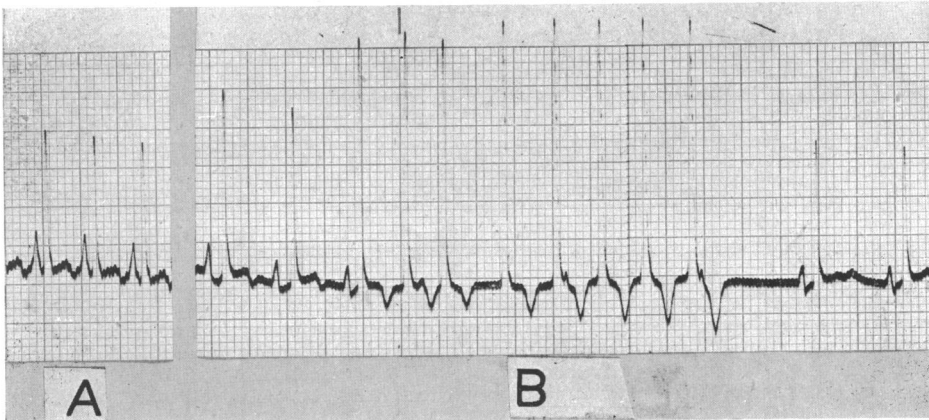
FIG. 4.—Segments of the electrocardiogram (lead II) record immediately before (A), and 5 sec. after (B), the intravenous injection of 2·0 mg. *MgATP* into a cat (2·1 kg. body wt.) under pentobarbitone (nembutal) anæsthesia. Shows the characteristic run of nodal extrasystoles preceding the full action of the *MgATP*.

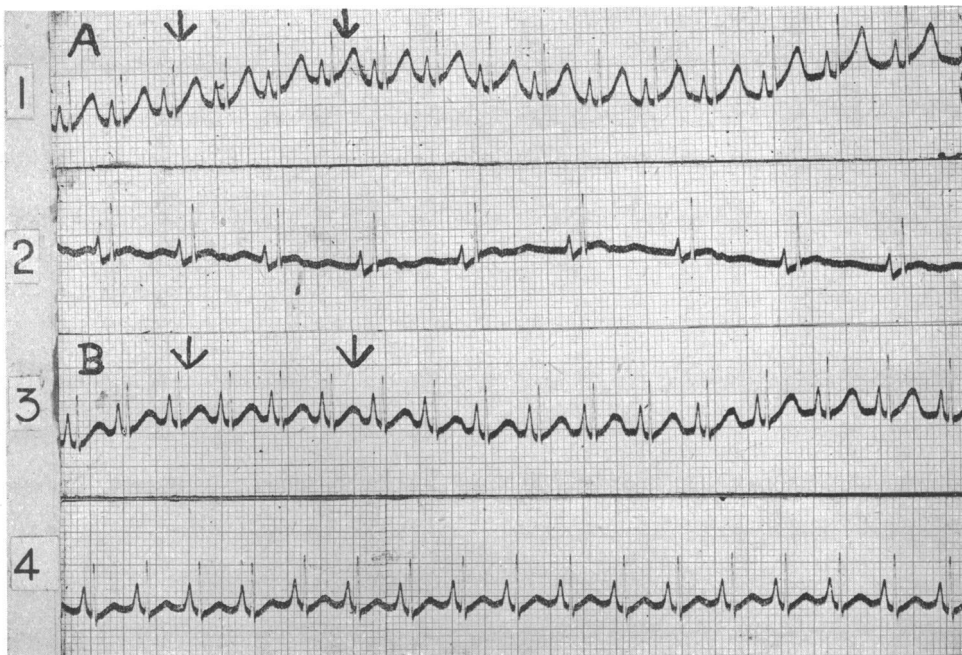1 mV = 1 c.cm.   1 sec. = 2·5 cm.

FIG. 5.—To be read from left to right and from above downwards. The effect of 2·0 mg. *MgATP* given intravenously on the electrocardiogram (lead II) of a cat (2·7 kg. body wt.) under pentobarbitone (nembutal) anæsthesia, (A) before, and (B) after, the intravenous injection of 0·75 mg. atropine sulphate per kg. body wt. The beginning and end of the injection of *MgATP* indicated with arrows.

(1) 0–5 sec.   (2) 11–16 sec.   (3) 0–5 sec.   (4) 11–16 sec.

Shows the decrease in the degree of sinus slowing produced by *MgATP* after paralysis of the vagus.

1 mV = 1·6 cm.   1 sec. = 2·5 cm.

TABLE I

The Effect of Intravenous Magnesium Sulphate on the Cardiac Response to *ATP* in the Guinea Pig

Dose No.	Duration of effect (sec.)	P–R interval (sec.)		Sinus rate Beats per minute		Ventricular rate Beats per minute	
		Before Injection	After Injection	Before Injection	After Injection	Before Injection	After Injection
1	18	0·06	0·09	220	180	220	80
2	18	0·06	0·09	200	180	200	100
3	31	0·11	0·16	120	60	120	20
4	36	0·10	0·18	120	80	120	0

The table shows the effect of successive doses of *MgATP* (0·5 mg. per kg. body weight) on the P–R interval, and sinus and ventricular rates, before and after intravenous doses of magnesium sulphate.

Between doses No. 2 and 3, 3·0 ml. MgSO₄ 0·154 M given i.v. and between doses No. 3 and 4, 2·0 ml. MgSO₄ 0·154 M i.v.
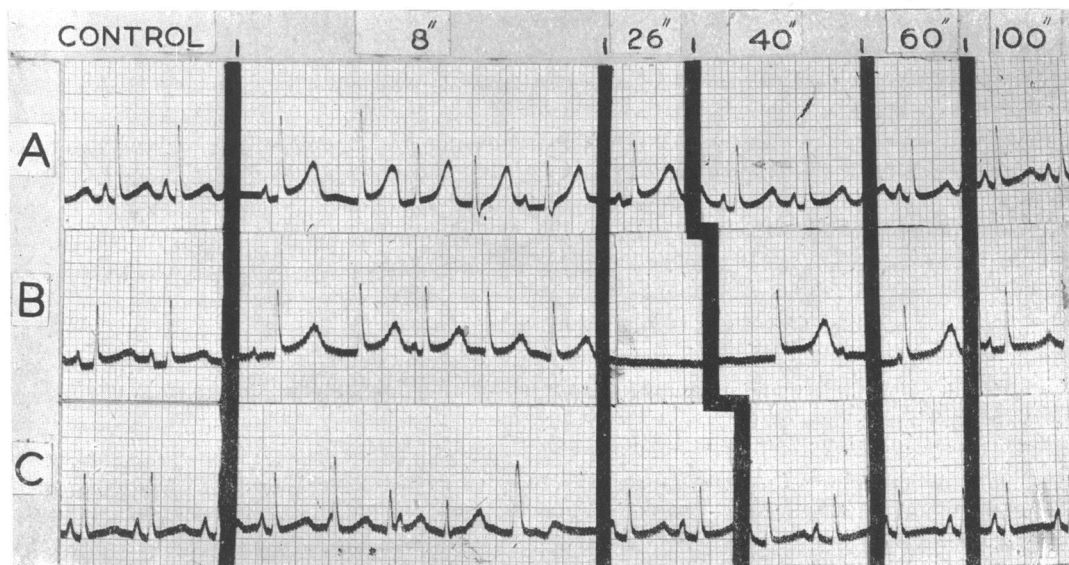

Fig. 6.—Segment of the electrocardiogram (lead II) record immediately before (control) and at stated intervals after the intravenous injection of 2·0 mg. *MgATP* into the same cat (2·7 kg. body wt.) in nembutal anæsthesia under varying conditions.

(A) Effect of *MgATP* alone.
(B) After intravenous injection of 0·125 mg. prostigmine.
(C) As for (B) except that both vagi have been divided.

Shows the great increase in the effect of *ATP* after prostigmine administration, which is prevented by division of the vagi.

1 mV=1·6 cm.   1 sec.=2·5 cm.

II. Observations on Human Subjects

The effect of adenyl compounds on the human heart has been comparatively little studied. Honey, Ritchie, and Thomson (1930) showed that adenosine could produce heart block in healthy men and von den Velden (1932) that adenylic acid would give bradycardia. Richards (1934a) studied the effects of both adenylic acids and adenosine on the blood pressure and electrocardiogram. He concluded that the blood pressure is unaffected but that in some individuals heart block can be produced by

either compound. Stoner and Green (1945) using the sodium and magnesium salts of *ATP* produced a rise of pulse rate with small doses and a rise followed by a large fall with large doses. Electrocardiograms were not taken but heart block was suspected in one case. The systolic blood pressure was raised during the period of tachycardia and fell slightly during the time when the pulse was slowing. Arteriolar dilatation occurred with a consequent rise of skin temperature.

ATP in the Treatment of Rheumatoid Arthritis. Lövgren (1945) has claimed that *ATP* has a beneficial effect on cases of rheumatoid arthritis. " Adynol," a crude preparation containing 50 to 60 per cent *ATP*, was given by intravenous injection in doses of 30 to 45 mg. or by intramuscular injection in doses of 7·5 to 30 mg. We decided to treat a series of cases with a purer preparation of *ATP* and at the same time to study the effect of this substance on the cardiovascular system.

The results of treatment of rheumatoid arthritis were most disappointing. Courses of daily injections of *MgATP* in doses of 15 to 30 mg. were given for periods up to three months to 15 patients. Several cases improved subjectively but we could not convince ourselves that there was any change in the degree of disability that would not have been obtained by simple rest in bed and physiotherapy. There was no significant alteration in the erythrocyte sedimentation rate.

Since, as will be shown, *MgATP* has a profound effect on the conducting system of the heart and since it was desired to give to each patient the maximum tolerated dose, very frequent electrocardiographic observations were made on each case. These will now be reported.

Plan of Investigation. Seven patients (6 male and 1 female), all with normal hearts, were chosen from the 15 treated for arthritis and were observed specifically for electrocardiographic changes immediately after injection. The patient rested comfortably on a couch, and control blood pressure readings and cardiograms were taken. *MgATP* was injected intravenously, taking 6 to 12 seconds over the injection. Blood pressure readings were taken at 15-second intervals, until the figures returned to pre-injection levels. Cardiograms were taken at the same time as the injection and continued for 1 minute and then for 10 seconds at half-minute intervals for a further minute. Small doses of 5 mg. were used initially on each patient and gradually increased by 5 mg. at each injection up to the maximum tolerated dose which varied from 15 to 40 mg. (0·21–0·57 mg. per kg. body weight). In all, 100 tracings were obtained in this manner from the 7 patients selected.

EFFECTS OF INJECTION

(1) *Subjective.* These were remarkably constant with doses above 10 mg. Ten to fifteen seconds after starting the injection, the subject noted a sharp taste in the mouth, which was followed by hyperpnœa, cough, and obvious flushing of the face with a brief sensation of faintness and throbbing in the head. All these effects had disappeared by the end of the first minute and were much less marked if the injection was made slowly.

(2) *Blood pressure.* Thirty observations were made on four cases with doses above 10 mg. A fall of blood pressure invariably occurred, the maximum being 100 mm. Hg with doses of 35–40 mg. and was usually greatest about 15 to 20 seconds after the beginning of the injection. The blood pressure recovered rapidly so that two minutes later it was at or above the pre-injection level. It is hardly surprising that very low readings were obtained in cases in which asystole or pronounced bradycardia occurred but in several instances with doses giving only sinus slowing, significant falls of pressure were recorded which we attributed to arteriolar dilatation. In general, the fall in systolic pressure was greater than in diastolic pressure but the latter is difficult to determine accurately in observations of this type. The fall in systolic pressure was considerably greater than that previously recorded (Stoner and Green, 1945).

(3) *Changes in the Electrocardiogram.* Lead II was used throughout the observations.

The effects of a given dose differed greatly in different patients but in the same patient, the response was sufficiently constant to enable variations produced by other procedures to be assessed. We did not observe the development of tolerance. In our observations on the effects of drugs, we always made at least one control observation immediately before giving the drug and one after the effect of the drug had worn off. We also always used samples of *ATP* from the same batch.

Small doses (5–15 mg.) of *MgATP* produced a sinus tachycardia preceded by a short period of sinus slowing. Larger doses (15–30 mg.) gave marked sinus slowing and always affected the conducting tissues producing first or second degree A-V block (Fig. 9A and C). Wenckebach periods were often observed (Fig. 10A). Maximum doses (30–40 mg.) produced similar changes of greater intensity with an increase in the duration of heart block and in the number of dropped beats. Ventricular standstill (Fig. 7) and complete asystole were observed in two patients. These effects are similar to those seen in the guinea pig (Fig. 1). The results in Case 1 are summarized in Table II.
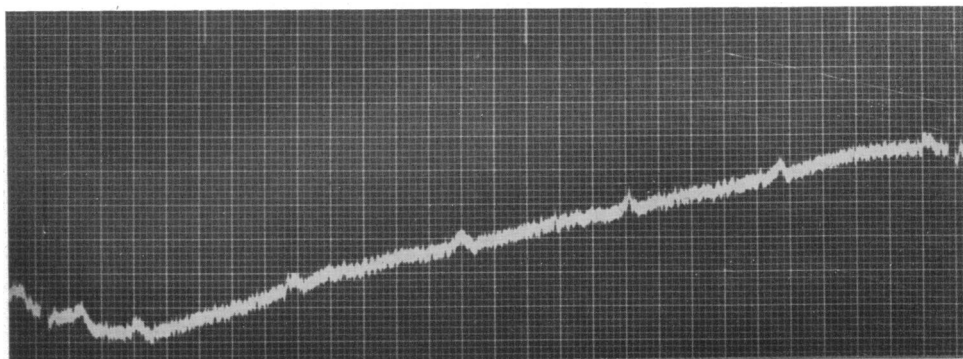
With the doses used, changes in the shape of the

FIG. 7.—Case IV. Effect of intravenous injection of *MgATP* on the electrocardiogram (lead II). Shows ventricular standstill for 5·5 sec. occurring 14 sec. after injecting 19 mg. *MgATP*.

1 mV=1 cm.   1 sec.=2·5 cm.

TABLE II

RESULTS OBTAINED IN CASE I

Dose of *MgATP* (Mg.)	Other drugs	Maximum increase in P–R interval (Sec.)	Wenckebach phenomenon	Number of dropped beats	Duration of block (Sec.)	Sinus slowing	Remarks
30	—	0·20	+	1	6	+	Typical single observation
30	—	0·14	—	1–2	8	+	Mean of 7 observations
30	After 400 mg. mepacrine orally	0·05	—	0	2·5	+	
30	After 100 mg. paludrine orally	0·22	—	1	9	+	
35	—	0·28	+	1	9	+	
35	—	0·16	+	1–2	6	+	Mean of 5 observations
35	After 1·2 mg. atropine intravenously	0	—	0	0	+	
35	After 2·4 mg. atropine intravenously	·0	0	0	0	+	
40	—	0·14	+	1	10	+	
40	—	0·16	+	1–0	7·5	+	Mean of 2 observations
40	After 1 g. quinidine sulphate orally	0·06	—	1	2	+ +	
40	After 3 g. quinine hydrochloride orally	0·04	—	0	0	+ +	

Table II shows the effects of *MgATP* on the heart and the effects of mepacrine, paludrine, quinidine, quinine, and atropine on the cardiac response to *MgATP*.
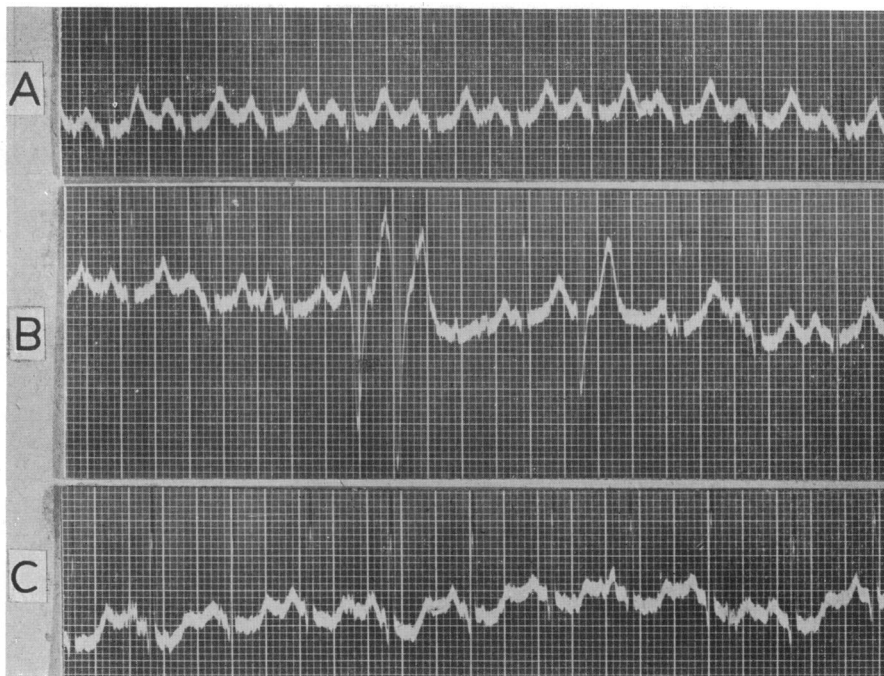
FIG. 8.—Case VII. Effect of intravenous injection of *MgATP* on the electrocardiogram (lead II).

(A) Before injection showing sinus tachycardia.
(B) 16 sec. after injection of 15 mg. *MgATP* showing 3 ventricular extrasystoles.
(C) 26 sec. after the same injection, showing depression of the S–T segment.

1 mV=1 cm.   1 sec.=2·5 cm.

complexes were not produced as consistently as in the observations on animals. In Case 3, with doses of 20 to 30 mg., the P wave was depressed, a small Q wave appeared and the T wave became isoelectric or inverted. In Case 7, with doses of 10 to 15 mg., premature ventricular contractions were observed and later the S–T interval was significantly depressed. Heart block did not occur in this case with these doses and it was thought inadvisable to increase them. The curves from this case which were obtained on three separate occasions resemble closely those obtained in the cat (compare Fig. 2 and 8).

Comparison of MgATP and Adenosine. The effects of adenosine and *MgATP*, given in equimolecular amounts, were compared in 2 subjects (Cases 1 and 2). It was found that although adenosine produced the same type of change in cardiac rhythm as *MgATP* it was not as active.

OBSERVATIONS ON THE RESPONSE TO *ATP* AFTER THE INJECTION OF OTHER DRUGS

These observations fall into two main groups.

Firstly an attempt was made to see whether the effects of magnesium sulphate and of vagal inactivation by atropine on the response to *ATP* in man were the same as those we had encountered in animals. The effects of adrenaline and quinidine were also investigated, the former because it is known to facilitate conduction down the bundle (Wiggers, 1927) and the latter because it might have been expected to increase the degree of conduction defect as in clinical cases of heart block (Lewis, 1925). Secondly, we investigated the effect of various antimalarial drugs on the response of the human heart to *ATP* in view of the animal experiments of Raventós which we had partially confirmed.

Magnesium Sulphate. This substance was given intravenously in a doze of 1·6 g. $MgSO_4. 7 H_2O$ (8 ml. of 20 per cent solution) to 2 subjects, 7 to 10 minutes before the injection of *MgATP*. In both, there was a definite increase in the degree of heart block produced by *MgATP*. The results therefore resemble those obtained in animals.

Adrenaline. Injections of *MgATP* were given to 2 subjects 5 minutes after an intramuscular injection
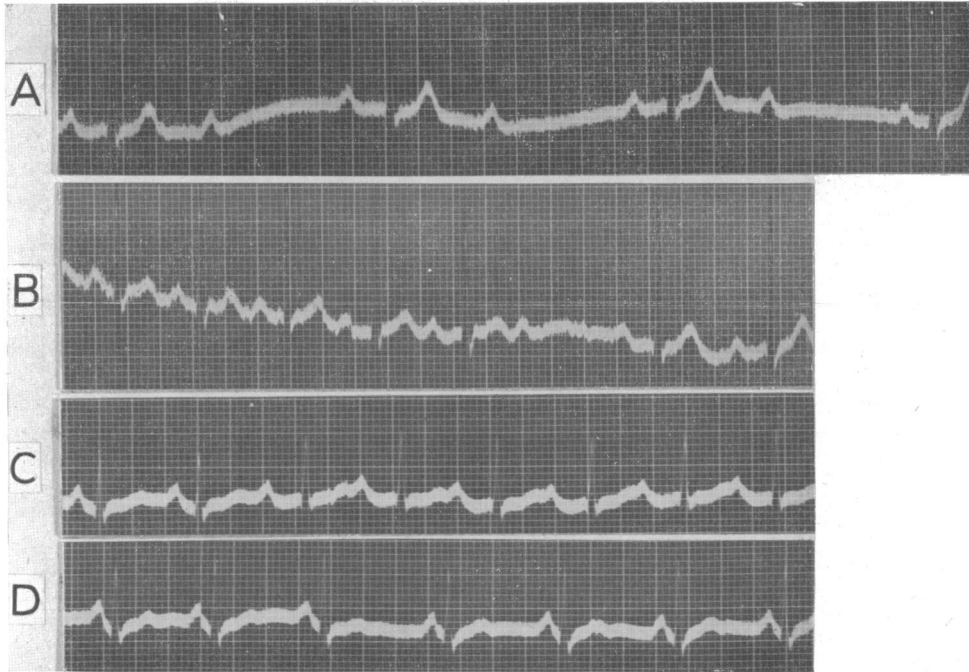
Fig. 9.—Effect of *MgATP* on the human electrocardiogram before and after intravenous injection of atropine.

    (A) Case IV, 15 sec. after injection of 17 mg. *MgATP*.
    (B) Case IV, 15 sec. after injection of 17 mg. *MgATP*. Five minutes previously 2·5 mg. atropine sulphate had been given intravenously.
    (C) Case I, 15 sec. after injection of 35 mg. *MgATP*.
    (D) Case I, 18 sec. after injection of 35 mg. *MgATP*. Five minutes previously 1·2 mg. atropine sulphate had been given intravenously.

    Both cases show reduction in the degree of heart block due to *MgATP* after atropine administration. Sinus slowing is still seen.

<div align="center">1 mV = 1 cm.   1 sec. = 2·5 cm.</div>

of 0·5 ml. 1 : 1000 adrenaline hydrochloride and to 1 subject after 1·0 ml. The number of dropped beats and the duration of the block was reduced in each instance.

Atropine. After control observations, 5 subjects were given atropine sulphate intravenously in doses usually considered sufficient to produce complete vagal paralysis. When the heart rate had risen to a stationary level, *MgATP* was given. Sinus slowing still occurred, but in two instances second degree A-V block was completely prevented. In the other observations the degree and duration of heart block was much less (Fig. 9 and Table II).

Quinidine. Two subjects (Cases I and VI) received 1 g. of quinidine sulphate in divided doses, the last dose of 0·2 g. being given half an hour before the injection of *MgATP*. The increase in P–R interval and the duration of heart block were significantly less than in the control observations

(Fig. 10 and Table II). The degree of sinus slowing was the same.

Antimalarial drugs. 1. *Quinine.* Three grammes of quinine hydrochloride were given orally over 3 days to 4 subjects (Cases 1, 2, 4, and 6), the last dose being administered half to two hours before the injection of *MgATP*. The effects were similar to those obtained using quinidine and in one case A-V block was almost completely prevented (Fig. 10E and Table II).

2. *Mepacrine.* Three subjects (Cases 1, 2, and 6) received 0·4 g. mepacrine hydrochloride by mouth over thirty-six hours, the last dose of 0·2 g. being given two hours before the injection of *MgATP*. The degree and duration of heart block were significantly less than in control observations (Fig. 10B and Table II).

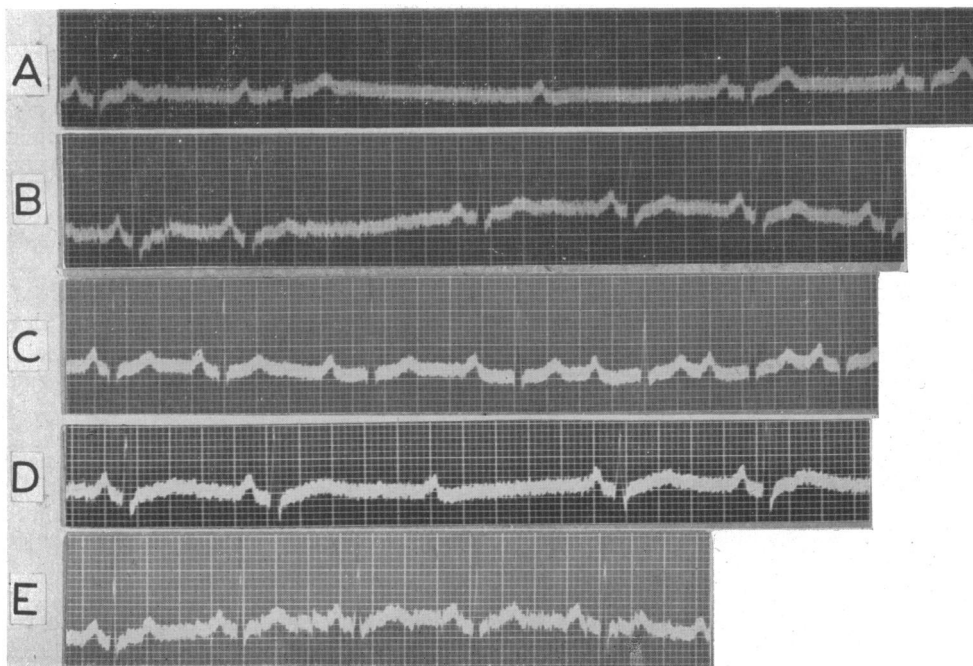3. *Paludrine.* Three subjects (Cases 1, 2, and 6) were given 100 mg. paludrine hydrochloride by

FIG. 10.—Case I. Effect of mepacrine, quinidine, and quinine on the response to the intravenous injection of *MgATP* (lead II).

    (A) Control, 17 sec. after injection of 30 mg. *MgATP*. Normal P–R interval for this case lay between 0·16 sec. and 0·18 sec.

    (B) Effect of mepacrine (for dosage, see text) : 18 sec. after injection of 30 mg. *MgATP*.

    (C) Control; 17 sec. after injection of 40 mg. *MgATP*.

    (D) Effect of quinidine (for dosage, see text): 16 sec. after injection of 40 mg. *MgATP*.

    (E) Effect of quinine (for dosage, see text): 17 sec. after injection of 40 mg. *MgATP*.

Shows the reduction in the effect of *ATP* after certain antimalarial drugs.

1 mV = 1 cm.   1 sec. = 2·5 cm.

mouth and one (Case 4) 200 mg. three hours before injection of *MgATP*. No reduction in the degree of block was noted. Indeed, in Case 4 the block persisted much longer than in control observations. We thought it inadvisable to investigate the effects of higher doses, because of toxic symptoms produced by the dosage given to Case 4.

DISCUSSION

These observations show that *ATP* has a profound effect on the conducting system of the heart causing changes in cardiac rhythm similar to those described for adenosine and muscle adenylic acid by Drury and Szent-Gyorgyi (1929). The action is essentially a depression of normal function with sinus slowing, prolongation of the P–R interval and the appearance of heart block. With sufficiently large doses this A-V block may be complete and complete asystole can also occur. In man these effects were often followed by a short period of sinus tachycardia but

the second phase of sinus bradycardia described by Drury and Szent-Gyorgyi (1929) was seldom seen in our observations, perhaps because we used smaller doses. With very small doses of *MgATP*, sinus tachycardia was (sometimes) the only effect produced. For the most part the effect of *ATP* was similar in the three species studied but there were certain interesting minor differences. Drury (1936) has emphasized that the site of the main action of the adenyl compounds differs in different species. As with the lower compounds, the main action of *ATP* in the guinea pig is upon the A-V node whereas in man and the cat, especially in the latter, the main effect is upon the S–A node. An illustration of this is the more frequent occurrence of complete asystole in the cat than in the guinea pig.

McDowall (unpublished report to the Medical Research Council, 1944) first pointed out that the vagi participated in the cardiovascular response to *ATP* in the cat and this has been fully confirmed by

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us both here and elsewhere (Bielchowsky, Green, and Stoner, 1946; Green and Stoner, 1949). We found that amongst the common laboratory animals this reaction was only seen in the cat and that in this animal it was only *ATP* which acted in this way. The present studies, in addition to giving some information on the efferent mechanism of this reflex, also show that the vagi are similarly involved in man. Experiments on the vagotomized cat indicate that the sinus bradycardia after *ATP* is in part due to its action through the vagi. In man, with the vagi paralysed by atropine, the reduction in the degree of sinus slowing was not so marked but the elimination of the A-V block was very striking.

Direct comparison of the changes in cardiac rhythm produced by equimolecular amounts of adenosine and *ATP* showed that the effects were the same in the guinea pig but not in the cat or man, i.e. in the two species where the vagus is involved. A similar effect was, however, seen in the cat after the vagi had been divided. These findings are in agreement with those on the isolated perfused rabbit's heart (Green and Stoner, 1949) which showed that the effect of these compounds on the conducting system is essentially due to their adenosine content.

Alterations in the cardiac rhythm are not the only changes seen after the injection of *ATP*. Various other changes occurred, notably ventricular extrasystoles and displacement of the S–T segment, which are best attributed to a direct action on the myocardium. This effect is not seen after adenosine for as Drury (1932) and Green and Stoner (1949) have shown it is only the phosphorylated derivatives which possess this action.

That *ATP* has this action on the myocardium may be of some practical importance. Adenosine and muscle adenylic acid, often mixed with other substances in the form of tissue extracts, have been widely used in the treatment of cardiac and peripheral vascular disease. The alleged beneficial effects have been attributed to vasodilatation of the coronary and peripheral vessels and to a direct action on the myocardium. It seems improbable that, in the doses given and using the routes of administration advised, beneficial results would be likely to ensue. But, in view of the greater general activity and more definite role of *ATP* in muscle metabolism, it is probable that attempts will be made to use this substance in the therapy of cardiovascular disease. In view of the ectopic beats and alterations in the S–T segment observed by us this would seem unjustifiable. If it is given in the treatment of other types of disease it should be given by slow intravenous injection or intramuscularly. Unfortunately, when given by the latter route the dose must be large and absorption is irregular.

It is of great interest that the cardiac effects of *ATP* are capable of being influenced by the previous administration of other substances, one of the most important of which is Mg^{++}. The striking effect of this ion in increasing the shock-inducing action of *ATP* and altering its action on the cardiovascular system have been dealt with elsewhere (Green and Stoner, 1944; Bielchowsky, Green, and Stoner, 1946). The electrocardiographic observations described here show that Mg^{++} administration increases the effect of *ATP* on the conducting system whilst decreasing its effect on the myocardium. Similar effects were observed in experiments on the isolated perfused rabbit's heart. This phenomenon is thought to be due to the interference of Mg^{++} in the enzymic breakdown of *ATP* (Green and Stoner, 1949).

Although *ATP* has such a powerful effect on the conducting system of the heart it would seem that this action can still be antagonized by adrenaline. This action of adrenaline in facilitating conduction through the bundle has been subject to very little experimental investigation in the past largely due to the difficulties of producing graded heart block under experimental conditions. Our observations, therefore, may indicate an approach to this problem.

Quinine, quinidine, and mepacrine also clearly hinder the development of the *ATP* effect but it is not at all clear why they should have this action. Indeed one might have expected *ATP* to have had a greater effect after the administration of these compounds. Our failure to elicit a similar effect with paludrine even when, in animals, very large doses were given, prevents us from agreeing with Raventós (1948), that there is an antagonism between the antimalarial drugs and the cardiac effects of the adenyl derivatives. The antagonism would seem to be between these compounds and certain members of the quinoline and acridine series. The further aspects of this antagonism are dealt with elsewhere (Green and Stoner, 1949). Whilst no explanation of the mechanism involved can yet be given there is no evidence to suggest that it is due to the interference of these quinoline and acridine derivatives in the metabolism of nucleotide.

SUMMARY

The effect of the intravenous injection of adenosine triphosphate (*ATP*) on the electrocardiogram has been studied in human subjects, cats and guinea pigs.

The effect of *ATP* on cardiac rhythm varies with the dose. Whilst very small doses may give sinus tachycardia, the normal effect is to cause sinus slowing, prolongation of the A-V interval and second degree A-V block. Large doses frequently

cause standstill either of the ventricles or the whole heart.

ATP acts mainly on the S–A node in the cat and man but mainly on the A-V node in the guinea pig.

It has been shown that part of the *ATP* effect in the cat and' man is mediated through the vagus.

Equimolecular amounts of adenosine will reproduce the effect of *ATP* on cardiac rhythm in the guinea pig and also in the cat if the vagi are first inactivated.

The effects of *ATP* are not confined to cardiac rhythm, and other changes in the electrocardiographic complexes were seen in both man and animals which were thought to be due to a direct action on the myocardium. These changes were not seen after adenosine.

The effect of the previous administration of certain compounds on the response to *ATP* was also observed with the following results.

(1) *Magnesium sulphate* increased the effect on cardiac rhythm and decreased the action on the myocardium.

(2) *Adrenaline* shortened the period of heart block.

(3) *Quinine, quinidine, and mepacrine* all decreased the effect on cardiac rhythm.

(4) *Paludrine* had no significant effect on the response.

ATP administered intravenously for periods up to three months produced no significant improvement in 15 cases of rheumatoid arthritis.

The significance of these observations and their relationship to other of our findings has been discussed.

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