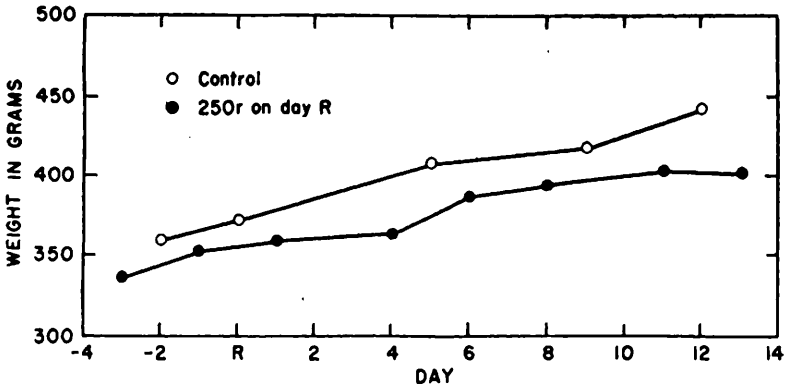

FIG. 1. Comparison of the mean weights in a typical lot of 4 guinea pigs from Exp. 1 with their corresponding litter mates given 250 r on day R.

termined for their nonirradiated litter mates up to 13 days following irradiation.

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Received August 25, 1952. P.S.E.B.M., 1952, v81.

Inotropic Action of Acetyl-Strophanthidin, Strophanthidin, and Tryptamine-Strophanthidin.* (19804)

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The partially synthetic ester, acetyl-strophanthidin. which has an extremely rapid onset of action after intravenous injection, has been suggested for use when digitalis action is urgently needed(1). It has proved valuable for slowing the ventricular rate in patients with auricular fibrillation, and for revision of paroxysmal auricular tachycardia(1,2). In pulmonary edema with normal sinus rhythm, where it has also been used, its value cannot be proven, for an experiment withholding other therapeutic measures would risk the life of the patient. Recently the clinical use of acetyl-strophanthidin has been challenged by Wedd and Blair. In strips of turtle ventricle they found that it failed to shorten the interval between action potentials (interpreted as the Q-T interval) without impairing contractility(3). Since digitalis glycosides do shorten the "Q-T interval" of turtle ventricle(4), Wedd and Blair concluded that acetyl-strophanthidin is not a digitalis-like substance, and that all its therapeutic benefit is due to vagal stimulation.

If acetyl-strophanthidin does not have a typical digitalis action, its use in patients with pulmonary edema and sinus rhythm should be discontinued. A reexamination of acetyl-

* This investigation was supported in part by a research grant from the National Heart Institute of the National Institutes of Health, U.S.P.H. Service, and in part by the Digitalis Fund of the Department of Pharmacology, Cornell University Medical College.

TABLE I. Effect of Strophanthidin Derivatives on Force of Contraction of Hypodynamic Myocardium.

Drug	No. of muscles	Avg hypodynamic contraction (% of initial force)	Drug response	
			Conc. (molar × 10^{-7})	Avg improvement in contraction (% of hypodynamic force)
Acetyl-strophanthidin	7	20	2.25	355
			4.5	770
Strophanthidin	3	28	4.5	212
			9	301
			13.5	381
Tryptamine-strophanthidin	4	19	4.5	333
			9	471

strophanthidin was indicated, with special attention to its effect on the force of contraction of failing myocardium free of nervous influence. For this purpose we utilized the papillary muscle from the right ventricle of the cat heart, as described by Cattell and Gold(5). In addition to acetyl-strophanthidin, strophanthidin, and tryptamine-strophanthidin were studied.†

Method. Details of the method may be found in a recent publication by Garb and Chenoweth(6). Suitable papillary muscles were rapidly excised, immersed in oxygenated Krebs-Ringer phosphate, and stimulated electrically at the rate of 40 contractions per minute. The cordi tendeni were tied to a tension lever with a mirror attached, and the contractile force recorded by the deflection of a light beam on a fixed scale. When the force of contraction had failed to about 25% its initial value, one of the compounds was added to the solution bathing the muscle, and the force measured at intervals for a period of hours. In many experiments the concentration of drug was increased after the force of contraction had reached a steady state. The concentration of each substance was chosen to approximate the value expected in the blood of human patients following intravenous injection of a therapeutic dose.

Results. Each of 14 hypodynamic papillary muscles developed an increase in force of contraction following one of the strophanthidin derivatives. The results are summarized in Table I. The inotropic response of each muscle lasted throughout the period of observation of from 2 to 8 hours, average duration 4.3 hours. Molecule for molecule, acetyl-strophanthidin was more potent than the other 2 compounds. Occasional extrasystoles were noted in one muscle which received acetyl-strophanthidin and one which received tryptamine-strophanthidin. In Fig. 1, acetyl-strophanthidin induced an inotropic response which persisted until the experiment was discontinued 6 hours later. The response of the muscle that received strophanthidin illustrates the common trend in which increased force of contraction follows each increase in concentration. The final concentration of strophanthidin in Fig. 1 (2.7×10^{-6} M) produced the typical sharp rise and rapid decline in force of contraction seen as the toxic effect of digitalis glycosides(7). There were also extrasystoles, increase in resting tension, and increase in the threshold of excitability. Another muscle, placed in 9.0×10^{-7} M acetyl-strophanthidin, showed similar toxic effects.

Discussion. The direct myocardial action of digitalis was first demonstrated by Cattell and Gold(5) with the isolated papillary muscle preparation. They observed that digitalis increases the force of contraction of failing mammalian heart muscle. Later, Gold and Cattell(8) concluded that this direct action is the primary therapeutic mechanism of digitalis. Their conclusion has aroused controversy, but no substantial evidence has weakened it; the data available in patients with heart disease, congestive failure, and sinus rhythm(9,10) are best interpreted by accepting the view that increased force of contraction is the mechanism of digitalis effect. Despite the agreement of laboratory and clinical evidence, there are no universally accepted criteria which distinguish a drug as

† These compounds were supplied through the courtesy of Dr. K. K. Chen of Eli Lilly and Co.

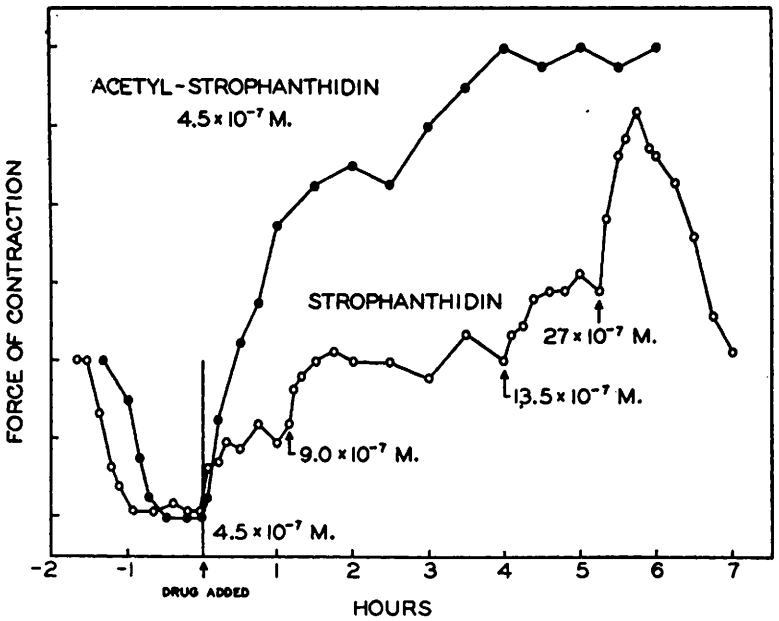

FIG. 1. Force of contraction of 2 representative papillary muscles illustrating the hypodynamic state, and the inotropic response to strophanthidin derivatives. The concentration of drug is given in molarity of the fluid bathing the muscle. The responses are similar to those from digitalis glycosides.

having the effect of digitalis. Changes in action potential, such as those described in strips of turtle ventricle, are sometimes used to characterize digitalis-like drugs. It should be noted that the relation between electrical activity and the therapeutic action of digitalis is not clear. Furthermore, the calcium ion, long associated with digitalis effect, is known to influence action potential and contractile force independently(11).

The effect on force of contraction might well be the critical issue in determining whether a drug is to be considered similar to digitalis, and for resolving that question, the isolated hypodynamic papillary muscle is the most convenient laboratory preparation. The concentration of drug in its bath fluid must be in the range possible after intravenous injection of digitalizing doses in human patients (the dose determined by slowing of the ventricular rate in patients with auricular fibrillation). As pointed out by Gold(12), with the proper concentration of the drug, only digitalis yields an improvement in contractile force of the papillary muscle which persists for many hours. The ester, acetyl-strophanthidin, the genin, strophanthidin, and the tryptamine derivative of strophanthidin increased the force of contraction of failing myocardium, and did so in concentrations provided by intravenous injections in patients with auricular fibrillation(1,13,14). Thus they meet our criteria for a digitalis-like substance. Acetyl-strophanthidin was the most potent of the 3 on the papillary muscle, just as it is in human patients.

Previous clinical investigations have established the value of acetyl-strophanthidin for the control of acute congestive failure with auricular fibrillation, and for the revision of paroxysmal auricular tachycardia(1,2). Its special advantage lies in facilitating rapid digitalization by the common scheme, in which a safe dose is given first, and then additional small doses are given until the therapeutic response or minor toxic symptoms appear. In order to avoid serious toxicity, additional doses must be delayed until the full effect of the previous doses has developed. The rapid onset of action of acetyl-strophanthidin reduces the interval between doses to 10 minutes (as compared to one hour for

ouabain), and provides the fastest digitalization possible with preparations now in use(1). The present demonstration of its positive inotropic action supports the continued use of acetyl-strophanthidin as one of the emergency measures in the treatment of acute congestive failure with pulmonary edema in the presence of normal sinus rhythm.

Summary and conclusions. 1. Papillary muscles from the right ventricle of the cat heart were stimulated in phosphate-buffered Krebs-Ringer solution until their force of contraction declined. 2. On addition of acetyl-strophanthidin, tryptamine-strophanthidin, or strophanthidin to the papillary muscles, their force of contraction improved, and the improvement persisted throughout the period of observation (average 4.3 hours). 3. It is concluded that these strophanthidin derivatives have a typical digitalis action on failing mammalian heart muscle.

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Received August 25, 1952. P.S.E.B.M., 1952, v81.

Poliomyelitis Viruses in Tissue Culture. III. Susceptibility of Testicular Tissue from Immune Monkeys.* (19805)

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Tissue culture technics have been applied in the study of poliomyelitis to the propagation of laboratory-adapted strains of the virus (1-8), to the quantitative estimation of virus and antibody(9-11), and to the isolation and immunologic identification of poliomyelitis viruses from various sources(12-14). The use of monkey testicular tissue by some investigators for these purposes raises a question of both theoretical and practical importance, *i.e.*, whether poliomyelitis viruses may be propagated in cultures of testicular tissue obtained from monkeys immune to these viruses. In an attempt to answer this, a comparison was made of the susceptibility of testicular tissue obtained from both immune and non-immune monkeys to poliomyelitis viruses. Observations of this nature also bear on the use of human tissues for the cultivation of poliomyelitis virus, for these are usually obtained from individuals whose immune status is unknown.

Materials and methods. Tissue cultures. Roller tube cultures were employed in these

* Aided by a grant from the National Foundation for Infantile Paralysis.

† Sheffield Fellow of Yale University 1950-1952. The data presented in this paper form part of a thesis presented by N. L. to the Graduate School of Yale University in partial fulfillment for the degree of Doctor of Philosophy.