Circulatory and Respiratory Effects of Adenosine Triphosphate in Man

By Dean F. Davies, M.D., Arthur L. Gropper, M.D., and Henry A. Schroeder, M.D.

The authors have studied the acute effects of the intravenous and intra-arterial injection of the sodium salt of adenosine triphosphate (ATP) in man. Rapid injection causes a frightening sensation in the chest and hyperpnea. The changes found agree with those reported in cats and are consistent with the concept that adenosine triphosphate is a vasodilator in somatic structures but causes an increase in pulmonary vascular and possibly in splanchnic resistance. Its principal action seems to be pharmacologic rather than in its role as an intracellular metabolite.

Although the important role of adenosine triphosphate (ATP) as a coenzyme in transfer of high-energy phosphate is widely recognized, there is no available information on its pharmacologic effects in man. Increasing attention has been directed toward adenosine compounds since the demonstration by Drury and Szent-Györgyi that adenosine and adenylc acid dilate the coronary vessels and lower arterial blood pressure in cats and dogs. They suggested that this activity was associated with the ease of deamination of the compounds. Fleish and Domenjoz compared the effects of muscle adenylc acid with adenosine triphosphate on blood flow in the hind limb of dogs and concluded that adenosine triphosphate was 70 times as effective as an equimolar concentration of muscle adenylc acid in its vasodilatory action. Kalekar and Lowry did not find that the presence of its two pyrophosphate groups made adenosine triphosphate any more potent in its vasodepressor effect on rabbits than muscle adenylc acid.

On the basis of its vasodilator effect several suggestions have been made that one of these compounds may be responsible for the vasodilatation occurring in states of shock. Potter suggested that the phosphorylating mechanism may be lost, a concept which could link shock with the high phosphate-bond energy of adenosine triphosphate rather than with its ease of deamination. By injecting a mixture of adenyx pyrophosphatase, alkaline phosphatase, and adenosine deaminase intravenously in rabbits receiving an infusion of adenosine triphosphate, Kalekar and Lowry were able to block the depressor effect of adenosine triphosphate. However, when these enzymes were injected into rabbits and dogs in traumatic shock, no protective action on blood pressure occurred and insignificant amounts of adenosine derivatives were found in the blood. They concluded that the release of adenylc acid compounds probably does not play a primary role in the etiology of traumatic shock.

It first seemed reasonable to Szent-Györgyi that the energy for the breakdown of adenosine triphosphate is necessary for the relaxation of muscle to a state of high potential energy. Ruskin claims this confirms what he "had already proved through the clinical use of the adenylc nucleotide." Clinical experience led him to believe that adenosine triphosphate does not seem to influence hypertension, while the iron salt of yeast adenylc acid (Ironyl) is clinically effective in hypertension, circulatory failure, muscle spasm and arthritic pain. One of us (H.A.S.) found no reduction in blood pressure from Ironyl in a hypertensive patient. However he observed a delayed, prolonged fall in blood pressure after adenosine triphosphate in 2 patients with malignant hypertension. One became increasingly resistant to daily intravenous injections of the drug over a period of two months. One patient with chronic glomerulonephritis and 1 with early

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malignant hypertension showed no response which could exclusively be attributed to adenosine triphosphate.

In spite of the claims of Ruskin and others\textsuperscript{16, 17} of the clinical effectiveness of adenosine triphosphate and adenosine derivatives in vasospastic diseases, there is growing evidence that the action of these compounds is not primarily due to their role in muscle metabolism. Vasoconstriction results from adenosine triphosphate\textsuperscript{18-19} and adenosine\textsuperscript{8} in the pulmonary vessels and from adenosine\textsuperscript{21, 29} in the kidney; prompt dilatation results from adenosine and adenylic acid in coronary and ear vessels in the absence of high-energy phosphate.\textsuperscript{5} These facts have not been explained. A study of the acute effects of adenosine triphosphate on the respiratory and hemodynamic physiology of man was therefore considered worthwhile in order to study its pharmacologic action and because of claims of its therapeutic possibilities.

**Methods**

**Subjects.** Twenty-eight white patients were studied; they were selected from the St. Louis City Hospital Divisions and Out-Patient Departments and ranged in age from 16 to 79 years. The group included 11 hypertensive and 17 normotensive patients convalescent from arthritis, acute alcoholism, pneumonia, peptic ulcer and a number of other conditions. Six were women, the remainder men. Each patient was studied for a 30 to 60 minute period in a quiet laboratory maintained at 22 to 25.5 C. during the experiment.

Three major approaches were made to the problem: (1) adenosine triphosphate was given intravenously to 19 subjects while estimates of changes in respiration, cardiac output, blood pressure, and digital blood flow were carried out; (2) intra-arterial injection was made into 4 lightly anesthetized and 6 unanesthetized patients while measurements of relative changes in blood volume in ipsi- and contralateral fingers were made; (3) adenosine triphosphate was given intravenously to 1 lightly anesthetized and 7 unanesthetized patients during renal clearance studies. Results of digital blood flow, cardiac output and blood pressure measurements made in several of these patients are discussed under the first approach. Satisfactory measurements of all parameters under each approach were obtained with a few exceptions.

**Respiration.** A pneumograph with rubber diaphragm and an air conducting system was used.

**Cardiac Output.** Tracings were taken on a high frequency ballistocardiograph of Wilkins' design.\textsuperscript{22} Oscillations of the table were recorded by means of a photoelectric pressure recorder using a rubber membrane of suitable natural frequency of vibration. The calculations were made from representative strips of the record, by applying the area formula of Starr.\textsuperscript{24}

**Blood Pressure.** Direct brachial arterial blood pressure was measured by the use of a Hamilton optical manometer in some instances; an aneroid sphygmomanometer was used in others.

**Blood Flow.** Qualitative changes in blood flow were estimated by photoelectric plethysmographs applied to the ear and finger.

**Venous Pressure.** A water manometer containing 2.5 per cent sodium citrate measured antecubital venous pressure directly. All electrical signals were led through direct-coupled amplifiers into Sanborn Galvanometers and recordings made optically on a photokymograph run at a speed of 5 or 25 mm. per second.

**Respiratory Function.** Two control urine collection periods of 10 to 12 minutes each were taken according to the constant infusion routine.\textsuperscript{25} In the patient who received sodium amytal only 300 cc. of water was given by mouth. Priming and sustaining infusion solutions were prepared with inulin and sodium paraaminohippurate (PAH) according to formulas based on weight, estimated renal function and age.\textsuperscript{26} Analysis for inulin was made by Harrison's method,\textsuperscript{27} modified for the Beckman DU Spectrophotometer. Analyses for paraaminohippurate were made by the method of Smith \textsuperscript{28} except that 1:15 acid zinc sulfate filtrates were used instead of cadmium sulfate and sodium hydroxide.

After careful reassurance during the time instruments were being applied, two or three control clearance periods and one or more control tracings were taken. Forty or more mg. of adenosine triphosphate\textsuperscript{*} freshly dissolved in 50 cc. of sterile saline was infused at a rate of approximately 5 cc. per minute depending somewhat on the subjective reactions of the patient; continuous measurements were taken during the injection interval. In most instances the total dose was 40 mg., the range being 20 to 75 mg. Records were taken at varying intervals during recovery.

**Results**

The subjective responses to intravenous injection of adenosine triphosphate were striking. Patients invariably experienced a sensation in

\* Sodium salt of adenosine triphosphate obtained from Rohm and Haas Company. Assay by the hexokinase reaction performed by Dr. David Brown on different batches of adenosine triphosphate from the same company yielded 67 to 72 per cent active substrate. The compound was kept desiccated in the refrigerator or in deep freeze.
their chest which they found difficult to describe. Some felt it was easier to breathe, while others felt suffocated. A few became very apprehensive, especially if they were not fully prepared for the effects. About half of them coughed if the injection was rapid. The subjective effects were always more marked than any of the objective changes noted, but they disappeared almost immediately when the injection was stopped.

On intra-arterial injection the subjective response was greatly lessened for an equal dose but was present if injection was sufficiently rapid. After injection in the brachial artery the chief sensations were warmth throughout the forearm and hand; the skin of the injected forearm was distinctly warmer to touch than that of the opposite side, and some patients experienced a feeling of fullness in it.

**TABLE 1.—Effect of Adenosine Triphosphate on the Heart**

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient</th>
<th>Age</th>
<th>ATP Dose</th>
<th>Cardiac Index</th>
<th>Pulse Rate</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yrs.</td>
<td>Mg.</td>
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<tr>
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<td></td>
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<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>40</td>
<td>3.31</td>
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<td>2.79</td>
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<td>3.96</td>
<td>3.78</td>
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<td>2.20</td>
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<td>L. F. ♂</td>
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<td>8</td>
<td>2.83</td>
<td>3.69</td>
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<tr>
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<td>A. S. ♂</td>
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<td>40</td>
<td>3.20</td>
<td>3.25</td>
</tr>
<tr>
<td>Mean</td>
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<td>3.06</td>
<td>3.30</td>
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</table>

| Intra-arterial               |        |     |         |     |             |           |     |             |           |           |           |
| 1   | J. W. ♂ | 73  | 40       | 2.61 | 2.62 | —          | 70        | 70        | —         |
| 2   | J. McC. ♂| 56  | 40       | 2.51 | 3.79 | 3.68       | 92        | 96        | 96        |
| 3   | F. P. ♂ | 24  | 40       | 2.32 | 2.18 | —          | 88        | 80        | —         |
| 4   | H. S. ♂ | 72  | 40       | 2.64 | 5.15 | 3.92       | 84        | 93        | 91        |
| 5   | J. ♂    | 26  | 25       | 2.40 | 3.26 | 3.41       | 92        | 126       | 123 Amytal sed. |
| 6   | H. L. ♂ | 53  | 40       | 3.46 | 4.08 | 3.69       | 89        | 100       | 98 Amytal sed. |
| 7   | E. V. ♂ | 16  | 40       | 2.88 | 3.12 | 3.32       | 93        | 118       | 110 Amytal sed. |
| 8   | C. S. ♂ | 50  | 40       | 3.08 | 5.35 | 3.78       | 100       | 117       | 99        |
| Mean                        |       |     |         | 2.74 | 3.69 | 88         | 100       |           |           |

Figures in italics were not used in estimating means in order to keep the data comparable.

"First recovery" values represent measurements made from 1 to 10 minutes after drug injection stopped.
Respiration. The most profound and consistent changes were observed in the depth of respiration. Although no quantitative measurement of respiratory volume was attempted, markedly constant in all but 2 subjects. One increased from 12 to 32 respirations per minute during intravenous injection, the other from 18 to 32 during intra-arterial injection.

### Table 2.—Blood Pressure Effects of Adenosine Triphosphate

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient</th>
<th>Age</th>
<th>Method*</th>
<th>Control</th>
<th>During Injection</th>
<th>Recovery</th>
<th>Post Injection</th>
<th>Remarks</th>
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<td>36</td>
<td>32 H</td>
<td>195</td>
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<td>88</td>
<td>189</td>
</tr>
<tr>
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<td>P. K.</td>
<td>62</td>
<td>20 C</td>
<td>230</td>
<td>114</td>
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<td>—</td>
<td>260</td>
</tr>
<tr>
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<td>F. T.</td>
<td>67</td>
<td>75 H</td>
<td>228</td>
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<td>203</td>
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<td>24</td>
<td>8 H</td>
<td>218</td>
<td>119</td>
<td>202</td>
<td>114</td>
<td>195</td>
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<td>20 H</td>
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<td>85</td>
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<td>40 H</td>
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<td>206</td>
<td>110</td>
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<td>40 C</td>
<td>130</td>
<td>74</td>
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<td>—</td>
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<td>94</td>
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<td>134</td>
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<td>180</td>
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<td>—</td>
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<td>90</td>
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<tr>
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<td>1</td>
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<td>40 C</td>
<td>130</td>
<td>75</td>
<td>—</td>
<td>—</td>
<td>150</td>
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<td>135</td>
<td>70</td>
<td>—</td>
<td>—</td>
<td>135</td>
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<td>—</td>
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<td>130</td>
<td>75</td>
<td>—</td>
<td>—</td>
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<td>5</td>
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<td>112</td>
<td>70</td>
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<td>—</td>
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<td>6</td>
<td>H. S.</td>
<td>72</td>
<td>40 C</td>
<td>138</td>
<td>78</td>
<td>—</td>
<td>—</td>
<td>150</td>
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<td>25 C</td>
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<td>180</td>
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<td>148</td>
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<td>40 C</td>
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† Expressed as adenosine triphosphate, given as sodium salt.
* C—cuff, H—Hamilton.

Figures in italics were not used in estimating means in order to keep the data comparable. "First recovery" values represent measurements made at varying intervals after injection was stopped as indicated in column labeled "Post Injection".

an approximation of this parameter was made from measurements of the pneumograph tracings (fig. 1). This indicated an average increase of 70 per cent during intravenous injection and a somewhat smaller increase during intra-arterial injection. Respiratory rate remained re-

Cardiac Effects. The effects of intravenous and intra-arterial injections on the heart are shown in table 1. No consistent effects on cardiac index were noted. On intravenous injection, the maximum change in cardiac index from its control value averaged +0.24 L per
minute per square meter of body surface, although there was either no significant change or a slight fall in 5 of 11 cases. On intra-arterial injection the cardiac index averaged 0.95 L per minute per square meter higher than the controls, although in 2 of 8 cases there was no essential change. All 3 of the subjects under Amytal sedation showed increases of more than 10 per cent. Statistical analysis of the changes produced by the intravenous injection gave a t value of 2.25, below the level of significance.

The increase in cardiac index was associated with an increase in pulse rate in every instance. An increase of 8 or more beats per minute occurred in 8 of 15 subjects on intravenous injection, the average being 10 beats per minute. Heart rate fell in one subject.

The observed rises in cardiac output were not accounted for on the basis of pulse rate alone in 4 subjects whose stroke index increased significantly.

Arterial and Venous Pressure; Volume Flow. It will be noted in table 2 that during intravenous injection both systolic and diastolic blood pressure showed small decreases in 7 of 9 subjects, the diastolic change being statistically significant, and averaging 7 mm. Hg. Observations of blood pressure during intra-arterial injection were incomplete, but measurements taken at varying intervals during recovery showed a return to control systolic values or above in every instance. In only one (W.H.) was the first diastolic pressure significantly below its control level after recovery.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Wt.</th>
<th>No. of Control Periods</th>
<th>Insulin Clearance</th>
<th>PAH Clearance</th>
<th>Filtration Fraction</th>
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<td></td>
<td>yrs.</td>
<td>lbs.</td>
<td></td>
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<td>Change During ATP Injection</td>
<td>Mean Control</td>
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<td>2</td>
<td>120.0</td>
<td>+0.7 to -1.9</td>
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<td>148.2</td>
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<td>3</td>
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<td></td>
<td>95.3</td>
<td>-15.7 to +4.9</td>
<td>356</td>
</tr>
</tbody>
</table>

* Normotensive patients. Remainder were hypertensive.
† Patient received a three-quarter dose of Sodium Amytal intravenously 20 minutes before beginning control clearance periods.
‡ Recovery periods followed injection periods.

Venous pressure showed small increases in 3 of 4 subjects during intra-arterial injections and in the only subject where this measurement was made during intravenous injection.

![Graph](image.jpg)
Photoelectric plethysmography in 3 subjects during injection into a brachial artery gave definitive evidence of increased finger volume in the ipsilateral but not contralateral side (fig. 2). During intravenous injection changes in ear and finger were less clear-cut. Six of 8 subjects showed evidence of increased blood volume in ear and 2 of 4 increased blood volume in finger.

Renal Function. Table 3 shows the effects of intravenous injection of adenosine triphosphate on glomerular filtration rate, effective renal plasma flow, and filtration fraction on 7 unanesthetized patients and 1 patient who had received 0.5 Gm. of Sodium Amytal intravenously before the control periods. With one exception, there was a fall in paraaminophenylurate clearance during the injection with a tendency to return to normal during the recovery period. Inulin clearance decreased during injection in 7 out of 8 subjects. Two patients who were apprehensive showed evidence of efferent arteriolar constriction by an elevated filtration fraction. Although this response would be expected after the administration of adenosine triphosphate, the net effect on filtration fraction during recovery was negligible.

Discussion

The many compensatory and defense mechanisms of an intact circulation tend to increase the number of possible interpretations of the results in a study such as the present one. When results are not consistent, they are more likely to be produced by such secondary mechanisms, and not reflect direct responses to the injection of a drug. According to this reasoning, the present data on changes of respiratory rate, renal blood flow, heart rate, and cardiac output may not represent direct responses to the action of adenosine triphosphate. The observations on patients under Amytal sedation suggest this measure was not successful in eliminating the secondary mechanisms. On the other hand, the moderate but more consistent changes in blood pressure, digital volume flow and venous pressure may well be a direct result of adenosine triphosphate, suggesting a vasodilatory action. There is ample documentation in other studies for such an effect. The lack of consistency in the response of the above functions suggest that they are not controlled by the direct action of adenosine triphosphate on muscle contraction. Indeed, Sandow has questioned the original theory of Szent-Györgyi on the role of adenosine triphosphate in muscle relaxation, and Szent-Györgyi himself has recently modified his views.

The one striking and consistent response was hyperpnea, which occurred even in subjects under moderate Amytal sedation who could not have been apprehensive. Of the chemical factors concerned with the regulation of respiratory rate and depth, hydrogen ion concentration, carbon dioxide tension and oxygen tension are known to be important. Adenosine triphosphate may prove to influence this chemical regulation through the central nervous system. On the other hand, the response could be secondary to local factors such as increased pulmonary artery resistance.

No significant difference was observed in the response of hypertensive and normotensive subjects. The decrease in renal function obtained in these acute experiments provide an argument against the therapeutic usefulness of adenosine triphosphate. Suggestive evidence that a delayed beneficial effect is not invariable was provided by the follow-up clearance on one patient (C.F.). Effective renal plasma flow and blood pressure carried out the morning after adenosine triphosphate administration in this case had returned to control levels.

Although the interpretation of these results cannot be definitively stated, they are on the whole in accord with published data on the effects of adenosine triphosphate in animals, particularly those of Emmelin and Feldberg. Comparison of their findings in chloralosed cats and our results in man is made in table 4. The results of the two approaches agree remarkably well. They are compatible with the concept that adenosine triphosphate is a vasodilator in somatic structures, causes a marked increase in pulmonary vascular resistance, and through chemical or reflex pathways produces an involuntary increase in respiratory volume. The evidence is suggestive that splanchic blood flow decreases. Some of the variable effects seen in blood pressures, heart rates, and
cardiac outputs may be attributed to the
dependence of the response on the concentration
of adenosine triphosphate as found by Gropp and
Bugachev in perfusion studies on frogs.
However, if neurogenic mechanisms are not
blocked by adenosine triphosphate, they may
exert varying degrees of compensatory re-
response. Either alternative would offer strong
support to the concept that injected adenosine
triphasate acts pharmacologically rather

than metabolically and does not have its effect
directly on the contractile system of the smooth
muscle of the vascular wall.

**SUMMARY**

1. Adenosine triphosphate (ATP) was in-
jected intravenously and intra-arterially into
hypertensive and normotensive patients while
various respiratory and cardiovascular func-
tions were measured.
2. Subjective response was striking and con-
sisted of a peculiar, painless sensation in the
chest and apprehension.
3. Depth of respiration increased markedly
without change of respiratory rate.
4. Cardiac output remained constant or rose.
5. Blood pressures, especially diastolic,
showed a moderate fall.
6. On intra-arterial injection vasodilatation
occurred in the injected extremity. On intra-
venous injection peripheral dilatation usually
took place where measured (finger and ear).
7. A rise in venous pressure occurred in 3 of
4 subjects during injection.
8. Effective renal plasma flow and glomerular
filtration rate usually decreased.
9. The compatibility of these results with
known effects of adenosine triphosphate in an-
imals is pointed out.

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**REFERENCES**

1. Lipmann, F., and Kaplan, N. O.: Intermediary
metabolism of phosphorus compounds. Ann.
2. Drury, A. N., and Szent-Györgyi, A.: The
physiological activity of adenine compounds
with special reference to their action upon the
3. Fleisch, A., and Domenjod, R.: The vasodila-
tory effect of adenine acid and adenosine-
984, 1940.
4. Kalckar, H. M., and Lowry, O. H.: The rela-
tionship between traumatic shock and the
release of adenylic acid compounds. Am. J.
5. Bennett, D. W., and Drury, A. N.: Further ob-
servations relating to the physiological activity
of adenine compounds. J. Physiol. 72: 288, 1931.
6. Green, H. N.: Shock-producing factor(s) from
striated muscle. I. Isolation and biological prop-
7. Bielschowsky, M., and Green, H. N.: Shock-
producing factor(s) from striated muscle. II.
Fractionation, chemical properties and effective
8. Stoner, H. B., and Green, H. N.: Adenosine
compounds and phosphates in the blood of
shocked rabbits. J. Path. and Bact. 56: 343,
1944.
9. —, and —: Further observations on the adeno-
sine equivalent of the blood of rabbits following
lethal forms of tissue injury. J. Path. and Bact.
57: 337, 1945.
10. Potter, V. R.: Coupling between phosphoryla-
tion and oxidation of the 4-carbon acids in
rat kidney homogenates. Arch. Biochem. 6:
439, 1945.
EFFECTS OF ADENOSINE TRIPHOSPHATE IN MAN

15 Schroeder, H. A.: Personal communication.
Circulatory and Respiratory Effects of Adenosine Triphosphate in Man
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