made over the ensuing 60 minute period. No significant reduction in bleeding time was noted following the injection of Adrenoxyl.

Discussion. Insofar as venous clotting time and prothrombin time reflect the speed of fibrin production, Adrenoxyl does not foster an accelerated process under the stated experimental conditions. It is, however, conceivable that tissue thromboplastic activity can be altered by Adrenoxyl and that the alteration is not evident where venous or heart sampling reduces the amount of tissue thromboplastin to the minimum.

After administration of Adrenoxyl, observations of the pulse rate, the blood pressure, the arterial wall tonus (as reflected by the pulse wave velocity), and the vaso-motor response of the superficial vessels (as evaluated by skin temperature determinations), do not reveal data which would suggest alteration in the vasomotor response that would not fall within normal physiological limits.

Bleeding time experiments are inconclusive since the experimental error of the technique used is of such great magnitude. We were unable to isolate real evidence that Adrenoxyl reduces the bleeding time under the stated experimental conditions. It is interesting to us to note that when an animal under light anesthesia responds to the stimulus of an incision on the ear, the bleeding time is reduced. This finding raises the question of advisability of collecting bleeding time data on unanesthetized animals.

Conclusions. 1. Under the stated experimental conditions Adrenoxyl does not influence (a) the speed of the coagulation process, and, (b) the vasomotor response.

2. The method of bleeding time determination in the experimental animal in our hands does not give conclusive results, therefore we are unable to confirm or deny the findings of Roskam and associates.

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Evaluation of Certain Dangers in the Use of Jet Injection Technic.

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As a substitute for the hypodermic syringe, a jet injector which utilizes the principles of the Diesel fuel injector has been described by Hingson and Hughes.[1] In the administration of substances by the hypodermic syringe, the possibility of an accidental intravenous injection is recognized. The present study was designed to investigate the possibility of a similar accidental intravenous injection with the "Hypospray."

Experimental Work. Dogs anesthetized with 30 mg per kg of sodium pentobarbital intravenously were given atropine sulfate by vein until electrical stimulation of the cut right vagus nerve failed to slow the heart. Both jugular veins were exposed by a medial approach so they could be seen by eversion of the edges of the incision. Blood pressure was continuously recorded by a mercury manometer connected to one carotid artery. Known doses of epinephrine were injected by syringe into the right jugular vein.

A "Hypospray"* with a 125 pound spring was loaded with a cartridge† containing 0.25 cc of a 0.4% solution of epinephrine hydrochloride. By eversion of the edge of the incision the left jugular vein was exposed to view. The tip of the cartridge was then pressed firmly against the skin on outside of the shaved neck and so aligned that the vein lay directly between the cartridge tip and the

1 Hingson, R. A., and Hughes, J. G., *Anesth. and Analg.*, 1947, **26**, 221.

* Courtesy of the R. P. Scherer Corp., Detroit.

† Courtesy of the Gelatin Products Corp., Detroit.

TABLE I.
Summary of Jet Injections Lodging as Much as One Per Cent Intravenously.

Dog No.	Wt	Blood pressure (mm Hg)		μg epinephrine base lodged in vein			State of vein
		Control	Maximum	Per kg	Per dog	%*	
1	5.5	96	226	18.74	103	15.2	D†
2	15.9	126	220	.49	8	0.9	D
		144	315	51.48	818	97.7	Empty
		135	306	35.32	562	66.8	D
3	5.0	128	247	10.34	52	6.2–	Empty
		122	240	8.09	40	4.8	D
4	4.7	108	188	3.38	16	1.9	D
		110	195	3.48	16	2.0	D
5	16.0	153	206	.52	8	1.0–	D

* Per cent of the total epinephrine available, *i.e.*, 833 μg.
† Distended.

incision. Any of the jet passing through the vein would escape into the room or be sponged out at once. The instrument was then discharged. The vein rested directly on the subcutaneous tissue or else was separated from it by about 5 mm of muscle. For some jet injections the jugular vein was emptied; for others the vein was distended by clamping and the clamps were removed immediately after the discharge.

A dose-effect curve was fitted for each animal by the method of least squares, using the equation: maximum blood pressure attained is equal to a constant multiplied by the dose per kilogram raised to a constant power. Accurate assays of epinephrine can be made from such dose-effect curves.[2-8] The maximum blood pressure reached after each jet discharge of epinephrine was measured. From the dose-effect curve or its equation the quantity of epinephrine required to produce the given maximum pressure can be determined either graphically or by calculation. The results of 12 jet injections which lodged intravenously as much as 1% of the epinephrine in the cartridge are listed in Table I; 22 discharges which lodged less than 1% are omitted.

Results and Discussion. The greatest amounts of the drug which lodged in the vein in 34 jet injections were 97.7, 66.8, 15.2, and 6.2% of the total discharged. Of these, the first and fourth quantities lodged in empty veins; the second and third lodged in distended veins. Thus if the jet is discharged over a large vein a significant fraction of the discharged drug may be administered intravenously.

When the "Hypospray" is used, several factors appear to determine the fraction of the epinephrine which lodges in the veins: (1) alignment of the blood vessel with the jet, (2) amount of pressure applied to the tissues, (3) diameter of the vein, (4) amount and toughness of the tissues separating the nozzle and the vein lumen, (5) ability of the vein to roll away from the discharge under impact of the jet.

Even though the vein was visible, we were not always successful in discharging the jet through the diameter of the vein. When the jet nicked the vein edge, little of the drug entered the lumen as the major portion was deflected. Further, such off-center discharges tended to roll the vein to one side.

2 Elliott, T. R., *J. Physiol.*, 1904-5, **32**, 401.
3 *Ibid.*, 1912, **44**, 374.
4 Lyon, D. M., *J. Pharmacol. and Exp. Therap.*, 1923, **21**, 229.
5 Rosenblueth, A., *Am. J. Physiol.*, 1932, **101**, 149.
6 Clark, A. J., Mode of Action of Drugs on Cells, Baltimore, 1933.
7 Hjort, A. M., de Beer, E. J., and Randall, L. O., *J. Pharm. and Exp. Therap.*, 1941, **71**, 105.
8 Brown, R. V., *Fed. Proc.*, 1948, **7**, 208.

Conversely, with direct hits the vein was seen to balloon out whether it was originally full or empty. Firm pressure of the cartridge tip against the tissues did not prevent such ballooning. After having passed through the proximal vein wall, the jet had lost so much velocity that much of it failed to penetrate the distal vein wall and thus remained in the lumen.

Inspection of Table I shows that the amount of the drug retained was not appreciably influenced by whether or not the vein was empty or full. In larger animals the veins are larger and are easier to hit through the diameter. Also the thicker vein walls decreased the jet velocity and less escaped through the distal wall. Since man has numerous large superficial veins, his risk of an intravenous injection may be greater than that of the dog when the jet is used.

The portion of a vein penetrated by a jet of epinephrine became blanched and constricted for several minutes. Sometimes small clots appeared on the vessel at the points of entrance and exit of the jet.

The shape of the blood pressure curve resulting from a jet injection of epinephrine differed from that following needle injection. With direct hits, the ascending limbs of the curves were similar, but the blood pressure always returned to the control level more slowly after a jet injection. This is taken to indicate: (1) a gradual entrance into the lumen of epinephrine lodged in the wall of the vein, (2) entrance of additional small quantities lodged in the small tributaries, (3) rapid absorption of epinephrine trapped in adjacent tissues (*cf.* Clark.[9]).

Massage of a jet injected muscle, connective tissue or even the vein itself elevated the blood pressure. In one case, the blood pressure rise induced by massage of a jet injected area was 12 mm of Hg, but lower responses were usually obtained. Luckhardt and Koppanyi[10] have reported a similar elevation of blood pressure from massage of areas containing needle-injected epinephrine.

As the blood pressure slowly returned to the control level, cardiac irregularities, showing as dropped beats, were much more frequent from jet injections than from needle injections. It is not known whether the dropped beats indicated premature systoles of the ventricles or heart block.

Ten attempts to make blind intravenous injections with the "Hypospray" at the junction of the jugular and subclavian veins or into the femoral vein were not successful.

Conclusions. 1. Under conditions very favorable for intravenous injection, the "Hypospray" has lodged as much as 97% of the total available drug in the vein, even when administered through the skin and subcutaneous tissues.

2. Large veins are easier to hit than small veins and retain a larger amount of the jet-injected material.

3. The probability of unintentionally penetrating a major vessel with the jet is small but the risk is always present.

4. Jet discharges should not be made in the neighborhood of large vessels unless the drug to be injected is safe for intravenous administration.

5. The jet may produce macroscopically visible damage to a vessel.

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9 Clark, A. J., and Raventós, J., *Quart. J. Exp. Physiol.*, 1939, **29**, 185.

10 Luckhardt, A. B., and Koppanyi, T., PROC. SOC. EXP. BIOL. AND MED., 1926, **23**, 774.