closed after the cataract developed the opacity cleared completely in about 60 minutes, even in a dead animal. Usually the opacity cleared first in the center of the anterior cortex, but occasionally random eccentric areas cleared first. Focal pressure on the opaque lens, through the intact cornea, immediately cleared that area of the lens compressed (Fig. 4).

Biomicroscopy with a slit beam 20 to 30 minutes after a cataract was well formed, showed that the anterior chamber or space between the iris and the cornea was narrowed very markedly in the cataractous eye as compared to the control eye. After maximal cataract development, the cataractous eye was notably softer and there was roughening of the corneal epithelium.

Discussion. Dehydration appears to be important in the pathogenesis of these lens opacities but may not be the only factor, since the opacity reverses while the dehydrating stimulus is still active. Investigations of lens and aqueous humor changes as well as atmospheric factors are in progress.

Summary. Several highly effective methods for production of unilateral reversible cataracts in hamsters are described. With each method, the eyelids must remain open to expose the cornea, and the lens opacity which develops will clear even if the eyelids remain open, but will clear more rapidly if the lids are closed. No cataract develops if the eyelids are kept closed or protected by an air tight seal. The mechanisms involved are being investigated.

The authors express gratitude to Lois Willenberg for valuable assistance.

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Received March 16, 1962. P.S.E.B.M., 1962, v110.

Acute Systemic and Coronary Hemodynamic Effects of Trimethidinium Methosulfate.* (27428)

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Ganglionic blocking agents have been used extensively in treatment of essential hypertension; however, none seem to be universally effective and all have limitations. The search for better blocking agents has led recently to development of a new synthetic compound, trimethidinium methosulfate, an asymmetric bis-quaternary amine. Pharmacological studies of this compound showed that ganglion blocking properties and hypotensive responses do not run necessarily parallel. Furthermore it has been suggested that the drug may have a central component of action(1). Clinical evaluation of trimethidinium methosulfate showed that it has a hypotensive action similar to that of other ganglionic blocking agents(2,3,4,5,6,7). Associated side effects on the gastrointestinal tract are reported to be mild and easily controlled when compared with those of pentapyrrolidinium and mecamylamine(5).

The following study of the hemodynamic effects of trimethidinium methosulfate on systemic and coronary circulations was undertaken in the hope that the information obtained would be of some value in guiding the clinician in his selection of therapeutic agents.

Material and methods. The present study was carried out in 10 mongrel dogs weighing

* Supported in part by grants from Nat. Heart Inst., U.S.P.H.S., Wisconsin Alumni Research Foundation, and Wisconsin Heart Assn.

TABLE I. Systemic and Coronary Hemodynamic Effects of Trimethidinium Methosulfate on the Dog.

	Control	Drug	% change	P value <
Cardiac rate	75 ± 17 †	143 ±25 †	+90.7	.001
Mean systemic arterial blood pressure (mm Hg)	117 ± 11	97 ±13	−17.1	.01
Mean pulmonary arterial blood pressure (mm Hg)	13 ± 2	10 ± 2	−28.1	.001
Mean right atrial blood pressure (mm Hg)	3.6 ± 1.2	1.6 ± .8	−55.6	.001
Minute vol respiration (l/min.)	2.4 ± .7	3.1 ± .9	+29.2	.001
Mixed venous carbon dioxide content*	52.8 ± 3.0	51 ± 3.3	− 3.4	.01
Arterial carbon dioxide content*	50.2 ± 3.0	48.1 ± 3.7	− 4.2	.001
Coronary sinus oxygen content*	5.1 ± 1.5	3.7 ± .7	−27.5	.02
Arterial coronary sinus oxygen difference*	10.8 ± 1.5	12.4 ± 1.1	+14.8	.01
Coronary sinus arterial carbon dioxide difference*	8.7 ± 1.6	10.8 ± 1.2	+24.1	.001
Cardiac respiratory quotient	.81± .1	.87± .05	+ 7.4	.02
Total pulmonary resistance (cgs units)	400 ±114	322 ±61	−19.5	.05
Left ventricular work (kg M/min.)	4.1 ± 1.1	3.2 ± 1.2	−22.0	.05
Right ventricular work (kg M/min.)	.4 ± .1	.3 ± .1	−25.0	.05
Stroke volume (ml)	35 ± 2	16 ± 2	−54.3	.001
Index of efficiency, LVW/$CMRO_2$	.41± .07	.29± .06	−29.3	.001

* (ml/100 ml blood). † ± S.D.

between 13 and 25 kg and averaging 18 kg. Anesthesia was secured by subcutaneous administration of 3 mg/kg of morphine sulphate followed 1 hour later by 0.25 ml/kg of a 50/50 mixture of veterinary pentobarbital and Dial-urethane.† During the ensuing hour after administration of the anesthetic, cardiac catheters were placed in the pulmonary artery, coronary sinus and right atrium and an indwelling needle was placed in the femoral artery. Complete air collection was insured by placing a cuffed endotracheal tube connected through a non-rebreathing valve to a Tissot spirometer and a 3-way stopcock which permitted rapid change from inhalation of room air to inhalation of a mixture of 21% oxygen, 64% nitrogen and 15% nitrous oxide. Cardiac output was determined by the Fick principle and coronary blood flow by the nitrous oxide saturation method. Pressures were measured by Statham strain gages with the mean pressure determined by electrical integration on the Gilson macropolygraph. Cardiac rate was measured from an appropriate electrocardiographic lead. pH was measured by the Cambridge model R pH meter. Analyses for nitrous oxide were done by the method of Orcutt and Waters whereas oxygen and carbon dioxide contents of expired air were determined by use of the Scholander apparatus.

After control measurements the drug was administered intravenously in a single injection through the catheter in the coronary sinus. The dose used was 0.25 mg/kg in 9 dogs and 0.175 mg/kg in one dog. The second determination of cardiac output and coronary blood flow was done an average of 26 minutes after administration of the drug.

Results. The results summarized in Table I reveal that after administration of trimethidinium there were significant decreases in systemic arterial blood pressure ($p<0.01$), pulmonary arterial blood pressure ($p<0.001$) and right atrial mean blood pressure ($p<0.001$) accompanied by an increase in cardiac rate ($p<0.001$) and in minute volume of respiration ($p<0.001$), but without significant change in oxygen consumption, carbon dioxide excretion or body respiratory quotient. Although there was significant reduction in mixed venous ($p<0.01$) and systemic arterial carbon dioxide contents ($p<0.001$) there was no significant change in the arterio-venous difference for either oxygen or carbon dioxide. The coronary sinus oxygen content decreased significantly ($p<0.02$), and there was significant widening of the arterio-coron-

† Dial-urethane, furnished by the courtesy of Dr. A. J. Plummer, CIBA Pharmaceutical Products, Inc., Summit, N. J., contains Dial 100 mg/ml, monoethylurea 400 mg/ml, and urethane 400 mg/ml. Veterinary pentobarbital contains 60 mg/ml of pentobarbital.

ary sinus oxygen difference ($p<0.01$) as well as widening of the arterio-coronary sinus carbon dioxide difference. Cardiac respiratory quotient increased slightly but significantly ($p<0.02$).

Calculated cardiac output and total peripheral vascular resistance decreased slightly but not significantly whereas total pulmonary resistance decreased significantly ($p<0.05$). As a result of the slight decrease in cardiac output and more pronounced and consistent decrease in systemic and pulmonary arterial pressures, both right and left ventricular works were reduced. Coronary blood flow decreased slightly but not significantly. Myocardial oxygen consumption and coronary vascular resistance did not change significantly in this series, nor were there significant changes in the hemoglobin, hematocrit, arterial or coronary sinus pH. The calculated index of cardiac efficiency (cardiac work divided by cardiac oxygen consumption) decreased significantly ($p<0.001$).

Discussion. Previous studies have shown that the hypotensive action of ganglionic blocking agents, *e.g.*, hexamethonium(8), pentolinium(9) and mecamylamine(10) could be accounted for largely on the basis of a decreased cardiac output. In the present study the systemic mean arterial blood pressure decreased significantly while the changes in cardiac output and total peripheral resistance were not statistically significant. Five of the 10 dogs studied showed considerable decreases in total peripheral resistance associated with slight changes in cardiac output, whereas in 3 dogs cardiac output decreased considerably and total peripheral resistance rose or did not change. These data are in agreement with those of Kirkendall *et al.*(6) who found that in man given trimethidinium there was a wide scatter in total peripheral resistance. The results also confirm the observations concerning ganglion blocking drugs of Grob and associates(11), Trapold(12) and Rowe *et al.*(10), that if cardiac output rises or does not decrease peripheral resistance falls, but when cardiac output decreases significantly total peripheral resistance rises or does not fall.

These observations therefore indicate that the hypotensive responses to trimethidinium are related to the combined changes in cardiac output and peripheral vascular resistance. The possibility that a portion of the hypotensive effect is due to a central component of action(1) is not excluded in this study. A striking finding in the data is the statistically significant increase in cardiac rate ($+90.7\%$, $p<0.001$). Similar responses in heart rate have been reported with hexamethonium(8) and mecamylamine(10). Though acceleration is probably related to hypotension the mechanisms concerned are not understood.

Coronary blood flow and coronary vascular resistance in this study did not change. For similar increases in heart rate ($+110\%$, $p<0.001$), Maxwell *et al.*(13), in a study of induced tachycardia, reported an increase in coronary blood flow ($+83\%$, $p<0.001$) and a decrease in coronary vascular resistance (-42%, $p<0.01$). The explanation for this discrepancy is unknown.

As in previous studies with hexamethonium (8), mecamylamine(10), and SKF 6890(14) the arterio-coronary sinus oxygen difference in this study increased ($+14.8\%$, $p<0.01$) indicating that the myocardial metabolic needs for oxygen are met by a greater oxygen extraction. The decrease in cardiac efficiency (left ventricular work/myocardial oxygen consumption) demonstrated in this study as well as in preceding studies of hexamethonium (8) and mecamylamine(10) may well be the effect of the considerable increase in cardiac rate.

Under the experimental conditions of this study, the hemodynamic effects of trimethidinium are similar to those of the previously mentioned ganglion blocking agents.

Summary. 1. The acute hemodynamic effects of trimethidinium methosulfate have been studied in 10 mongrel dogs. 2. Administration of the drug results in a decrease in blood pressure in the systemic and pulmonary arteries and the right atrium. 3. Associated with these decreased pressures, the stroke volume decreased, but there was sufficient increase in cardiac rate so that cardiac output did not change significantly. Pulmonary vascular resistance decreased significantly where-

as peripheral resistance fell slightly but not significantly. 4. Both right and left ventricular work decreased significantly while left ventricular myocardial oxygen consumption was unchanged and calculated cardiac efficiency decreased. 5. These hemodynamic effects are similar to those of hexamethonium, pentolinium, mecamylamine and SKF 6890.

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Received January 15, 1962. P.S.E.B.M., 1962, v110.

Serotonin Metabolism in Paralysis Agitans.* (27429)

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An abnormality of serotonin release or metabolism in paralysis agitans is suggested by two lines of evidence. In the first place, the mesencephalic and diencephalic structures contain the highest 5-hydroxytryptamine (5-HTA) content in human brain(1). Certain anatomic foci within these areas—the substantia nigra, globus pallidus and locus caeruleus—appear to undergo cellular destruction in paralysis agitans(2). Secondly, extrapyramidal syndromes may be pharmacologically induced by agents which release 5-HTA from tissue stores (*i.e.*, reserpine)(3) or exert chemical antagonism to serotonin (*i.e.*, phenothiazine derivatives)(4,5).

The purpose of this study is to investigate the urinary excretion of 5-hydroxyindole compounds in patients with paralysis agitans under basal conditions and following administration of the serotonin precursor, 5-hydroxytryptophan. The latter procedure has been utilized to detect the possible existence of impaired decarboxylation and/or oxidative deamination(6).

Procedure. Patients. This report concerns metabolic observations in 10 cases of paralysis agitans and 12 (control) patients afflicted with other neurologic diseases, including cerebrovascular accidents, multiple sclerosis, anoxic brain disease, spastic paraplegia, and peripheral neuropathy. All were hospitalized within the same ward, permitting some control of nutrition and physical activity. Cases selected for investigation were free of liver dysfunction(6) and azotemia, and did

* This work was supported in part by grants from U. S. Public Health Service and Gastrointestinal Fund of Peter Bent Brigham Hospital.