there was no evidence of fluid retention. Patient noted a slight decrease in functional ability of right hand on reduction of dosage and increase in interval.

Case No. 6, M.C. Age: 46. Occupation: dietitian. Diagnosis: rheumatoid arthritis. Duration of disease: 38 years. All joints involved. Many joints "burned-out" and ankylosed. Clinical activity most pronounced in right knee. Marked soft tissue swelling in hands and knees with grade II dependent edema in ankles. Patient not given cholesterol but started immediately on 21-acetoxypregnenolone, 300 mg daily. Reduction in swelling noted 48 hours after onset of therapy. Grade ++++ reduction in pain and swelling of right knee noted after 3 days of therapy.

Case No. 7, S. K. Age: 19. Occupation: student. Diagnosis: rheumatoid arthritis. Duration of disease: 3½ years. Joints chiefly involved: knees, metacarpophalangeal joints and interphalangeal joints. This patient was hospitalized for metabolic study, which will be included in a later report. No improvement during 3 days of cholesterol therapy. Significant improvement first noted on 3rd day of administration of 21-acetoxypregnenolone. Evaluation on the 5th day of therapy revealed grade ++++ improvement in swelling, function, and tenderness. Patient noted only minimal stiffness upon arising in morning.

Summary and conclusions. 1. 21-Acetoxypregnenolone was selected for a limited study in 7 ambulatory patients with rheumatoid arthritis because in the rabbit synovial membrane screen it was at least as good as cortisone in decreasing permeability and it showed powerful anti-DOCA action on synovial membrane.

2. The effect on the end organ seen in the screen in rabbits manifested itself in each of the seven patients by reduction in swelling, lessening of the pain, and increased motion in the joints.

Received December 9, 1949. P.S.E.B.M., 1950, v73.

Inotropic Action of Epinephrine, Nor-epinephrine, and N-Isopropyl-Norepinephrine on Heart Muscle.*† (17602)

SOLOMON GARB. (Introduced by McKeen Cattell)

From the Department of Pharmacology, Cornell University Medical College, New York City.

In a recent report, Goldenberg *et al.*(1) stated that "nor-epinephrine hypertension is due to an increase of total peripheral resistance, with no significant change, or even a drop in cardiac output whereas epinephrine hypertension is the result of a significant increase of cardiac output." It is not clear which of the factors that determine cardiac output are responsible for the difference of response to epinephrine and nor-epinephrine. One factor which can be evaluated is the effect of the two substances on the contractile force of myocardium. Krop(2) has shown that epinephrine exerts a marked inotropic action on heart muscle, but similar studies have not been reported with nor-epinephrine. Therefore, a comparison was made of the effects of U.S.P. epinephrine, d-l nor-epinephrine (Arterenol) and N-isopropyl-nor-epinephrine (Isuprel) on the contractile force of heart muscle, in an attempt to determine whether the differences in cardiac output reported by Goldenberg *et al.* are due to a lack of inotropic effect by nor-epinephrine.

* This work was done during the tenure of a New York Heart Association Research Fellowship.

† The author wishes to thank Dr. M. L. Tainter of the Sterling-Winthrop Research Institute who supplied the d-l nor-epinephrine and the N-isopropyl-nor-epinephrine.

1. Goldenberg, M., Pines, K. L., Baldwin, E. deF., Greene, D. G., and Roh, E. C., *Am. J. Med.*, 1948, v5, 792.

2. Krop, S., *J. Pharm. and Exp. Therap.*, 1944, v82, 48.

TABLE I.
Increase in Contractile Force of Heart Muscle Produced by 3 Sympathomimetic Amines.

Muscle	Epinephrine		d-l Nor-Epinephrine		N-Isopropyl-Norepinephrine	
	1:10^7 %	1:10^6 %	1:10^7 %	1:10^6 %	1:10^7 %	1:10^6 %
1	12	45	23	63	44	60
2	13	20	9	14	9	17
3	57	86	139	209	89	176
4	40	70	67	111	71	83
5	79	126	94	169	83	117
Avg	40	69	66	113	59	91

Method. The papillary muscle preparation of Cattell and Gold(3) was used, since it permits the measurement of contractile force without the complications attending studies on intact animals or isolated hearts. The chorda tendina of the isolated muscle was attached to a strain gauge whose output was recorded by a Grass electroencephalograph. The muscle was immersed in oxygenated Locke's solution, and stimulated electrically at a rate of 30 per minute. A series of 5 muscles was studied. After an equilibration period of at least 30 minutes, the contractile force was measured, and a drug added to produce a total concentration of 1:10,000,000. After 2 minutes, the contractile force was measured again, and the concentration of the drug was then raised to 1:1,000,000, and further measurements made, before the onset of a spontaneous rhythm. The drug was then removed, the chamber rinsed, and fresh Locke's solution added. After another equilibration period of at least 15 minutes, a new control reading was taken, and the procedure repeated with another drug. The sequence in which the drugs were tested on the 5 muscles was varied.

Results. The results were expressed as percentage of increase of the control force of contraction (Table I). All of the drugs studied produced an increase in the force of contraction of each muscle. There was a considerable variation in the degree of the increase, so that accurate quantitative relationships between the drugs cannot be derived from this study. Nevertheless it is clear that both d-l nor-epinephrine and N-isopropyl-norepinephrine exert an inotropic action on heart muscle which is at least as great as that produced by U.S.P. epinephrine.

Discussion. Since many factors other than contractile force determine cardiac output, these results cannot be interpreted as evidence against the conclusions of Goldenberg *et al.*(1) However, they indicate that the differences in cardiac output which these authors reported are probably not due to a lack of inotropic effect by d-l nor-epinephrine.

Summary and conclusions. d-l Nor-epinephrine (Arterenol) and the N-isopropyl-norepinephrine (Isuprel) exert a powerful inotropic action on mammalian heart muscle.

3. Cattell, McK., and Gold, H., *J. Pharm. and Exp. Therap.*, 1938, v62, 116.

Received December 19, 1949. P.S.E.B.M., 1950, v73.