response consisting of squealing and struggling was elicited from the rat whenever the foot was flexed ventrally with firm pressure. A sterile abscess usually developed at the site of the injection.

Anteroposterior and mediolateral measurements of the ankle were made with calipers 48 hr after injection, and the circumference was calculated, assuming the ankle at this level to be rectangular. An example of the great increase that occurs in the dimensions of the ankle is illustrated in Table 1. The average circumference was 2.49 cm in the controls and 4.51 cm in the injected rats.

TABLE 1

EFFECT OF $AgNO_3$ INJECTION ON SIZE OF ANKLE JOINT OF RAT

Treatment	No. rats	Circumference 48 hr after injection (in cm)
Uninjected	8	2.49 ± 0.20
Injected with $AgNO_3$	8	4.51 ± 0.27

The compounds aspirin, acetophenetidin, and sodium gentisate were administered by stomach tube, 1 mg/g, 40% suspensions in 2% starch solutions, 24 hr after the $AgNO_3$ injections. The control rats received 2% starch solution. Measurements were made at 24 hr after the tube feedings. It was evident from the marked reaction of the rats to flection of the joint that they were obtaining no analgesic effect from these compounds at this time. The results of the measurements are summarized in Table 2. Aspirin and acetophenetidin reduced the swelling significantly, but sodium gentisate did not. Sodium gentisate is less toxic than the other two compounds, and it is possible that better results would have been obtained with higher doses, but on a milligram for milligram basis it was less effective.

TABLE 2

EFFECTIVENESS OF VARIOUS DRUGS IN REDUCING INFLAMMATORY EDEMA RESULTING FROM INJECTION OF 1% $AgNO_3$ INTO ANKLE JOINT OF RAT

Compound	Method of administration	Dose (mg/g)	No. rats in group	Av circumference* and SD (in cm)	Diff (in cm)	P†
Aspirin	Oral	1.0	6	3.45 ± 0.32	0.71	< 0.01
Starch control	"	—	7	4.16 ± 0.18		
Acetophenetidin	"	1.0	5	3.64 ± 0.35	0.52	< 0.01
Starch control	"	—	7	4.16 ± 0.18		
Sodium gentisate	"	1.0	8	4.40 ± 0.16	0.11	> 0.05
Starch control	"	—	8	4.51 ± 0.27		
Morphine	Subcu-	0.01	5	4.03 ± 0.06	0.08	> 0.05
Control	taneous	—	5	4.11 ± 0.29		
Demerol	Subcu-	0.10	5	3.88 ± 0.19	0.23	> 0.05
Control	taneous	—	5	4.11 ± 0.29		

* Measurements made 48 hr after $AgNO_3$ injection.
† Test of significance was made by calculating statistic t.

Morphine sulfate, 0.01 mg/g as 0.5% solution, and demerol hydrochloride, 0.1 mg/g as 5.0% solution, were each injected twice subcutaneously, once 24 and once 46 hr after $AgNO_3$ irritations. Measurements were made 2 hr after the last injection. At this time these narcotics were at the peak of their analgesic activity and no response at all was given by the rat to firm flection of the swollen joint. The circumferences of the ankles at this time are included in Table 2. Neither compound produced a statistically significant change.

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Levels of Nucleotide in the Blood during Shock

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The work of Green (*1*) and his collaborators is based on the hypothesis that shock is produced by the release of adenine nucleotides from tissue into the blood stream. This idea was suggested by observations that when substances like ATP and related compounds were injected into the intact animal shocklike symptoms occurred. Green was never able to prove his hypothesis because specific methods for the determination of blood ATP and related substances were not available to him.

During the past 18 months we have been studying levels of adenine nucleotides in normal persons and patients with Hodgkin's disease. Blood levels in a number of other pathological conditions were also measured for comparison, and among these were samples from patients suffering from various kinds of shock (Table 1).

The method used in these studies is that of Albaum and Lipshitz (*2*), a modification of a procedure devised by Kalckar (*3, 4*), in which ATP, ADP, and AMP are measured spectrophotometrically after successive dephosphorylation and deamination to inosinic acid. In addition to measuring blood levels of these adenine compounds, we also determined the absorption spectrum of the blood filtrates between 2300 A and 2800 A.

In the blood samples from patients in shock there were no significant alterations in the levels of ATP,

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ADP, and AMP, nor were any of these substances found in the serum. In some cases, however, there was an alteration in the absorption spectrum of the blood filtrate characterized by a flattening of curve between 2500 A and 2600 A, producing a broad absorption maximum. In two cases this alteration was so marked that sharp peak absorption was found to be around 2500 A, rather than at 2600 A, the normal level (Fig. 1). Moreover, it was found that in the blood of

TABLE 1

Cause of shock	Blood pressure	Hematocrit	Wavelength of peak absorption (in A)*	ATP†	ADP	AMP
Massive arterial hemorrhage	0/0	50	2510	—	—	—
Multiple fractures	135/55	41	2450–2600‡	—	—	—
Crush (no fractures)	60/30	43	2560	—	—	—
Coronary occlusion	40/0	45	2570	6.6	0	0
Coronary occlusion	0/0	47	2570	6.9	2.0	0
Bleeding peptic ulcer	80/60	20	2570	4.1	0	0
Diabetes mellitus	44/24	51	2570	2.4	0	0
Coronary occlusion	0/0	49	2500–2600‡	7.7	0	0
Ruptured ectopic pregnancy	40/0	33	2500	4.3	0	0
Ruptured esophageal varices	90/40	23	2500–2600‡	1.9	0	0
Acute alcoholism	80/60	41	2500–2600‡	6.5	0	0

* Normally, peak absorption is between 2580 A and 2600 A.
† Normal ranges established by us are:
ATP, 4.0–9.0 mg% expressed as adenine;
ADP, 0.0–2.0 " " " " ;
AMP, 0.0–2.0 " " " " .
‡ Flat plateau.

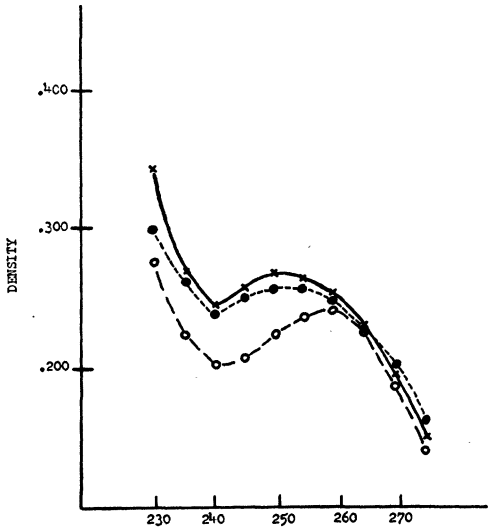

FIG. 1. ○—— ——○, normal blood; ×———×, normal blood with added inosinic acid, 15 mg %; ●– – – –●, blood of patient in shock. Wavelength in mμ.

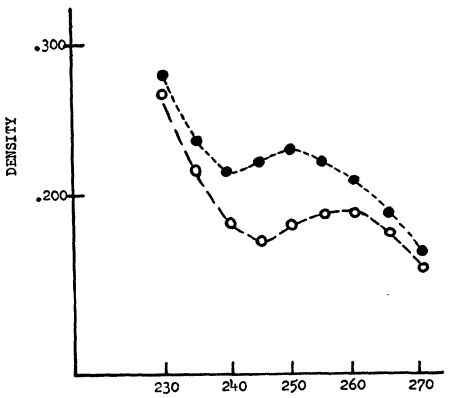

FIG. 2. ●– – – –●, shock from ruptured ectopic pregnancy; ○—— ——○, 24 hr after operation and transfusions. Wavelength in mμ.

a patient in deep shock caused by rupture of an ectopic tubal pregnancy the aberration of the absorption spectrum was reversible. Peak absorption was at 2500 A when the patient was first admitted to the hospital in profound shock. Twenty-four hr later, after operation, control of hemorrhage, and transfusion, the absorption curve reverted to the normal pattern (Fig. 2).

Although we were unable to confirm Green's hypothesis directly, since circulating ATP, ADP, and AMP were not increased, the alteration in the absorption spectrum suggested an increase in blood level of some substance, closely related to adenine nucleotides, which absorbs maximally in the vicinity of 2500 A. Inosine nucleotides absorb at this wavelength, and they can be formed by deamination of adenine nucleotides.

To test the effect of increased amounts of inosine on the absorption spectrum of blood, we added varying amounts of sodium inosine monophosphate to normal blood and found that an amount corresponding to a blood level of 15 mg% produced an alteration in the absorption spectrum exactly corresponding to that seen in cases of severe shock (Fig. 2).

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