to 40 times.

Ultraviolet irradiation, producing definite erythema in guinea pigs, results in an occasional but very slight increase of these enzymes, contrary to the Arthus phenomenon, which in 2 rabbits did not result in increased amounts. It is noteworthy that the ultraviolet treatment and the Arthus phenomenon primarily concern the cutis, whereas the heat-induced inflammation and the epidermal allergic challenge reaction concern mainly the epidermal tissue.

Although the previous experiments on the influence of antihistaminics upon the hyaluronidase reaction[1] suggest a relationship between skin inflammation and the liberation of hyaluronidase, further experiments are necessary to determine whether hyaluronidase plays an active role during these inflammations or is only a concomitant factor subsequent to an inflammatory process. Another unsolved problem is the source of the liberated enzyme.

Conclusion. The content of polysaccharide-depolymerizing substances (probably chiefly hyaluronidase) during allergic dermatitis (paraphenylenediamine) and heat-induced inflammation on guinea pig skin is markedly increased.

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Effect of Intravenous Cytochrome C on Capacity for Effort Without Pain in Angina of Effort.

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Within the past few years, reports have appeared on the effect of Cytochrome C* on tissue anoxia. From the clinical point of view, Proger and his co-workers have presented evidence that myocardial anoxia can be relieved by intravenous injection of Cytochrome C, as demonstrated by the prevention or reversal of the electrocardiographic changes induced by breathing 10% oxygen.[1] It is their contention that, under such circumstances, Cytochrome C enhances the uptake of oxygen by the myocardium.

Another method of testing the effect of a drug on myocardial anoxia is to determine the capacity for effort without pain in patients who have angina pectoris brought on by effort. Since this method depends on a subjective end-point, it is necessary to use careful controls and a completely "blind" technique, as described by Gold and his co-workers, in order to eliminate variable psychosomatic effects.[2] This method has been used by us in an evaluation of the effect of intravenous aminophylline on angina of effort, and it proved to be a satisfactory investigative technique.[3]

The subjects of the study were all selected from the active attendance of the Cardiac Clinic. All of them had either arteriosclerotic or hypertensive heart disease or a combination of both, and all presented the symptom of chest pain on effort. No patients were included in this study who had spontaneous chest pain unrelated to effort, excitement, heavy meals, or very cold weather. Also excluded were patients who showed any clinical evidence of congestive failure.

The method consisted of determining the subject's capacity for effort without pain by having him walk back and forth over a

* Cytochrome C used in this study was furnished by Wyeth, Inc., Philadelphia, Pa.

1 Proger, S., and Dekaneas, D., *J. Pediat.*, 1946, **29**, 729.

2 Gold, H., Kwit, N. T., and Otto, H., *J. A. M. A.*, 1937, **108**, 2175.

3 Bakst, H., Kissin, M., Leibowitz, S., and Rinzler, S., *Am. Heart J.*, in press.

standard set of steps until the onset of his usual type of chest pain. The rate of walking was set by the subject himself, and in any subsequent tests on that same subject, he was kept to the same rate. Every test with Cytochrome C was coupled with a control test on the same day, thus eliminating the effect of the spontaneous variations in pain on different days in the same subject. All tests were preceded by a rest period of one hour, and were conducted in the early afternoon, at least 4 hours after the last meal. In a typical experiment, the patient came to the laboratory at 12:30 o'clock without having had any lunch. He rested at least one hour and was then given the first intravenous injection at a rate of one cc per minute (total of 5 cc per injection). This was followed by a 5 minute rest period, and then the first trial was carried out. As soon as the end-point was reached, the subject sat down and rested for another hour. He was then given the second injection in the same manner, followed by a 5 minute interval, and then the second trial was conducted.

Cytochrome C was given intravenously in doses of 50 mg in 5 cc of solution. The control material used was physiological saline solution, and because Cytochrome C is red, it was necessary to prevent the patient from seeing what was being injected, lest he have a different psychological effect from a red medicine than from a white one. For this reason, a cloth screen was interposed between the patient and the investigator giving the injections, and the subject's arm was extended through a slit in the screen. The injections were all given by one person, and the observations on capacity for effort were made by the other investigator, who was unaware of which substance had been administered. The sequence of injections was varied so that in some instances the control test preceded the test with Cytochrome C, and in other instances the order was reversed. There was no indication that the subjects of the study were aware that different materials were being injected. There were no consistent reactions to the injection of Cytochrome C which would enable the subjects to detect that they were receiving a material different from the control solution.

Results. There were 12 pairs of tests conducted on 8 patients. In 4 of the pairs, the trial with Cytochrome C preceded the control trial; in the remaining 8 pairs, the control trial was conducted first. Analysis of the results reveals that Cytochrome C produced no increase in capacity for effort without pain. In fact, there was a mean decrease in performance equal to 2.33 $\pm$ S.E. 1.95 trips following the injection of Cytochrome C, as compared with the results obtained with the control injections. Expressed in percentages, this is a decrease of 8.7 $\pm$ 7.2%. Since the "t" value derived from these figures is only 1.19, it is concluded that there is no statistically significant difference between the results obtained following injection of Cytochrome C and the results following injection of physiological saline. A summary of the results is found in Table I.

Discussion. Cardiac pain as exemplified by angina of effort has been suggested to be due to an inadequate supply of oxygen to the heart to meet its demands.[4] The stimulus for pain is believed to be an accumulation of acid metabolites produced by the heart muscle under ischemic conditions.[5] The possibility of enhancing the tissue uptake of oxygen by means of Cytochrome C in instances of myocardial anoxia is then of special interest in patients with angina of effort. Proger and Dekaneas showed that 50 or 60 mg of Cytochrome C injected intravenously was able to revert to normal in as little time as two minutes an abnormal electrocardiogram produced by breathing a 10% oxygen mixture.[1] Rabinowitch, Elliott, and McEachern have shown that Cytochrome C in doses of 50 mg is taken up by tissues or destroyed within a matter of minutes after injection.[6]

We can assume that the dose of 50 mg of Cytochrome C given intravenously is taken

[4] Keefer, C. S., and Resnik, W. H., *Arch. Int. Med.*, 1928, **41**, 469.

[5] Katz, L. N., *Am. Heart J.*, 1935, **1**, 322.

[6] Rabinowitch, R., Elliot, K. A. C., and McEachern, D., *Canad. M. A. J.*, 1948, **58**, 92.

TABLE I.
Clinical Data and Results of Exercise Tolerance Tests.

Subject	Sex	Age	Diagnosis	No. of trips performed 1st trial	No. of trips performed 2nd trial
A.L.	M	55	Arteriosclerosis, hypertension, enlarged heart, dilated aorta. ECG: Prolonged A-V conduction	24 (S)*	27 (C)†
J.G.	M	63	Arteriosclerosis, enlarged heart, coronary sclerosis. ECG: Ventricular premature contractions	12 (S)	11 (C)
J.M.	M	66	Arteriosclerosis, myocardial fibrosis, sclerotic aorta. Myocardial infarction in 1940. Diabetes mellitus	11 (S) 18 (C)	11 (C) 16 (S)
S.K.	F	66	Arteriosclerosis, hypertension, enlarged heart, myocardial fibrosis. ECG: Bundle branch block	16 (S)	17 (C)
S.S.	M	65	Arteriosclerosis, enlarged heart, myocardial fibrosis, dilated aorta. ECG: Myocardial damage	29 (C) 48 (S)	42 (S) 49 (C)
M.W.	M	70	Arteriosclerosis, enlarged heart, dilated aorta, myocardial, fibrosis. ECG: Myocardial damage. Myocardial infarction, 1938	30 (S)	11 (C)
F.P.	F	58	Arteriosclerosis, hypertension, enlarged heart, myocardial fibrosis. ECG: Myocardial damage	22 (S) 38 (C)	22 (C) 36 (S)
M.F.	M	47	Arteriosclerosis, myocardial fibrosis, aortic sclerosis. ECG: Myocardial damage. Myocardial infarction, 1942	26 (S) 39 (C)	22 (C) 39 (S)

* (S) Physiological saline.
† (C) Cytochrome C.

up or utilized by the tissues within 5 minutes. However, we were unable to demonstrate any increase in the capacity for effort without pain in patients with angina of effort following intravenous injections of 50 mg of Cytochrome C as compared with placebo injections of physiological saline solution.

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The Delay in the Action of Digitalis Glycoside (Lanatoside C.)*

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Since the studies of Clark[1] were published, it has been believed[2] that after the administration of digitalis glycosides, a latent period occurs before a cardiac effect is produced.

In our previous studies however, concerning the effect of different concentrations of Lanatoside C upon the embryonic duck heart, we observed that although the above described latent period did exist, nevertheless, its duration appeared to vary inversely with the

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1 Clark, A. J., *Proc. Roy. Soc. Med.*, 1912, **5**, 181.

2 Gold, H., Cattell, M., Modell, W., Kurt, N. T., and Kramer, M. L., *Proc.*, 1943, **2**, 80.