

Effects of Atropine and Scopolamine on the Cardiovascular System in Man

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The cardiovascular effects of atropine and scopolamine were compared in male volunteers. The bases of atropine and scopolamine were found to be equipotent. Scopolamine was faster in onset and shorter in duration of action. Both exerted their principal effect on heart rate; low doses decreased and large doses accelerated heart rate. Cardiac output changed parallel to the changes of heart rate. Stroke volume was not affected. Both atropine and scopolamine were equally effective in enhancing the action of mephentermine on heart rate and blood pressure.

ATROPINE and scopolamine are among the most frequently and commonly used agents in anesthesia, yet a comparative study of the cardiovascular effects of these two drugs in healthy man, has, to our knowledge, not been published. The effects of atropine and scopolamine on blood pressure, heart rate, and cardiac output in normal man were therefore measured.

According to classic concepts of physiology, increased sympathetic tone will trigger a reflex resulting in increased parasympathetic activity. Hence the blocking of cholinergic receptors with atropine or scopolamine should cause greater changes after the injection of a sympathomimetic drug than before such an injection. Effects of atropine and scopolamine not seen in the resting subject might emerge in subjects with increased parasympathetic tone, and possible differences between the two belladonna drugs might manifest themselves here more clearly than in subjects with normal parasympathetic activity. We chose to elicit increased parasympathetic tone by injecting mephentermine (Wyamine), a long-lasting sympathomimetic amine.

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Methods

Six male students without known cardiovascular disease served as subjects. Four subjects participated in all experiments. The remaining two students were present in only one experiment each. The subjects fasted and were studied early in the morning after they had rested for at least one hour in the supine position. The radial artery was cannulated with an 18-gauge Courmand needle, the cephalic vein with a 17-gauge, 12 inch plastic catheter which was advanced into the subclavian vein. Arterial pressure was recorded continuously using a Statham transducer and a Grass polygraph. Cardiac output was determined by the dye dilution method with indocyanine green* and a Colson densitometer. Heart rate was counted from an ECG tracing, total peripheral resistance was calculated in the conventional way from mean arterial blood pressure and cardiac output. The mean blood pressure was assumed to be equal to the diastolic pressure plus one-third of the pulse pressure.

Commercially available solutions of atropine sulfate (Lilly) and scopolamine hydrobromide (Burroughs Wellcome) were used. Atropine sulfate contains 833 μg . base per milligram of the salt, and scopolamine hydrobromide contains 692 μg . of the base per milligram of the salt.¹ The sulfate salt of mephentermine (Wyamine, Wyeth Laboratories) was used. All doses are expressed as the weight of the base. All medications were given intravenously in single injections. After each dose the tubing was quickly flushed with 10 ml. of normal saline.

For a meaningful comparison it was neces-

* Cardio-Green was supplied by the Pharmaceutical Laboratory of Hynson, Westcott & Dunning, Inc.

TABLE 1. Effects of Atropine and Scopolamine
Mean Differences Between Control Values and Values After Atropine and
Scopolamine Injections Are Given

	Four Minutes After Dose I		Four Minutes After Dose III		Ten Minutes After Dose III	
	A†	S‡	A	S	A	S
Systolic pressure (mm. Hg)	+1.0	-0.6	+2.6	+7.4	+4.5	+7.8
Diastolic pressure (mm. Hg)	0	-5.4*	+1.0	+1.2	+4.2	+2.8
Heart rate (beats/min.)	-6.4	-8.2*	+16.2*	+21.2*	+15.0*	+12.6*
Cardiac output (l./min.)	-0.58	-1.49*	+1.30	+1.00	+1.80*	+1.14*
Total peripheral resistance (dynes sec. cm ⁻⁵)	+134	+298*	-218*	-179	-271*	-190

* Significantly different at 5% level or less.

† A = Atropine.

‡ S = Scopolamine.

sary to record the responses to different dosages. Three successively larger doses of atropine and scopolamine were, therefore, used. The doses were chosen to add up to a total dose of 8.58 $\mu\text{g./kg.}$ atropine base, and 7.8 $\mu\text{g./kg.}$ scopolamine base, or about 0.72 mg. atropine sulfate per 70 kg. body weight, and 0.79 mg. scopolamine hydrobromide per 70 kg. body weight.

The three doses of each belladonna drug were injected in 5-minute intervals so that in a little more than 10 minutes the entire dose could be given. This allowed the observation of the effect of every additional dose, and permitted the construction of cumulative dose response curves.

Two experiments were done. In the first experiment 3 of 5 subjects received 1.43, 2.86,

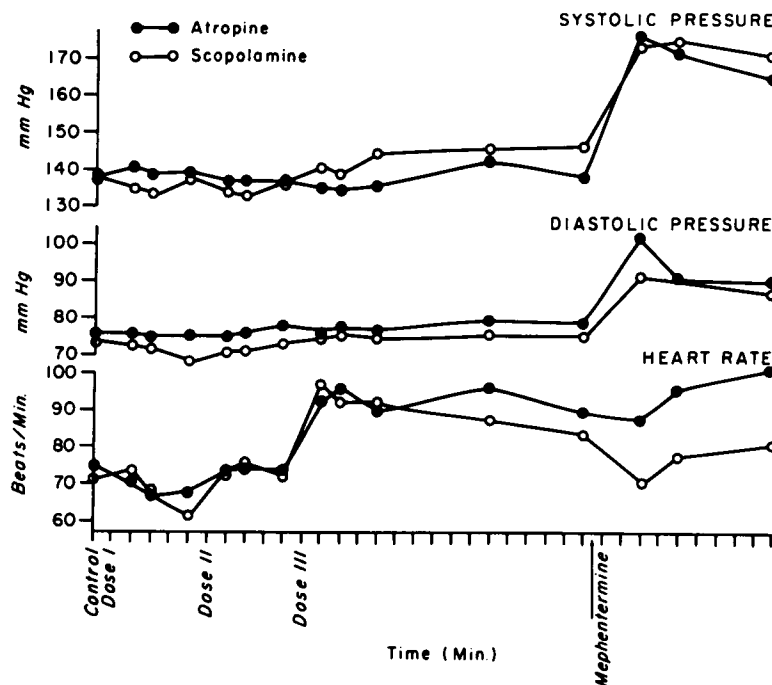


FIG. 1. Mean values from 5 volunteers, who were given intravenous doses of atropine or scopolamine and mephentermine. (See text for dosages.)

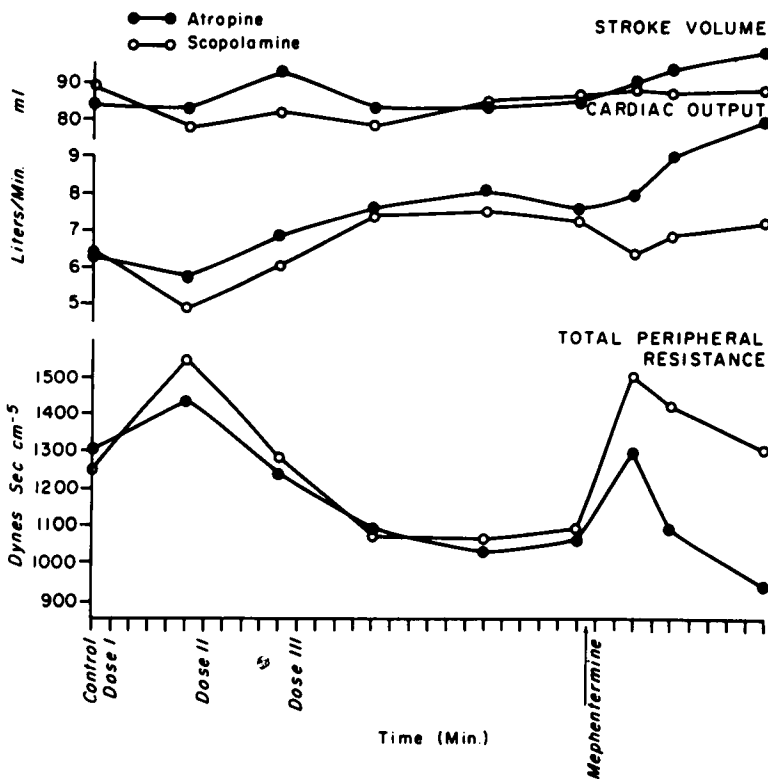


FIG. 2. Mean values from 5 volunteers, who were given intravenous doses of atropine or scopolamine and mephenetermine. (See text for dosages.)

and 4.29 μg . of atropine per kilogram body weight. The doses will be referred to as doses I, II, and III. Fifteen minutes after dose III, 0.3 mg./kg. body weight of mephenetermine base was injected intravenously. Two subjects received scopolamine 1.3, 2.6, and 3.9 μg ./kg. body weight instead of atropine. These doses will also be called doses I, II, and III. Again mephenetermine 0.3 mg./kg. body weight was given intravenously 15 minutes after dose III. One week later all subjects were retested according to the same schedule, except that scopolamine 1.3, 2.6, and 3.9 μg ./kg. was now given to those who had had atropine, and atropine 1.43, 2.86, and 4.29 μg ./kg. to those previously tested with scopolamine.

In the second experiment, the five subjects were first given intravenous mephenetermine base, 0.3 mg./kg. Fourteen minutes later, atropine or scopolamine was injected as in the first experiment. Again some subjects had atropine on one day and scopolamine a week later, while others were treated with scopola-

mine on the first day of the second experiment, and with atropine a week later.

For the statistical analyses, two tailed paired *t* tests were used.²

Results

First Experiment. Figures 1 and 2 show the mean effects of the injection of the three doses of atropine or scopolamine into resting subjects on systolic and diastolic blood pressure, on heart rate, on stroke volume, cardiac output, and total peripheral resistance. Statistically significant changes were seen in heart rate and cardiac output which were lowered by the small dose and raised by larger doses of both atropine and scopolamine, and in total peripheral resistance which rose with small and fell with large doses of atropine and scopolamine (table 1).

Figures 1 and 2 also show the effects of mephenetermine in the subjects pretreated with atropine or scopolamine. Reference to these data will be made below after the results of the second experiment have been outlined.

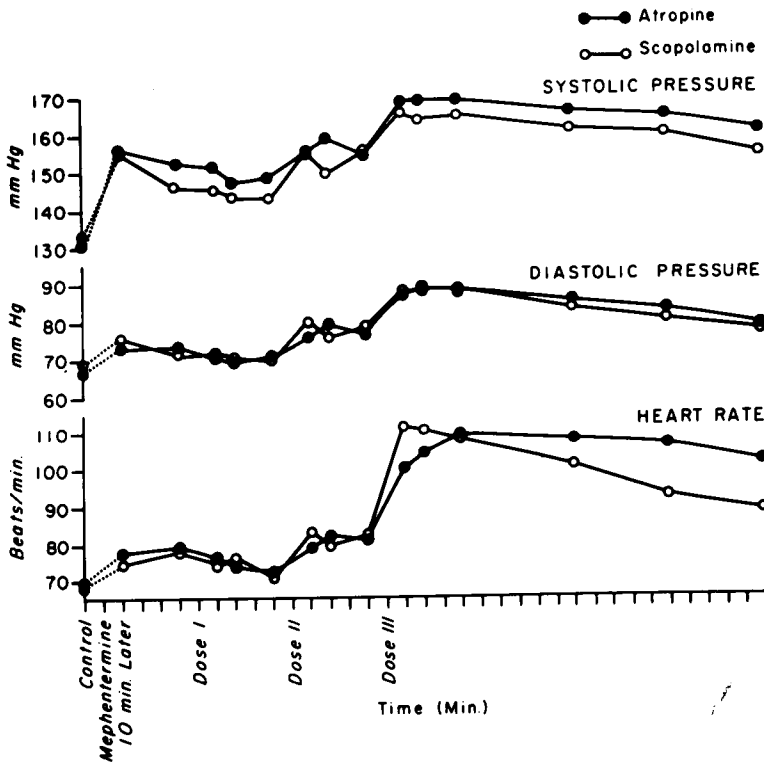


FIG. 3. Mean values from 5 volunteers, who were first given mephenetermine and then atropine or scopolamine intravenously. (See text for dosages.)

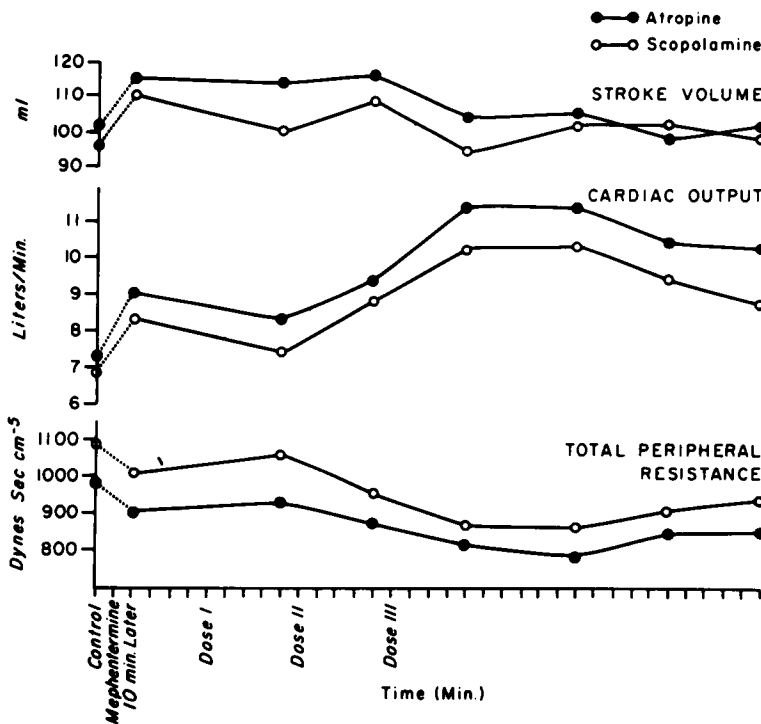


FIG. 4. Mean values from 5 volunteers, who were first given mephenetermine and then atropine or scopolamine intravenously. (See text for dosages.)

TABLE 2. Effects of Atropine and Scopolamine After Pretreatment with Mephentermine
Mean Differences Between Last Control Values After Mephentermine Administration
and Values After Atropine and Scopolamine Injections Are Given

	Four Minutes After Dose I		Four Minutes After Dose III		Ten Minutes After Dose III	
	A†	S‡	A	S	A	S
Systolic pressure (mm. Hg)	-4.0	-2.6	+16.2	+18.6*	+12.6	+15.0*
Diastolic pressure (mm. Hg)	-2.4	-2.0	+15.6*	+17.0*	+12.0*	+12.4*
Heart rate (beats/min.)	-7.0*	-7.2*	+29.6*	+29.8*	+28.2*	+22.6*
Cardiac output (l./min.)	-0.73	-0.86	+2.35*	+1.54	+2.41*	+2.05
Total peripheral resistance (dynes sec. cm ⁻⁶)	+31	+51	-83	-142	-116*	-150

* Significant differences with $P < 0.05$.

† A = Atropine.

‡ S = Scopolamine.

Second Experiment. Here the students were first given the standard 0.3 mg./kg. mephentermine intravenously. Figures 3 and 4 show that ten minutes after the injection of this dose, systolic and diastolic blood pressures were elevated, heart rate had quickened, cardiac output and stroke volume had increased, and total peripheral resistance was somewhat lowered. These mephentermine effects will gradually decay. Since an enhancement rather than a reduction of the mephentermine effects was expected to occur with atropine and scopolamine, any error due to the decay of the mephentermine activity would tend to decrease rather than magnify our experimental results. Fourteen minutes after the mephentermine injection, the first of the three doses of atropine or scopolamine was given. Now the administration of atropine and scopolamine caused not only significant changes in heart rate, cardiac output, and total peripheral resistance, but also in systolic and diastolic blood pressure (table 2).

In none of the data presented so far was there any indication of a difference in potency between atropine and scopolamine. However, inspection of figures 1 and 2 suggests that scopolamine was of shorter duration of action. In all these figures, the decay of the scopolamine effect appears to have progressed further than that of the atropine effect on heart rate, cardiac output and total peripheral resistance. In figures 1 and 2 both the last heart rate and the last cardiac output recorded

in the atropine group were significantly higher ($P < 0.05$) than those in the scopolamine group. All other differences between the atropine and the scopolamine group at the last recording of the other measurements may have been due to chance.

In the second experiment (figs. 3 and 4) the data from the atropine-treated subjects were almost always parallel or equal to the data from the scopolamine-treated subjects. However, again the heart rates diverged at the end of the experiment and the tachycardia persisted longer in the atropine treated group than in the scopolamine group. Here scopolamine appeared to have had a quicker onset of action in addition to a shorter duration. Computing the mean difference between the atropine and scopolamine group at the time of the peak effect on heart rate (after dose III) and comparing it to the difference between the two groups at the end of the experiment demonstrate that scopolamine and atropine were different in onset and different in duration of action ($P < 0.05$) on heart rate. Their peak effects, however, were identical. For an easy comparison of the potency of atropine and scopolamine figure 5 with dose response curves for heart rate was prepared. Cumulative doses on a logarithmic scale are given on the abscissa, and the changes of heart rate in beats per minute on the ordinate. All differences between the atropine and the scopolamine responses seen in figure 5 are likely to be due to chance.

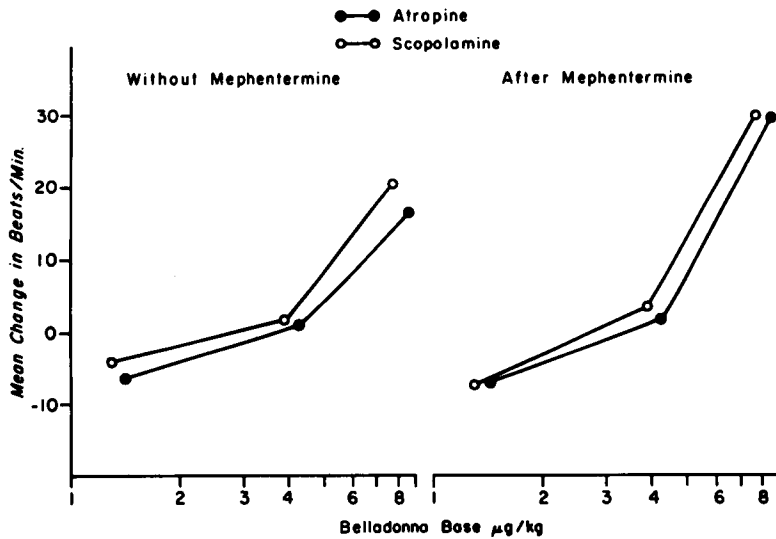


FIG. 5. On the left, the mean differences between heart rates counted before any drug administration and rates 4 minutes after the injection of the belladonna drugs are shown. On the right are the respective values in subjects pretreated with 0.3 mg./kg. mephentermine. The abscissa shows the cumulative dosages of atropine or scopolamine base plotted on a logarithmic scale.

The effect of 0.3 mg./kg. mephentermine alone can be seen in figures 3 and 4. Since the action of mephentermine in man as a function of dose and time has been discussed elsewhere³ only the modification of the action of mephentermine by the belladonna drugs will be discussed. The interactions between mephentermine and scopolamine are similar to those between atropine and mephentermine. The discussion will, therefore, be limited to the interaction between mephentermine and atropine. A comparison of the effect of atropine after mephentermine with the effect of atropine given prior to mephentermine or a comparison of the effect of mephentermine given alone to the effect of mephentermine given after atropine (tables 1 and 2, and figs. 1 through 5) demonstrates that one drug affected the action of the other. Thus, atropine did not cause significant changes in blood pressure when given to unmedicated subjects, but it did raise the blood pressure in the subjects pretreated with mephentermine. The atropine effect on heart rate was also significantly ($P < 0.05$) enhanced by the pretreatment with mephentermine (see also fig. 5). Conversely, mephentermine was a stronger vasopressor and positive chronotropic drug after atropine than before.

Discussion

In a recent, exhaustive review of the belladonna drugs in this Journal⁴ Eger discussed studies on heart rate, cardiac output, total peripheral resistance, and stroke volume. Our observations confirm the findings by others in showing that small doses of either drug can decrease and larger doses can increase heart rate, that stroke volume was unaffected, and that total peripheral resistance was significantly decreased by large doses. The principal effect of both atropine and scopolamine appeared to be on heart rate. The changes in heart rate were responsible for the changes in cardiac output.

The quicker onset and shorter duration of action of scopolamine as compared to atropine is of clinical interest. Foltz *et al.*⁵ believe that scopolamine penetrates the blood-brain barrier faster than does atropine. If such a quick penetration of scopolamine to effector sites could be assumed to occur also in the periphery, a quicker onset of action of scopolamine compared to atropine might find an explanation.

Sarnoff and Cope⁶ compared atropine and scopolamine effects on heart rate in hyperthyroid patients, and found atropine to be more potent. It is not clear from their paper whether the authors refer to atropine sulfate

and scopolamine hydrobromide, or to the bases of these drugs. If atropine sulfate and scopolamine hydrobromide rather than the bases were compared only 83 per cent of scopolamine base was pitted against 100 per cent atropine base. The failure to specify exactly what was used has made the interpretation of many other publications difficult. It may be appropriate to mention here that it is rarely adequate to compare single doses of two drugs when an experiment is designed to evaluate the relative potency of two compounds.

Scopolamine has a marked and long lasting sedative effect. One of our subjects was heavily sedated for more than twelve hours by the scopolamine which he had received during the experiment, but noticed no psychological effect from the atropine. Whether or not this sedative action of scopolamine can influence the autonomic nervous system in certain subjects has not been explored. It is conceivable that a very excited patient could be sedated by scopolamine and that the sympathetic tone could be reduced secondary to the sedative effect of scopolamine. In such a person atropine would appear to have a more potent effect on heart rate than scopolamine. This possibility deserves study.

A comparison of tables 1 and 2 shows that the pretreatment with mephentermine markedly affected the action of atropine and scopolamine on heart rate and blood pressure. This interaction (or synergism) between atropine or scopolamine and mephentermine can be explained by postulating an increased parasympathetic activity in response to the sympathomimetic mephentermine. Inhibiting parasympathetic receptors with atropine added 15 beats/minute to the tachycardia produced by mephentermine. Similarly systolic and diastolic pressure rose with the administration of atropine or scopolamine after mephentermine, but not when atropine or scopolamine was given to subjects not premedicated with mephentermine. We must assume that a reflexly heightened parasympathetic tone inhibited the mephentermine effect on blood pressure. By counteracting this parasympathetic inhibition, the belladonna drugs added about 10 mm. of mercury to the systolic and diastolic blood pressure already

elevated by mephentermine. This experiment throws no light on the mechanism by which parasympathetic activity influences blood pressure.

Atropine is *d,l*-hyoscyamine and scopolamine is *l*-hyoscine. *In vitro* *l*-hyoscyamine is much more potent than *d*-hyoscyamine.⁷ If this difference also holds for the cardiovascular actions of *d* and *l*-hyoscyamine in man we must conclude that *l*-hyoscyamine is about twice as potent as *l*-hyoscine.

Both atropine and scopolamine may undergo hydrolysis into tropic acid and the respective alkaloid.⁸ It was, therefore, necessary to test the concentration of atropine and scopolamine in the solutions used in the study. This was done after the completion of the study. Both the drugs for the pharmacologic investigation and the drugs for the chemical analyses were obtained from our hospital pharmacy. At both times, atropine sulfate from Lilly and scopolamine hydrobromide from Burroughs Wellcome were used, but we cannot be certain that the batch tested for purity and degradation was the one employed for the pharmacologic study. Using ultra-violet light spectroscopy for the detection of the apo form and titration for free acid and the alkaloid,† scopolamine was found to be pure, and no tropic acid was discovered in the sample. Atropine was also pure, but about 15 per cent had undergone hydrolysis. If we assume that the atropine lot used by us was also 15 per cent weaker than stated, the total atropine dose was 7.3 $\mu\text{g./kg.}$ as compared to the total scopolamine dose of 7.8 $\mu\text{g./kg.}$ This difference would not affect our conclusion that the bases of atropine and scopolamine were equipotent in their action on the cardiovascular functions studied by us. Indeed, the dose response curves of figure 5 would show the curves for atropine and scopolamine to lie very close to each other, with the atropine a little to the left of the scopolamine curves.

Summary

The cardiovascular effects of atropine and scopolamine were studied in fit volunteers.

† These determinations were done by Mr. D. J. Weber from the College of Pharmacy, University of Florida.

The bases of atropine and scopolamine were found to be equipotent. Scopolamine was faster in onset and shorter in duration of action. Both drugs exerted their principal effect on heart rate. Low doses decreased and large doses accelerated heart rate. Cardiac output changed parallel to the changes of heart rate. Stroke volume was not affected. Both atropine and scopolamine were equally effective in enhancing the action of mephentermine on heart rate and blood pressure.

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STATUS OF THE ANESTHESIOLOGIST The old concept has to be abandoned that an operation is the accomplishment only of the man wielding the scalpel and that all others concerned are only more or less qualified helpers. The anesthetist not only provides a prerequisite for the operation but is an integral part of it. This division of responsibility is a fact which has developed in the best interest of medical care and cannot be reversed. The anesthetist cannot discard his own judgment by obeying a dogmatic or incorrect direction of the surgeon, for he will be held responsible for any negligence in his field while the surgeon will be held responsible for incorrect actions in his sphere of activity. Smooth cooperation between anesthetists and surgeons can only be achieved when there is an equalization of rights and responsibilities and by abandonment of hierarchic subordination. (*Stratenwerth, G.: Concerning the Position of the Anesthesiologist, Der Anaesthetist* **12**: 269 (Sept.) 1963.) (ABTRACTOR'S NOTE: The author is Professor of Criminal Law at the University of Basle, Switzerland.)

ACUTE RENAL FAILURE Controversy exists over the cause, incidence, and best method of prevention of acute renal failure which occasionally follows operations in which the abdominal aorta is temporarily occluded below the renal arteries. The operative and postoperative urinary output of 55 patients who underwent surgery for abdominal aortic aneurysms and occlusive disease was recorded. There were five cases of postoperative anuria among 28 patients who received no free fluid in the immediate postoperative period. No cases of anuria occurred in 27 patients who received either: (1) a water load of 5 per cent dextrose in water or (2) 20 per cent mannitol solution. The patients who received mannitol had a markedly greater operative and postoperative urinary output. (*Baird, R. J., and others: Protection of Renal Function During Surgery of the Abdominal Aorta, Canad. Med. Ass. J.* **89**: 705 (Oct. 5) 1963.)