TABLE I. Range of Arterial Pressure in 400 Street Dogs.

| Mean systolic pressure in mm Hg | 100–110 | 111–120 | 121–130 | 131–140 | 141–150 | 151–156 | 175 | 205 |
|---|---|---|---|---|---|---|---|---|
| No. of dogs | 19 | 82 | 123 | 114 | 53 | 7 | 1 | 1 |

tively normal renal clearances of 3 dogs with sustained elevation of arterial pressure studied by Stamler, Katz and Rodbard(1); the clearance rates of one of these were 10.2 (effective renal plasma flow) and 3.5 (glomerular filtration rate) cc per kg per minute. No data are available as to the appearance of the kidneys of this animal; however, the kidneys of the other two, whose renal plasma clearances were somewhat more depressed below mean normal did show "slight to moderate chronic focal lesions". Thus, renal plasma clearances while within the range of normal have been found to lie below the normal mean in 5 dogs with seeming spontaneous hypertension; 4 of these for which data are available demonstrated renal lesions at autopsy.

Focal lesions, such as occur in some dogs with experimental renal hypertension, do not necessarily depress plasma clearances (Corcoran and Page(4)) so that normal rates of plasma clearance are observed in some dogs with experimental renal hypertension(1,4). Demonstration of normal or slightly subnormal rates of plasma clearance in dogs found to be hypertensive does not therefore establish that the hypertension is of extrarenal origin. Actually, focal or diffuse renal lesions are not uncommon in dogs (Bloom(5)), and it would be surprising if these did not sometimes elicit renal hypertension. Hamilton *et al.*(6) observed that dogs with hyalinized arterioles and with glomerular nephritis have higher pressures than the average population.

*Summary.* Hypertension resembling "clinical essential" hypertension may occur in dogs, but the weight of the evidence inclines us to the view that this condition must be very rare; what seems to be "spontaneous" canine hypertension is usually attributable to renal disease. The relatively narrow spread of arterial pressures in this series of street dogs indicates that the skill of the observer is at least as important as the training of the dog.

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## Action of 3-Acetyl-Strophanthidin in Isolated Mammalian Heart.* (20565)

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An ester of strophanthidin, 3-acetyl-strophanthidin, has been found to be effective for slowing ventricular rate in auricular fibrillation and for treating paroxysmal tachycardia. After intravenous administration, the onset of action is rapid and the duration of effect is relatively short(1). However, the positive inotropic action of 3-acetyl-strophanthidin has been questioned by Wedd and Blair(2) who found marked differences in the response of the turtle heart to digitalis and to 3-acetyl-strophanthidin. From their results, the authors concluded that this ester cannot be an

* We are indebted to Messrs. Thomas Lenahan and Darrell Caldwell for their capable assistance in these experiments.

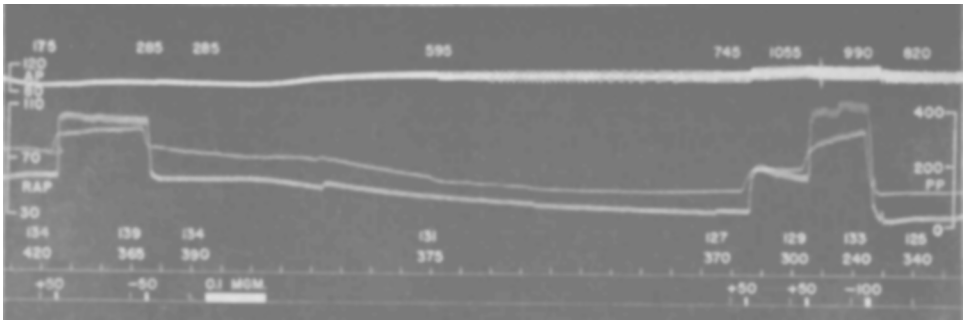

FIG. 1. Action of 3-acetyl-strophanthidin on the failing dog heart. Heart-lung preparation. Wt of heart-lung dog, 11.4 kg. Approximate blood vol 850 ml. Arterial resistance 48 mm mercury. Tracings from top to bottom: arterial blood pressure (scale on left in mm of mercury); pulmonary pressure (scale on right in mm of water); right auricular pressure (scale on left in mm water); time in 1-min. intervals; signal. Horizontal rows of figures from top to bottom: systemic output in ml/min., heart rate per min., reservoir vol in ml, and changes in inflow level in mm. At signal, 0.100 mg 3-acetyl-strophanthidin inj.

effective cardiac drug with digitalis-like action. Using the cat papillary muscle preparation, Greiner and Reilly(3) were able to demonstrate that 3-acetyl-strophanthidin has a positive inotropic action and that, mole for mole, it is more effective than strophanthidin. They concluded that the clinical use of 3-acetyl-strophanthidin is justified and that the effects seen in patients are due to its rapid digitalis-like action.

Although Greiner and Reilly employed mammalian heart muscle, they did not study the effect of the drug on the entire heart. Since the question of the presence or absence of a positive inotropic action of 3-acetyl-strophanthidin is of major importance for its clinical use, experiments were performed using the heart-lung preparation of the dog in order to compare the cardiac action of this ester with that of ouabain.

*Method.* Mongrel dogs of either sex, weighing from 8.9 to 12.4 kg, were used in all experiments. The animals were fasted for 18 hours and were then anesthetized with Secobarbital Sodium.† Heart-lung preparations were made as described by Krayer and Mendez(4). Systemic output was measured with a rotameter‡ and the float level read visually each minute. Heart rate was recorded on an ink-writing oscillograph. The initial total blood volume varied from 800 to 900 ml. Heart failure was produced by the administration of 50 to 80 mg of Secobarbital Sodium injected into the inflow tubing in divided doses. Ouabain and 3-acetyl-strophanthidin§ were prepared as 1:1000 stock solutions in 47.5% ethanol. Fresh dilutions of the stock solutions were made daily in 0.9% sodium chloride solution.

*Results.* Two experiments were performed with ouabain and four with 3-acetyl-strophanthidin. That 3-acetyl-strophanthidin does produce a positive inotropic effect in the failing dog heart can be seen clearly in Fig. 1. During the production of cardiac failure the systemic output had decreased from 840 to 285 ml/min and both the right auricular and pulmonary arterial pressures had increased greatly. Within 2 minutes after the injection of 100 $\mu$g of 3-acetyl-strophanthidin into the inflow tubing, the right auricular pressure began to decrease and the systemic output increased. Ten minutes after the injection the right auricular and pulmonary pressures had returned nearly to normal and the systemic output had increased to above its initial value. Although the ability of the heart to compensate for an increased work load (increased venous inflow) was not completely restored to its initial status, it was greatly improved.

In Table I are summarized 2 experiments in which repeated doses of ouabain or of 3-acetyl-strophanthidin were administered until toxic

† 'Seconal Sodium' (Secobarbital Sodium, Lilly).

‡ The rotameter was made by C. Wilson of the Lilly Clinic.

§ The 3-acetyl-strophanthidin was prepared in our laboratories by Mr. John S. Welles.

TABLE I. Effect of Repeated Doses of Ouabain or 3-Acetyl-Strophanthidin on the Isolated Dog Heart.

| Time, min. | Systemic output, ml/min. | Heart rate/min. | Arterial pressure, mm Hg | Pulmonary pressure, mm $H_2O$ | Right auricular pressure, mm $H_2O$ | Competence index* | Reservoir vol, ml | Blood temp., °C |
|---|---|---|---|---|---|---|---|---|
| | | | Experiment 31 | | | | | |
| 5 | 595 | 137 | 95 | 65 | 35.0 | | 630 | 38.2 |
| 8 | | | | | | .90 | | |
| 15 | Secobarbital sodium—50 mg | | | | | | | |
| 35 | " | " | 20 " | | | | | |
| 53 | " | " | 10 " | | | | | |
| 70 | " | " | 10 " | | | | | |
| 74 | 265 | 126 | 79 | 175 | 68.5 | | 485 | 38.0 |
| 77 | | | | | | .24 | | |
| 82 | 280 | 125 | 80 | 180 | 68.5 | | 470 | 37.9 |
| 83 | O†—50 μg | | | | | | | |
| 92 | 285 | 123 | 83 | 160 | 63.5 | | 470 | 38.0 |
| 93 | O — 20 μg | | | | | | | |
| 100 | 330 | 122 | 87 | 150 | 60.5 | | 465 | 38.0 |
| 101 | O — 50 μg | | | | | | | |
| 110 | 415 | 121 | 93 | 125 | 53.5 | | 460 | 38.1 |
| 111 | O — 50 μg | | | | | | | |
| 116 | 480 | 107 | 96 | 105 | 46.5 | | 460 | 38.4 |
| 117 | C† | | | | | | | |
| | | | Experiment 27 | | | | | |
| 3 | 675 | 131 | 109 | 60 | 29.5 | | 520 | 38.0 |
| 12 | | | | | | .93 | | |
| 26 | Secobarbital sodium—50 mg | | | | | | | |
| 39 | " | " | 50 " | | | | | |
| 43 | 330 | 136 | 102 | 170 | 66.5 | | 350 | 37.5 |
| 45 | | | | | | .09 | | |
| 48 | 335 | 136 | 100 | 175 | 73.5 | | 305 | 37.2 |
| 49 | 3-A†—50 μg | | | | | | | |
| 63 | 470 | 132 | 108 | 100 | 55.5 | | 350 | 37.9 |
| 65 | | | | | | .35 | | |
| 72 | 510 | 131 | 110 | 90 | 50.5 | | 360 | 38.0 |
| 73 | 3-A — 50 μg | | | | | | | |
| 82 | 605 | 128 | 113 | 60 | 43.5 | | 380 | 38.0 |
| 84 | | | | | | .89 | | |
| 93 | 595 | 129 | 114 | 55 | 40.0 | | 335 | 37.8 |
| 94 | 3-A — 50 μg | | | | | | | |
| 97 | 595 | 128 | 113 | 50 | 39.0 | | 320 | 38.0 |
| 99 | C† | | | | | | | |

* Competence index(5) is the ratio: $\frac{\text{Increase in inflow level—increase in right atrial pressure}}{\text{Increase in inflow level}}$

Although both 50 and 100 mm increases in inflow level were used in the experiments, only the effects caused by the 50 mm rise were used to compute the competence index.

† O = Ouabain; 3-A = 3-Acetyl-strophanthidin; C = Cardiac irregularities started.

effects (as evidenced by cardiac irregularities) were produced. A total dose of 170 μg of ouabain was necessary, under these circumstances, to produce cardiac irregularities. When 3-acetyl-strophanthidin was administered to another preparation in a similar manner, cardiac irregularities began after administration of 150 μg. Although only one experiment has been performed with each substance administered in this manner, it is clear that they are very similar with regard to potency, toxicity, and ratio between therapeutic and toxic doses.

The dose producing a clear-cut positive inotropic action is about 75 μg for ouabain and 100 μg for 3-acetyl-strophanthidin. In the second experiment with ouabain, cardiac irregularities, beginning about 20 minutes after administration of the glycoside, were produced by 75 μg.

When 3-acetyl-strophanthidin was used, irregularities were produced by 150 μg in each

of 3 experiments and 350 $\mu$g in the fourth.

*Discussion.* The cardiac action of 3-acetyl-strophanthidin has been shown to be a positive inotropic one in the dog heart-lung preparation. This confirms the positive inotropic response of the cat papillary muscle found by Greiner and Reilly(3), and indicates that the therapeutic action of the drug in man is similar to that of digitalis. Apparently, the cold-blooded turtle heart used in the experiments of Wedd and Blair(2) reacts in a different manner to different cardiac drugs than does the warm-blooded mammalian heart.

The experiments reported here are not sufficient in number to permit any quantitative comparison of the activity of ouabain and 3-acetyl-strophanthidin, but the results indicate that the two drugs have approximately the same therapeutic and toxic potencies. This would agree with the comparative toxicity of the two substances as measured by the cat lethal dose assay. The mean (geometric) cat lethal dose is 0.116 mg/kg for ouabain(6) and 0.1866 mg/kg for 3-acetyl-strophanthidin(7).

*Summary.* In the failing heart-lung preparation of the dog, 3-acetyl-strophanthidin has been found to produce a positive inotropic effect comparable to that produced by ouabain.

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## Esophagitis in Dogs Following Operations Employed in the Treatment of Mega-Esophagus.* (20566)

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The most severe complication resulting from the operative treatment of mega-esophagus, esophageal dystonia, or cardiospasm is chronic esophagitis. Indeed, this may become more disabling than the original condition which the operation was designed to correct. This study was devised to determine, in dogs, the incidence of esophagitis following the two standard surgical procedures for the treatment of mega-esophagus which have been most popular in recent years. These are the Heller operation and the Wendel operation, which are described in detail below.

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*Materials and methods.* Mongrel dogs weighing 8 to 16 kg were used in this study. Pentobarbital sodium was administered intravenously in a dosage of 30 mg per kg of body weight for anesthesia, and a mechanical respirator was used during surgery. The esophagogastric junction was exposed through an incision in the 10th left intercostal space, and where necessary the stomach and pyloroduodenal junction could be delivered easily into the chest by enlarging the esophageal hiatus. The Heller operation consists of an extramucous myotomy of the esophagogastric junction. In this study, the myotomy was made by incising the muscularis of the distal 4 to 5 cm of the esophagus and proximal 4 cm of the stomach longitudinally down to the submucosa with a sharp knife. Care was taken to leave no muscle fibers undivided. The Wendel procedure consists of a longi-