THE PHARMACOLOGICAL ACTIVITY OF EPINEPHRINE AND RELATED DIHYDROXYPHENYLALKYLAMINES

A. M. LANDS

Sterling-Winthrop Research Institute, Rensselaer, New York

The pharmacology of sympathomimetic amines has been the subject of several previous reviews (33, 116, 117, 247). The large volume of published research now available makes it advisable to limit this review to a part of the entire subject.

An attempt has been made to present here the pharmacological actions of epinephrine and the structurally related dihydroxyphenylalkylamine derivatives on smooth and cardiac muscle. The publications cited must be considered merely as representative of this field of investigation. The principal compounds described are identified by the commonly used names.

EPINEPHRINE, 'ADRENALIN', 'SUPRARENIN', LEVO 1-(3′,4′-DIHYDROXYPHENYL)-2-METHYLAMINOETHANOL

Earlier publications have reviewed the isolation, structural determination and synthesis of epinephrine (116, 247). A marked rise in blood pressure following the intravenous injection of extracts of the adrenal glands was demonstrated in 1895 (193), and shortly thereafter the similarity of this response to the effects produced by stimulation of sympathetic nerves was described (36, 77, 154, 159). More recent investigations have indicated that epinephrine-like substances may be produced in many organs.

The intravenous injection of small amounts (1–5 mcg./kgm.) of epinephrine (63, 77) causes a prompt rise in blood pressure. The resulting rise has been divided into 4 phases as follows; (a) vasoconstriction, (b) decremental phase of (a), (c) a secondary rise associated with stimulation of the vasomotor center, (d) a fall below the preinjection level. A similar analysis by the 3 manometer method of Nolf has shown (a) a marked increase in stroke volume associated with a distinct increase in heart action, (b) a fall in blood pressure induced by the sinus reflex mechanism, (c) a diminution in the output of the heart, partly reflex in origin and partly the result of diminished venous return, (d) a period in which peripheral actions are dominant and wherein there is an increased stroke volume due to an increased venous return associated with constriction of capillaries and veins and (e) a fall in pressure as the peripheral action diminishes (215). The fall in pressure below the preinjection level which follows the pressor response (182) probably results from the vasodepressor action of epinephrine (51) or from reflex vasodilatation (119). There is a marked, but transient, increase in the output of the heart coincident with an increase in heart rate (22, 99), which takes place within a few seconds after intravenous injection. This rise precedes the peripheral vasoconstriction which in turn tends to diminish cardiac output (22). The sudden increase in arterial pressure associated with the increase in cardiac output stimu-

lates pressoreceptors in the aorta and carotid sinus and thereby reflexly induces some vasodilation (119).

The peripheral effects of epinephrine are quite variable in different organs and in the same organ under varying physiological conditions. Epinephrine usually causes constriction in the cutaneous vascular bed (58, 98, 127). Small amounts of epinephrine may cause an increase (66, 98, 114, 129) followed by a decrease (199) or a primary decrease (67, 199) in blood flow through muscles. Slow intravenous infusion causes an increase in blood pressure along with a marked increase in the volume flowing through the limbs of experimental animals and man (5, 130). Limb volume and venous outflow studies in the hind limbs of dogs after the removal of the skin reveal only vasodilation after epinephrine whereas in the intact leg the net effect is usually a reduction in volume due to the marked constriction of the skin vessels (127). In anesthetized cats, intravenous injections of 0.5 mcg.*/kg./min. caused a marked increase in the blood flow through the hind limb but this increase diminished as the rate of injection was increased (102). A decrease in the rate of flow through bones has been observed with epinephrine in perfusion experiments (74).

Epinephrine frequently increases the volume of abdominal organs (75, 126) and increases the volume flow (5, 19, 75, 126, 192). However, constriction of mesenteric vessels has been reported (44, 58, 83, 113, 129, 173, 192). Small doses of epinephrine may cause an increase in portal flow and liver volume with a reduction in venous pressure (19, 27, 40, 75, 97, 138, 217), whereas large doses cause a reduction in both hepatic flow and liver volume (19, 27, 40, 75, 97, 138, 173, 180, 217). Epinephrine causes contraction of the splenic capsule (129, 211). An initial contraction followed by marked relaxation may occur (129).

Subcutaneous or intravenous injection of epinephrine in man causes tachycardia, an increase in systolic and usually a decrease in diastolic pressure associated with a reduction in peripheral resistance (5, 88, 90, 94, 201). The determination of cardiac output, pulse pressure and total peripheral resistance during slow intravenous infusion has led to the conclusion that, in man, epinephrine is predominantly a vasodilator agent (5, 94).

Epinephrine is a potent cardiac stimulant. Isolated frog heart preparations respond to dilutions of 1:10 million to 1:1 million by an increase in both rate and amplitude of contraction. Greater concentrations cause arrhythmia and cardiac arrest (1, 9, 112, 162, 169). Similarly, mammalian heart strips, excised mammalian hearts and heart-lung preparations respond to epinephrine by an increase in rate and force of contraction associated with an increased oxygen consumption (59, 96, 118). Epinephrine causes a reduction in the length of systole and shifts the time of maximum ejection into the early part of systole. There is an increase in contractile activity and this may result in increases in stroke volume and cardiac output if peripheral resistance is not too greatly increased. Doses which markedly increase peripheral resistance also increase diastolic volume and reduce cardiac output and work (110, 204). In the intact animal, there may be a reduction in the rate of contraction which is prevented by atropine or by cutting

* Microgram.

the vagi above the heart (37, 128, 184). A similar reflex slowing of the heart, associated with an increase in pressure, which may be prevented by atropine has been reported in man (88, 90). Slow intravenous infusion (10 mcg./kg./min.) in man has been observed to increase cardiac output without an increase in venous pressure or heart rate (183).

The determination of the effect of epinephrine on coronary flow is made difficult by the mechanical factors involved. An increase has been reported for saline perfused beating hearts (21, 35, 77, 105). Determinations in the heart-lung preparation of dogs indicate that epinephrine causes an increase in coronary flow (174); this is also observed when heart rate and total output are maintained constant (10). Very small amounts (0.1 mcg.) have been reported to diminish coronary flow without change in cardiac action, whereas larger doses (1.0 mcg. or more) caused transient constriction followed by dilatation (174). Coronary flow was decreased by epinephrine in the human heart-lung preparation (145); this reduction was associated with an increased vigor and rate of contraction. In the non-beating human heart (145) and in cat, rabbit and dog hearts (137), an increased flow was observed. Isolated rings of coronary arteries of the ox (153) and sheep (60) are relaxed by epinephrine whereas those from man are reported to contract with dilutions greater than 1:50,000 and to relax at higher concentrations (145). Stromuhr determination of coronary flow has revealed a decrease during systole but an increase during diastolic inflow (100, 207). Flow determinations in unanesthetized dogs have indicated that epinephrine causes a distinct increase, the increase being relatively greater than would be expected from the increase in mean blood pressure (253).

The determination of the effect of epinephrine on pulmonary blood flow is also made difficult by the simultaneous stimulating action on the heart. Experiments with isolated strips of pulmonary arteries obtained from various species of animals and from man have indicated that epinephrine causes constriction (20, 44, 60, 170, 186). Rings taken from the extrapulmonic arteries respond to dilutions of 1:1 million to 1:10 million by constriction. Intrapulmonic arteries gave small and variable responses but with constriction predominating (87, 109, 208). Constriction has also been reported for the perfused pulmonary vascular bed (44, 91, 198, 249, 256). The various results obtained have been described in a recent summary (68).

An increase in right along with a decrease in left auricular pressure has been observed following intravenous epinephrine injection and has been interpreted as an indication of pulmonary vasoconstriction (198, 257). However, such results could be expected to follow an increased output from the heart, as described earlier in this article. Numerous experiments indicate that epinephrine can cause pulmonary vasoconstriction (68, 212) but it seems doubtful if this plays an important role in the regulation of pulmonary blood flow (135).

Epinephrine is an effective bronchodilator drug. This action has been demonstrated on excised tracheal tissue (55, 172, 245, 246) and on the isolated perfused lung (233, 240, 252) when contraction had been induced by histamine, barium chloride and other bronchoconstrictor agents. Experimentally induced bronchospasm in cats and dogs is readily relaxed by small intravenous doses (0.01–

0.02 mg./kg.) of epinephrine (42, 95, 131, 134, 195, 231). The inhalation of a histamine mist induces marked bronchospasm in guinea pigs. This can be prevented by the previous intraperitoneal injection of 0.1 mg./kg. of epinephrine (225). Histamine and acetylcholine mists induce bronchoconstriction in guinea pigs which is relaxed by epinephrine (214, 244). The inhalation of an epinephrine mist has also been found effective in inducing bronchodilatation in bronchial asthma (69, 223).

The action of epinephrine on the gastro-intestinal tract varies with the segment studied, with the degree of initial tonus and with the species of animal. With cat and human stomachs, the pyloric sphincter is contracted while all other parts are relaxed. The preantrum of the dog's stomach is relaxed while the body, fundus and cardiac sphincter are contracted (54, 226). The frog stomach may respond by either contraction or relaxation whereas the turtle stomach is contracted

TABLE 1

*Effect of epinephrine on the uterus**

ANIMAL	NON-GRAVID	GRAVID	REFERENCE
Mouse	−	−	104
Rat	−	−	104, 107, 141, 168
Guinea pig	−	−	104, 107, 168, 179
	+	+	60, 104, 139, 149
Rabbit	+	+	33, 104, 149, 168, 247
Cat	−	+	33, 104, 247, 254
Dog	+	+	104, 146
	−	−	104, 139
Monkey	+	+, −	66, 104
Human	+	+	103, 104, 139, 146, 191, 209

* − inhibitory; + constriction.

by epinephrine (29). In anesthetized dogs, small intravenous doses (2.5–20 mcg.) of epinephrine diminish gastric tonus (226). Epinephrine stimulates the lower oesophagus and cardia and inhibits the stomach in cats. In rabbits, epinephrine inhibits the cardia and contracts the stomach (54).

Tonus and peristalsis in the small intestine are diminished by epinephrine. Isolated segments of rabbit intestine are relaxed by dilutions as great as 1:500 million (125). Segments of guinea pig ileum are relaxed by dilutions of 1:20 million but may be contracted by dilutions of 1:1 million to 1:4 million (149). The pyloric (50, 140, 229) and ileocecal (50, 66) sphincters are contracted. Marked inhibition of the intestine follows intravenous injection of epinephrine and the duration of this action parallels that of the pressor action (248). Denervation of the small intestine increases its sensitivity to this inhibitory action (260). Epinephrine also causes relaxation of the gall bladder (18, 160).

The action of epinephrine on the uterus is quite variable, being influenced by the condition of the organ (gravid, non-gravid) and by the species of animal used. These various actions have been summarized in table 1 and in the review

articles cited (33, 104, 247). Epinephrine has been reported to increase the force of uterine contractions during delivery, this effect being followed by a short period of diminished activity (258).

The isolated urinary bladder of the cat is contracted by small and relaxed by large concentrations of epinephrine (76). Intravenous injection causes a transient contraction which may be followed by a reduction in tonus (159). Activity of the ureter of the cat is increased and the urethra is strongly contracted (78, 166). The dog bladder usually responds by a small increase in tonus (78). The rabbit bladder may be weakly contracted or may relax (2), whereas the human bladder is contracted and rhythmic activity of the ureters is increased by epinephrine (171, 222).

TABLE 2

The acute toxicity of epinephrine

ANIMAL	ADMINISTERED	TOXIC DOSE	REFERENCE
		mg./kg.	
Mouse	i.v.	2.7 ± 0.2 (LD_{50})	123
	i.p.	4.6 ± 0.55 (LD_{50})	149
	s.c.	1.0–1.5	33, 80
		1.98–2.17	157
		4.0–8.0	221, 247
	oral	50.0	33
Rat	i.v.	0.04 ± 0.004 (LD_{50})	123
		0.005–0.05	33
	s.c.	5.0–10.0	33
		10.0–20.0	247
	oral	30.0	33
Rabbit	i.v.	0.2–0.3	33
		0.05–0.4	32, 82, 156
	s.c.	10.0–20.0	33
		4.0–10.0	26, 247
	oral	30.0	33
Guinea pig	i.v.	0.15–0.2	157, 216
Cat	i.v.	0.5–8.0	33, 247
	s.c.	20.0	33, 247
Dog	i.v.	0.2–2.0	33, 247
	s.c.	5.0–6.0	8, 33, 247
Human	i.m.	>7	124, 181

Epinephrine, perfused through the superior cervical sympathetic ganglion of the cat, causes depression of the response to repetitive stimulation of the preganglionic trunk (175). This inhibitory action appears to be similar in nature to the inhibition obtained on the intestine and bronchi (176). Other investigators have reported increased transmission with large doses (38).

Epinephrine is a very toxic drug. Data on acute toxicity are summarized in table 2. The symptoms of intoxication in rats following intravenous administration are depression, blanching of the extremities, dyspnea, loss of muscular

coordination which may be followed by clonic convulsions and death from respiratory arrest (123). Chloroform (158) and cyclopropane (194) increase the sensitivity of the heart to the toxic actions of epinephrine. Accidental epinephrine intoxication in man has been reported (124, 181), with intramuscular doses of 5–7 mg. not causing death. Symptoms observed were headache, excessive perspiration, a feeling of constriction in the neck with fullness in the chest, precordial distress, mild tremor and vomiting.

DEXTRO-EPINEPHRINE

The pharmacological responses to the dextro-isomer of epinephrine appear to be qualitatively the same as those obtained with epinephrine (89). The pressor potency of epinephrine has been reported to be 12–51 (64), 20 (234), 18.5 ± 0.7 (232) times greater than that of the *d*-isomer. The toxicity of the *d*-isomer is distinctly lower than that of epinephrine. It is $\frac{1}{6}-\frac{1}{8}$ as toxic as this latter drug when injected subcutaneously in rats (64), $\frac{1}{15}-\frac{1}{30}$ as toxic when injected intravenously in mice (123) and $\frac{1}{2}-\frac{1}{3}$ as toxic when injected intravenously in rabbits (247).

ARTERENOL,* NOR-EPINEPHRINE, 1-(3′,4′-DIHYDROXYPHENYL)-2-AMINOETHANOL

Arterenol was synthesized in 1904 by Stolz and Flächer (230) and by Dakin (65). The racemic compound has recently been resolved by Tullar (250).

The pressor potency of arterenol has been reported to exceed that of epinephrine; arterenol is 1.25–1.5 times more pressor in dogs when the racemic compounds are compared (25, 220). The size of the dose injected may influence the ratio obtained. Arterenol and epinephrine are reported to be equipressor at small doses but an increase in the relative potency of arterenol was observed as the dose was increased (179). Arterenol has been reported to be 1.3 times more pressor than epinephrine in cats (179, 237, 254) and the *l*-isomer 1.7 times more pressor than epinephrine in dogs (168). Epinephrine is 1.5–2.5 times more active than arterenol in causing vasoconstriction in the perfused rabbit ear (179) and has also been reported more effective in causing vasoconstriction of the renal, mesenteric and femoral vascular beds after intra-arterial injection (4). An equal increase in coronary flow of the perfused rabbit heart was observed with both arterenol and racemic epinephrine (179). A decrease in coronary flow has also been reported (4).

Arterenol has been reported to be less stimulating than epinephrine on the perfused frog heart (254). Equal effects on rate and amplitude of the perfused rabbit heart (179) have been reported when the racemic salts were compared. Equipressor doses of the *l*-isomers were reported to be equally stimulating on the dog heart *in situ* (168) or on the denervated heart (259). In other experiments, arterenol has been reported to be 1.7 times more stimulating than epinephrine (62).

The effects of intravenous infusion of 10–20 mcg./kg./min. *l*-arterenol for 3

* Arterenol and other optically active sympathomimetric amines are referred to as the racemic compound unless otherwise designated. Epinephrine is the l-base.

minutes in 7 normal adults were compared with those obtained with this dose of epinephrine. Arterenol caused bradycardia, whereas epinephrine caused tachycardia. The subjective effects of arterenol were insignificant whereas with epinephrine there was mild palpitation, hyperventilation, tightness in the chest and muscular fatigue (23). Intravenous infusion of lesser amounts (0.11–0.4 mcg./kg./min.) of *l*-arterenol for 14 to 22 minutes caused either no change or a decrease in cardiac output, a significant rise of systolic and diastolic arterial pressures with a rise of mean pressure, an increase in total peripheral resistance, a decrease in pulse rate and a significant rise in mean pulmonary arterial pressure (94).

Isolated segments of small intestine are relaxed by arterenol. The relative activity varies with the species of animal used; the inhibitory potency of epinephrine is reported to be equal to that of arterenol in the cat, but greater in the rabbit and rat (4, 79, 168, 179). Racemic epinephrine and arterenol have been reported to be equally active on the isolated guinea pig ileum (179). Epinephrine was found to be 1.4 times more active than arterenol when the *l*-isomers of both compounds were used (168).

The isolated cat uterus is inhibited by arterenol, but less readily than by epinephrine (25). Inhibition of the isolated guinea pig uterus requires 2.5–10 times more arterenol than epinephrine (25, 149, 169). The isolated rat uterus, stimulated with acetylcholine, is relaxed by *l*-arterenol in a dilution of 1:10 million–1:3 million or at concentrations 30 times greater than the effective concentration of epinephrine (168).

The bronchioles of the isolated perfused guinea pig lung are dilated by racemic arterenol in doses 7–17 times greater than the effective dose of epinephrine (168, 179, 240). Bronchoconstriction, induced in unanesthetized guinea pigs by inhalation of histamine mists, may be prevented or diminished by the parenteral administration of arterenol. However, the dose required is about 3 times greater than that required for epinephrine (168). Studies in pithed dogs have shown epinephrine to be 7.4 times more active than arterenol in relaxing bronchoconstriction induced by arecoline (195). Histamine-induced bronchospasm, in this preparation, was found to be more readily relaxed by epinephrine, arterenol being only moderately effective in producing bronchodilatation (42).

The central nervous system stimulation of arterenol and epinephrine was compared in rats. Epinephrine was found to be about twice as stimulating as *l*-arterenol (168). This is somewhat at variance with an earlier report which indicated no central nervous system stimulation from *dl*-arterenol (219).

The acute toxicity of arterenol is somewhat less than that of epinephrine. The various results obtained are shown in table 3 (p. 286).

The pharmacologic activity of the *d*-isomer of arterenol is qualitatively the same as that of the *l*-isomer but the potency is much lower. The relative potencies of the *d*-isomer, expressed as multiples of the effective dose of the *l*-isomer, have been reported as follows: vasopressor and cardiac action—27; inhibition of the guinea pig ileum—62; inhibition of the isolated rat uterus—4; dilatation of the bronchioles of the isolated perfused guinea pig lung—50, 60; bronchodilatation by the histamine mist method—20 (168).

The acute intravenous toxicity of *d*-arterenol in mice and rats is shown in table 3. The *d*-isomer is distinctly less toxic than the *l*-isomer.

HYDROXYTYRAMINE, 1-(3',4'-DIHYDROXYPHENYL)-2-AMINOETHANE

The pressor action of hydroxytyramine is much less than that of arterenol or epinephrine. Results obtained on cats and dogs suggest that it is $\frac{1}{50}-\frac{1}{75}$ as potent as epinephrine (6, 25, 108, 235). Action on the dog heart-lung preparation and on the isolated perfused cat heart indicates a potency of about $\frac{1}{75}$ that of epinephrine

TABLE 3

The acute toxicity of arterenol

ANIMAL	DRUG	ADMINISTERED	TOXIC DOSE	REFERENCE
			mg./kg.	
Mouse	levo	i.v.	5.0 ± 1.0 (LD_{50})	123
	racemic	i.v.	7.5 ± 2.0 (LD_{50})	123
	racemic	i.v.	9.8 ± 1.9 (LD_{50})	71
	racemic	i.v.	5.0 ($LD_{\infty-\infty}$)	179
	dextro	i.v.	60.0 ± 20.0 (LD_{50})	123
	racemic	i.p.	12.0 − 30.0 ($LD_{\infty-\infty}$)	179
	racemic	i.p.	15.6 ± 3.8 (LD_{50})	71, 149
	racemic	s.c.	40.0	33
Rat	levo	i.v.	0.10 ± 0.01 (LD_{50})	123
	racemic	i.v.	0.13 ± 0.02 (LD_{50})	123
	dextro	i.v.	1.40 ± 0.14 (LD_{50})	123
	racemic	s.c.	>2.0	23
Rabbit	racemic	i.v.	0.25–0.30	33
	racemic	i.v.	1/2–1/3 epinephrine	247

(108). In the perfused hind limb of the dog, hydroxytyramine is $\frac{1}{60}$ (108) and in the perfused rabbit ear $\frac{1}{3000}$ (92a) as active as epinephrine.

Dilator action on the bronchioles of guinea pigs, dogs and cats is $\frac{1}{50}$ that of epinephrine (7). Isolated intestinal segments are relaxed by hydroxytyramine when present in concentrations 17 (cat) or 20–40 (rabbit) times that of epinephrine (108). Similarly, the non-pregnant cat uterus is relaxed by doses 80–85 times greater; the uterus *in situ* by doses 100 times greater than the effective dose of epinephrine (108).

'EPININE', 1-(3',4'-DIHYDROXYPHENYL)-2-METHYLAMINOETHANE

The pressor potency of 'Epinine' has been reported as $\frac{1}{7}$ that of racemic epinephrine (25). Comparisons with epinephrine indicate a pressor potency $\frac{1}{3}-\frac{1}{10}$ in cats (61, 131) and $\frac{1}{3}-\frac{1}{13}$ in dogs (121, 149, 234). 'Epinine' acts like epinephrine on peripheral blood vessels, causing dilatation in small doses and dilatation followed by constriction with larger doses (197). Constriction of renal vessels has been described (197, 202).

Bronchodilatation in isolated perfused guinea pig lungs in which constriction

was induced by histamine, barium chloride or pilocarpine was found to require 50 times more Epinine than epinephrine (149, 240). Bronchodilatation in dogs, in which constriction was induced by arecoline or histamine, was obtained by doses of 0.4–1.0 mg./kg. (42, 195).

Isolated segments of rabbit small intestine (12, 73) and rat colon (92a) are relaxed by 'Epinine' in doses 100 times the effective dose of epinephrine. Isolated segments of guinea pig ileum are relaxed by low concentrations (1:4 million) but contracted by higher concentrations (1:400,000) (149). The pupil of both the rabbit and cat is dilated by Epinine at 10 times the effective dose of epinephrine (73). The retractor penis of the dog is contracted by intravenous doses of 10–25 mcg./kg., being somewhat less active than epinephrine (167). The isolated non-gravid uteri of rabbits and guinea pigs are contracted by concentrations of 1:4 million (149).

'KEPHRINE', ADRENALON, 3,4-DIHYDROXYPHENYL METHYLAMINOMETHYL KETONE

'Kephrine' has been reported to be distinctly less pressor than hydroxytyramine (25). Pressor potencies relative to epinephrine are somewhat variable, being reported as 1/200 (132), 1/150 (234), 1/80 (111, 149). Bronchodilatation in isolated perfused guinea pig lungs requires doses approximately 10 times greater than those of epinephrine (149). The isolated guinea pig ileum is relaxed by concentrations 10–20 times greater than those for epinephrine. The isolated guinea pig uterus is relaxed whereas the rabbit uterus is contracted by dilutions of 1:1 million (149). Acetylcholine induced activity of the isolated rat uterus is diminished by concentrations 25 times greater than equiactive concentrations of epinephrine (92a).

Acute intraperitoneal toxicity in mice is distinctly lower than that of epinephrine. An LD_{50} value of 902 ± 25 mg./kg., or 196 times that of epinephrine, has been reported (149). The toxic dose intravenously in rabbits is 30 mg./kg.; subcutaneously in mice, 2000 mg./kg. (33).

'COBEFRIN', CORBASIL, 1-(3′,4′-DIHYDROXYPHENYL)-2-AMINOPROPANOL

The pressor potency of 'Cobefrin' in dogs following intravenous injection has been reported to be one-half that of epinephrine (213). Similarly, intravenous injection into cats gave a pressor potency of 0.3–0.4 that of epinephrine (238, 241). With intravenous infusion in dogs, pressor potency was found to be $\frac{1}{8}$ that of epinephrine (213). Both epinephrine and arterenol are reported to be more vasoconstrictor than 'Cobefrin' when these drugs are injected intraarterially (4).

The heart is strongly stimulated by 'Cobefrin' and responds to effective doses by an increased output, diminished diastolic and systolic volumes, decreased stroke amplitude and increased rate. By comparison with epinephrine, it is 4.3 times more stimulating (62). It is also less effective than epinephrine and dioxyephedrine in increasing coronary flow in the isolated perfused rabbit heart (4).

The bronchodilator action of 'Cobefrin' in the isolated perfused guinea pig lungs is $\frac{1}{15}$ that of epinephrine. Histamine bronchoconstriction in anesthetized dogs is antagonized by 'Cobefrin' in doses of 1–3 mg./kg. (42). Isolated segments of the

small intestine of the rabbit are relaxed by 2–5 times the effective concentration of epinephrine (73, 215). The effective concentration for relaxation of the isolated rat uterus is 10 times that of epinephrine (92a).

The levo-isomer has been reported to be 2–3 times more effective than epinephrine on the intestine and 200 times more potent than its dextro-isomer (79). Both epinephrine and arterenol are reported to be more stimulating on the ureter, dilator pupillae and nictitating membrane (4). No stimulating effect on the central nervous system of rats was observed with subcutaneous injections of 0.25–5.00 mg./kg. (219).

DIOXY-EPHEDRINE, 1-(3′,4′-DIHYDROXYPHENYL)-2-METHYLAMINOPROPANOL

The blood pressure response to dioxy-ephedrine is somewhat variable. Some investigators have found this drug to be distinctly pressor, with a dioxy-ephedrine: epinephrine dosage ratio of 41–140 (61, 238, 240). A fall in pressure follows a transient rise and the magnitude of both these responses varies with the dose, the depressor response being prominent with small doses (0.5–100 mcg./kg.) and diminishing as the dose is increased (61, 215). Cardiac stimulation is less than with epinephrine, the potency ratio being 1.0:1.5. However, a better amplitude contraction is maintained (62). Dioxy-ephedrine induces peripheral vasoconstriction and diminishes the cardiac output of cats (188). In the perfused hind leg of the cat, an epinephrine vasoconstrictor ratio of 31.4 has been obtained (187).

The isolated rabbit uterus is stimulated but this action requires a drug concentration 50 times greater than epinephrine (215). The isolated guinea pig intestine is relaxed by doses 5 times larger than the effective dose of epinephrine (215). Bronchodilatation of the isolated perfused guinea pig lung requires doses 14.7 times greater than the effective dose of epinephrine (240). Histamine-induced bronchoconstriction in dogs was found to be effectively relaxed by intravenous doses of 1–2 mg./kg. and dioxy-ephedrine was therefore rated as an excellent bronchodilator (42).

No central nervous system stimulation in rats was observed after subcutaneous injections of 1–40 mg./kg. (219).

The minimum lethal dose intravenously in rabbits is about 1.0 mg./kg.; this produces marked pulmonary edema (215). Subcutaneous doses of 40 mg./kg. in rats caused only a 10 per cent mortality (219).

'BUTANEFRINE', ETHYLNORSUPRARENIN, 1-(3′,4′-DIHYDROXYPHENYL-2-AMINO-1-BUTANOL

Butanefrine is predominantly a depressor drug. Intravenous doses of 0.1–1.0 mg./kg. cause a sharp fall of blood pressure in anesthetized cats which lasts about 9 minutes (238). Pressor action becomes apparent only after repeated intravenous injections; the depressor response is then replaced by a diphasic action which after further doses is replaced by a purely pressor response (41, 43). In the cat leg perfused with Locke solution, when the doses of 'Butanefrine' and epinephrine were matched quantitatively by repeated injections, 'Butanefrine' was reported to have a mean constrictor potency 1/1273 ± 190 that of epinephrine.

Small doses of the drug were found to be without effect. When defibrinated blood was substituted for Locke's solution, the potency for constrictor action was 1/238 ± 15.3 (43, 187). This suggests that the presence of small amounts of epinephrine (or sympathin) is important for this vasoconstriction. Recent experiments have shown that small amounts of epinephrine or adrenochrome will restore vasoconstriction in perfused rabbit ears when the constrictor response has been exhausted by sympathetic nerve stimulation (70). Excised hepatic veins are constricted by 'Butanefrine', the epinephrine ratio being about 50. Simultaneously with the fall of blood pressure, after intravenous administration, there is an increase in limb and intestinal volumes, a rise in portal and venous pressures and a constriction of the liver. Pooling of blood in the splanchnic bed has been suggested as the principal cause of the fall in blood pressure (41).

The cardiac action of 'Butanefrine' in the Starling heart-lung preparation was less than that of epinephrine. The epinephrine ratio for cardiac output was 5.3 ± 1.2; for systolic volume, 6.2 ± 1.9 (41).

'Butanefrine' is an effective bronchodilator drug but in the excised perfused guinea pig lungs the doses required are about 71 times greater than those of epinephrine (240). Histamine bronchoconstriction in anesthetized dogs is readily diminished or abolished by the intravenous injection of 1.0 mg./kg. of 'Butanefrine'. Inhibitory action on the isolated rat colon is approximately twice greater than that of epinephrine (92a).

The intravenous, intramuscular or subcutaneous administration of 0.5–2.0 mg./kg. was found effective in relieving bronchial spasm in asthmatic patients. These doses cause a distinct decrease in diastolic without a significant change in systolic pressure. The pulse rate is moderately increased. Subjective side-effects such as precordial pain, nausea, vomiting and excitation are reported to be less than with epinephrine (239).

Acute intravenous toxicity (LD_{50}) in mice was found to be 117 ± 1.04 mg./kg. for 'Butanefrine' and 0.98 ± 0.184 mg./kg. for epinephrine (239).

'ISUPREL', 'ALEUDRINE', 1-(3',4'-DIHYDROXYPHENYL)-2-ISOPROPYLAMINOETHANOL

'Isuprel', like 'Butanefrine', is a potent vasodepressor drug. The inhibitory actions characteristic of epinephrine have been enhanced by the replacement of the methyl group on the nitrogen by an isopropyl group. Intravenous injection causes a marked fall of blood pressure in anesthetized or decapitated cats, dogs and rabbits (4, 149, 150, 179). Intravenous injection of 0.6–1.0 mcg./kg. into anesthetized dogs causes a 38–46 mm. Hg. fall in blood pressure lasting 3–17 minutes (149, 150). Intramuscular or intra-intestinal injection of 0.10–0.25 mg./kg. causes distinct falls in pressure lasting more than 200 minutes. Similar results are obtained in unanesthetized dogs after oral administration (150). Intra-arterial injection of 'Isuprel' causes a reduced peripheral resistance in the renal, mesenteric and femoral vascular beds (4). Subcutaneous administration of 0.15 to 1.0 mgm. to man causes a marked increase in pulse pressure, due in part to a reduction in diastolic pressure. Occasionally, systolic pressure may

increase slightly; this appears to result from increased cardiac action. Similar results have been obtained after sublingual administration (179). 'Isuprel', in these doses, is a potent vasodilator drug (190, 229).

The dog heart-lung preparation reveals a marked cardiac stimulation as evidenced by an increase in stroke and minute volume, a reduction in right auricular pressure and a marked increase in rate (143). The isolated perfused frog, cat and rabbit hearts are stimulated and there is a distinct increase in both rate and amplitude (149, 150, 179). The isolated frog and cat heart give positive inotropic and chronotropic responses to 'Isuprel' and this drug is 10 times more potent than epinephrine in inducing these changes (161). An analysis of the effect on the heart reveals a marked increase in stroke volume and work per beat. As with epinephrine, there was a distinct reduction in the duration of systole (204). Myocardiograms of the dog heart *in situ* (149) and pulse rates in anesthetized and unanesthetized dogs reveal marked tachycardia after intravenous doses of 1.0 mcg./kg. and after intramuscular or oral doses of 0.1-0.2 mg./kg. (149, 150). Cardiac inhibition in man, induced by the application of pressure over the carotid sinus, can be prevented by prior medication with 'Isuprel'. The increased sympathetic tone induced by this drug is dominant and therefore prevents the appearance of vagal effects. This stimulant action appears to be largely on the sinus node, lower auricular foci or auriculo-ventricular node and seldom on lower ventricular foci. By contrast, epinephrine and arterenol were reported frequently to induce foci from lower ventricular centers (190).

Histamine bronchoconstriction in the isolated perfused guinea pig lung preparation is readily relaxed by 'Isuprel'. In this action, it seems to be somewhat more effective than epinephrine (179, 225). The bronchoconstriction induced by horse serum in sensitized guinea pigs is abolished (225) and pilocarpine-induced bronchoconstriction in anesthetized dogs is readily antagonized (142). In the latter preparation, it is about 10 times more potent than epinephrine. 'Isuprel' is about 1.5 times more potent than epinephrine in protecting unanesthetized guinea pigs from histamine mists (225).

'Isuprel' has been reported to be an effective bronchodilator drug in man and to be useful in the treatment of bronchial asthma. It is effective when administered intravenously (0.5–1.0 mg.), subcutaneously (1.0 mg.), by inhalation (1.0 per cent solution) or orally (10–12.5 mg.). These doses cause some tachycardia and palpitation, a small increase in systolic and usually a decrease in diastolic pressure (143, 150, 239). Following the inhalation of 0.5–1.0 per cent solutions, there is a marked increase in vital capacity of asthmatic patients and of subjects with bronchoconstriction induced by histamine or 'Mecholyl' (223).

Isolated intestinal segments are relaxed by concentrations equal to or somewhat less than those of epinephrine (4, 28, 143, 149, 150). The rabbit small intestine and colon *in situ* are promptly relaxed by intravenous doses of 0.03–0.05 mg./kg. Isolated uteri of the rabbit and guinea pig, stimulated by histamine or pituitrin, are relaxed by dilutions of 1:40 million (149, 179). The denervated nictitating membrane of the cat is not contracted by doses of more than 100 mcg./kg. (143). The dog retractor penis is relaxed by intravenous doses of 1–2 mcg./kg. (168).

The acute intravenous toxicity (LD_{50}) in mice is 77 ± 7 mg./kg.; intraperitoneal toxicity 494 ± 14 mg./kg. Subcutaneous injections of 2–20 mg./kg. in dogs cause salivation, restlessness, vomiting, cardiac arrhythmias and occasionally death at 15–20 mg./kg. Subacute and chronic toxicity determinations also suggest that this drug has low toxicity (71).

GENERAL CONSIDERATIONS INVOLVED IN SYMPATHOMIMETIC DRUG ACTION

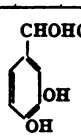
The similarity of the action of epinephrine to sympathetic nerve stimulation (36, 46, 50, 164) has been emphasized previously in this review. Secretion of this hormone by the adrenal gland is probably continuous and it has been determined that cats and dogs secrete about 0.023 mcg./kg./min. (228). Large amounts may be secreted in emotional states and this observation has given rise to the theory that epinephrine aids the organism in carrying out the activities associated with pain, fear and anger (45, 47, 49). Recent investigations have demonstrated the presence of *l*-arterenol in extracts of the adrenal medulla (84, 93, 122a, 251). The *l*-isomer has been isolated from commercial epinephrine in pure form (251) and its content estimated as 10–18 per cent of the total (11). These results compare favorably with determinations of the *l*-arterenol content of fresh gland extracts (84). Adrenal medullary tumors have been shown to contain large amounts of *l*-arterenol, this substance accounting for a major portion of the pressor action obtained from extracts of these tumors (93, 122). Experiments in eviscerated spinal cats with the kidneys excluded from the circulation have provided evidence that splanchnic nerve stimulation causes the liberation of both epinephrine and arterenol from the adrenal gland. It was estimated that the arterenol content varied from less than 20 to as much as 80 per cent of the total active material secreted (39).

The possibility that epinephrine, *l*-arterenol or other substances are liberated at sympathetic nerve endings and are the mediators of the nerve impulse has been suggested (13, 50, 72, 165, 193). Stimulation of the sympathetic nerves to the heart, liver, intestine, uterus, pilomotor muscles and other organs liberates a humoral sympathomimetic substance (or substances) which has an effect on the denervated heart, nictitating membrane, intestine, iris and other indicator organs similar to that of epinephrine (34, 46, 48, 52, 53, 56, 136, 206, 210). This possibility was strengthened by the observation that the response to the liberated substance was increased by denervation or by cocainization. Concentrates of solutions obtained by perfusion of stimulated organs were found to have an ultraviolet absorption spectrum quite similar to that of epinephrine (16, 17), were rendered inactive upon exposure to air or heat (155), gave the Viale color reaction (13) and a green fluorescence when exposed to strong alkali. These data suggest that epinephrine is liberated by nerve stimulation. However, certain observations are not wholly in accord with the assumption that epinephrine is the only substance liberated. The pressor response to arterenol in ergotaminized decapitate cats resembles the response to hepatic nerve stimulation more than that to epinephrine (227). An analysis of the physiological responses to epinephrine, arterenol and liver sympathin also supports the assumption that hepatic nerve

stimulation releases a substance which resembles arterenol (101, 196). Subsequently, it was shown that these arterenol-like extracts do not give the fluorescence reaction which characterizes epinephrine (92). Extracts of mammalian adrenergic nerves, bovine and mammalian blood, spleen heart and urine have been described as containing arterenol or an arterenol-like substance (15, 85, 122a). Inasmuch as both epinephrine and *l*-arterenol are obtained from the adrenal medulla, it is not improbable that these substances would be obtained from adrenergic nerve fibers and from organs which contain a large number of adrenergic nerve fibers. The chromaffin cells of the adrenal medulla are analogous to the

TABLE 4

The effect of varying the N-alkyl group on the adrenergic inhibitory potency of sympathomimetic amines



Compound No.	Structure R	Relative activity (In terms of multiples of the effective dose of racemic epinephrine)							
		Uterus					Bronchioles		
		Rat			Guinea pig		Guinea pig		
		(168)	(92a)	(148)	(179)	(254)	(168)	(179)	(225)
1*	H	30	75–300**	10	2.5	100	17	5–7	140
2*	CH_3	1	1	1	1	1	1	1	1
3	C_2H_5		0.5–1.0		1			0.3–0.5	1
4	$CH(CH_3)_2$		0.5–1.0	0.1	1			0.1–0.3	0.7
5	C_3H_7				5.0			3–5	
6	$C(CH_3)_3$				1			0.08–0.12	

* For compounds Nos. 1 and 2, in references 148 and 168, the comparison is on the basis of the *l*-isomers; 179 and 225, racemic compounds used for comparison; 254, racemic No. 1 with *l*-isomer of No. 2.

** l-Arterenol was used in this investigation.

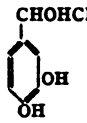
postganglionic sympathetic neurones. As with adrenal medullary cells, stimulation may cause the liberation of both of these substances.

The theory has been advanced that *l*-arterenol is identical with sympathin E and that this substance plays an essential role in the transmission of adrenergic excitatory nerve impulses (101, 227). However, the inhibitory action of *l*-arterenol is quite marked and can be demonstrated easily. Examination of the data shown in Tables 4 and 5 indicates, in an approximate manner, the relative inhibitory and excitatory actions of both epinephrine and arterenol. The guinea pig uterus is inhibited by these drugs when stimulated or when showing spontaneous activity, and excited when in a quiescent state. The inhibitory dose is 2.5 times (table 4) and the excitatory dose 2 times that of epinephrine (table 5). This suggests that arterenol has the same action as epinephrine for this organ but is somewhat less potent. *l*-Arterenol is more effective than epinephrine in causing

relaxation of the isolated rat colon (92a). The vasoconstrictor potency of epinephrine is 1.5–2.5 times greater than *l*-arterenol in perfused rabbit ears (168). Similarly, arterenol and racemic epinephrine were compared as vasoconstrictors in dogs. The drugs were injected intra-arterially and the resultant change in vasomotor resistance determined. Epinephrine was more vasoconstrictor in the renal, equal in the mesenteric and less in the femoral circulation (4). The similarity of the vascular response to these substances is also illustrated by figure 1. It will be noted in this experiment that the differences in response between epinephrine and *l*-arterenol are quantitative rather than qualitative. By com-

TABLE 5

The effect of varying the N-alkyl group on adrenergic inhibitory and excitatory actions



Compound No.	Structure R	RELATIVE ACTIVITY (In terms of multiples of the effective dose of racemic epinephrine)				
		Uterus*		Nictitating Membrane	Blood Pressure*	
		Guinea Pig	Rabbit	Cat	Dog	
		(149)	(149)	(92a)	(149)	(179)‡
1	H	E, 2.0	E, 2.0	E, 1*	E, 0.67	1.0
2	CH_3	E, 1.0	E, 1.0	E, 1	E, 1.0	1.0
3	C_2H_5	E, 20	E, 2.0	E, 45	E/I, 3.3/2.7†	E/I, 2.3/2.7†
4	$CH(CH_3)_2$	I, 0.5	I, 0.5	I	I, 0.35	I, 0.8
5	C_3H_7					I, 2.7
6	$C(CH_3)_3$	I, 20	I, 2.0		I, 0.35	I, 0.7
7	C_4H_9	I, 20	I, 20		I, 5.5	

N-dimethyl analog, cat non-gravid uterus, I, 1/50; blood pressure of spinal cat, E, 1/25, anesthetized dog, 1/40 (251a); spinal dogs, 1/30–1/50 (230a).

* E, excitation or pressor response; I, inhibition or depressor response.

† E followed by I. Ratio based on changes observed, whether pressor or depressor.

‡ Results estimated from published graph showing responses at various dose levels.

* l-Arterenol was used in this investigation.

parison, the vascular response to 'Isuprel' is vasodilator only. Equal vasoconstrictor potency was observed with the *l*-isomers of both drugs in the isolated perfused dog lungs (144). The greater pressor potency of *l*-arterenol may result from greater vasoconstriction in some vascular areas, as noted above for the femoral circulation, from greater stimulation of the heart (in which the drug is reported to be almost 2 times more stimulating than epinephrine (62)), or from a combination of these two effects. Arterenol has been reported to be more excitatory than epinephrine to the pregnant cat uterus. Excitatory action is equal or less in all other organs examined (254). Similarly, the inhibitory action of arterenol can be demonstrated with those organs inhibited by epinephrine but it is less than that observed with the latter substance. The observation that adrenolytic drugs

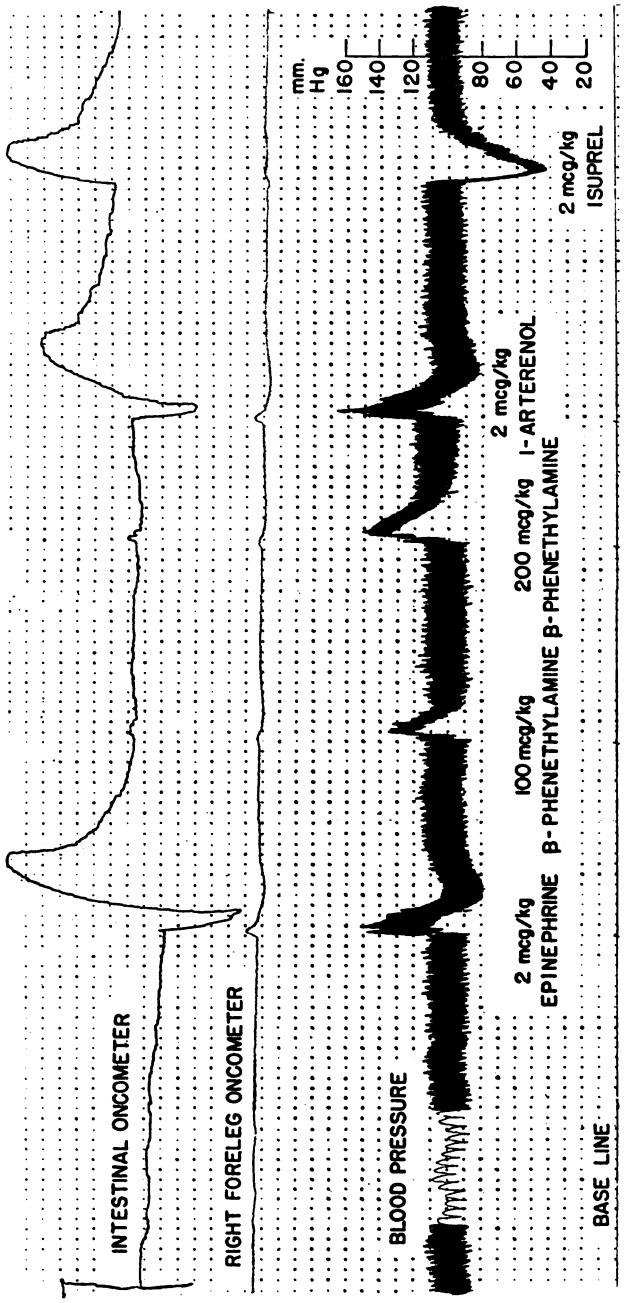


FIG. 1. A COMPARISON OF THE EFFECTS OF SYMPATHOMIMETIC AMINES ON BLOOD PRESSURE AND ON LEG AND INTESTINAL VOLUMES, AS DETERMINED BY ONCOMETRY

Upward movement in the oncometer record indicates an increase in volume. The axigraph rulings are 5 mm. apart. All injections were made into the exposed femoral vein.

which readily reverse the pressor action of epinephrine depress but do not reverse the pressor action of arterenol is difficult to understand (86, 185). It is interesting to note that the pressor action of arterenol is reversed in ergotaminized cats. However, the dose of arterenol required to produce a vasodepressor response is about 20 times greater than the vasodepressor dose of epinephrine. The significance of this observation is uncertain inasmuch as the investigators report that arterenol did not cause vasodilatation in perfused hind limbs of cats treated with Dibenamine (255).

Neither epinephrine nor arterenol is purely excitatory. Epinephrine appears to be equal or more active than arterenol as an excitatory agent in most sympathetically innervated organs. Arterenol liberation may be important for vasoconstriction but its function in other organs where it is much less potent than epinephrine is not clear. Inasmuch as it does not differ greatly from epinephrine as a vascoconstrictor agent, it is difficult to assign to it functions that could not be equally well explained by the release of epinephrine alone. However, *l*-arterenol is secreted by the adrenal medulla and is probably released by the stimulation of adrenergic nerves. If *l*-arterenol is an intermediate in the synthesis of epinephrine, rapid secretion or an arrest at the terminal stages of synthesis (15) of this hormone might lead to the appearance of some of the intermediate substance or substances in the circulation.

It is generally agreed that epinephrine is formed from tyrosine. Suggested steps in this synthesis are:

a. Introduction of the second phenolic hydroxyl group (dopa);
b. Decarboxylation (hydroxytyramine);
c. Introduction of the side chain hydroxyl group (arterenol);
d. N-methylation (epinephrine).

It has been suggested that reaction (b) must precede (d) and follow (a), since both tyrosine and N-methyl-dopa apparently are not decarboxylated. Perfusion of the suprarenal gland of the cow with N-methyl-dopa does not give rise to epinephrine. These data suggest that the primary amine is formed first and that the secondary amine is produced from it by N-methylation (30).

Barger and Dale suggested that the primary amines are imperfect sympathomimetic substances, that their action is mainly excitatory and that they do not possess all the inhibitory effects of epinephrine. Investigation of arterenol derivatives in which there are groups larger than methyl substituted on the nitrogen has disclosed that still greater inhibitory potency is obtained with some of these analogs.

The rat uterus and guinea pig bronchioles respond to epinephrine and other related sympathomimetic amines by relaxation only and may, therefore, be used as indicators of relative inhibitory potency (table 4). The primary amine (No. 1—arterenol) is distinctly less active than the N-methyl analog (No. 2—epinephrine). The N-ethyl derivative (No. 3) equals or exceeds the N-methyl compound in inhibitory action. The greatest potency is obtained with the N-isopropyl (No. 4) and N-tertiary butyl (No. 6) compounds. The N-*n*-propyl (No. 5) compound is much less potent than the N-isopropyl derivative and is comparable

to the primary amine as an inhibitory agent. These data suggest that the adrenergic inhibitory receptors respond more readily to compounds in which there is an N-alkyl substitution and in which the substituent is methyl or derivatives obtained by replacing the hydrogens of the methyl group by other methyl groups (Nos. 3, 4 and 6). This structural requirement for high inhibitory action was first pointed out with a series of phenolic derivatives (151, 178, 179). The importance of this arrangement is readily seen by comparing compounds No. 3–6. No. 3 may be considered as

$$\begin{array}{c} H \\ -NH-C-CH_3 \\ H \end{array}$$

with a single methyl group substituted for one of the hydrogens, and Nos. 4 and 6 as having two and three methyl groups, respectively. When the methyl substituent of No. 3 is replaced by an ethyl group (No. 5), inhibitory potency is greatly reduced.

Interesting results are obtained in organs in which both adrenergic inhibitory and excitatory actions are demonstrable. Representative results are shown in table 5. Derivatives in which the substituent on the nitrogen is ethyl, methyl or hydrogen are excitatory and, except possibly for action on the nictitating membrane and blood pressure, the N-methyl derivative (No. 2—epinephrine) is the most potent. Compound No. 3 is interesting in that both pressor and depressor actions are obtained. Also, compound No. 2 may cause depressor responses under some conditions. If pressor responses alone are considered, we might assume that excitatory action is greatest with the primary amine (No. 1) and diminishes progressively with methyl, ethyl, isopropyl and tertiary butyl substitution. However, the pressor response is the result of a complex reaction in which an increased output of the heart and changes in splanchnic, skeletal muscle and skin blood volumes all contribute. As previously pointed out, epinephrine equals or exceeds arterenol as a vasoconstrictor agent when the action is determined by perfusion.

The isolated rabbit or guinea pig uterus provides a comparatively simple indicator of inhibitory and excitatory action. Results obtained with both of these preparations suggest that the N-methyl derivative epinephrine is most excitatory. This action is less with the primary amine and the N-ethyl derivative and is not observed with compounds containing larger N-alkyl groups. The action of these latter substances is predominantly inhibitory. Inasmuch as these uteri respond by both excitation and inhibition to some drugs in this series, it seems probable that both adrenergic inhibitory and excitatory receptors are stimulated by each drug in varying degrees. Motility of the guinea pig uterus may be increased (table 5) or diminished by all of these predominantly excitatory compounds (table 4). As with changes in blood pressure, it may be more accurate to consider these uterine responses as the net result of two opposing actions.

The alcoholic hydroxyl on the side chain is important for both excitatory and inhibitory actions. This is illustrated by the results shown in table 6. Compound No. 2 (racemic epinephrine) is twice as potent a uterine stimulant as the corre-

sponding ethane derivative (No. 9). The N-methyl ketone derivative (No. 14) is about 1/200 as potent as No. 2. With histamine-constricted bronchi, No. 2 is distinctly more active than either Nos. 9 or 14. This indicates the importance of the alcoholic hydroxyl for both excitatory and inhibitory actions. Further evidence is obtained by comparing the N-isopropyl derivatives Nos. 4, 11 and 16. When the alcoholic hydroxyl is replaced by hydrogen, inhibitory potency is diminished more than 200 times; by oxygen, the compound is inactive.

TABLE 6

The effect of the alcoholic hydroxyl on sympathomimetic potency

Compound No.	Structure R	Structure R'	Relative activity (In terms of multiples of the effective dose of racemic epinephrine) Uterus* Rabbit (149)	Bronchioles* guinea pig (149)	Colon rat (92a)	Blood pressure* dog (149)	Blood pressure* cat (25)
1	H	OH	E, 2.0	I, 140	I, 0.2-1.0**	E, 0.67	E, 0.7
2	CH_3	OH	E, 1.0	I, 1.0	I, 1.0	E, 1.0	E, 1.0
3	C_2H_5	OH	E, 2.0	I, 1.0	I, 1.0	E/I, 3.3/2.7	
4	$CH(CH_3)_2$	OH	I, 0.5	I, 0.5	I, 1.0	I, 0.35	
5	C_3H_7	OH				E/1, 4/2.5 (179)	
6	$C(CH_3)_3$	OH	I, 2.0	I, 0.5		I, 0.35	
8	H	H				E, 50 (108)	E, 50
9	CH_3	H	E, 2.0	I, 25	I, 100	E, 6.5	E, 7
10	C_2H_5	H					E, 23
11	$CH(CH_3)_2$	H	I, 200	I,100		E/I, 620/380	
12	C_3H_7	H					E, 140
13	H	O					E, 23
14	CH_3	O	E, 200	I, 10	I, 4, 20	E, 52	E, 23
15	C_2H_5	O					E, 15
16	$CH(CH_3)_2$	O	Inactive	I, 1000		E/I, 1000/680	
17	C_3H_7	O					E, 140

* E, excitation or pressor reponse I, inhibition or depressor response.

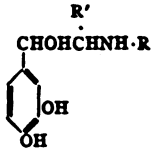
** l-Arterenol was used in this investigation.

Results obtained with the cat uterus have shown No. 2 to be more inhibitory than No. 1 and Nos. 9 and 14 more than Nos. 8 and 13 (24). The excitatory action of sympathomimetic amines is easily demonstrated with the dog retractor penis preparation (24), although this organ may have adrenergic inhibitory receptors inasmuch as it responds to No. 4 by relaxation (168). Compound No. 2 is distinctly more excitatory than No. 1 (24, 168). The ethane derivatives cause contraction of the retractor penis, the most potent one being No. 9 and, in order of diminishing potency, No. 10, No. 8 and No. 12. This order of potency is identical with that found for blood pressure and for the non-pregnant uterus of the cat (24).

These facts are also apparent when the effect on blood pressure is considered. Compound Nos. 9 and 14 are much less pressor than No. 2. As in the case of the primary amines, there is a marked reduction in pressor potency when the hydroxyl is replaced by hydrogen or oxygen. Compound Nos. 3 and 5 are both pressor and depressor, both actions requiring relatively large doses to produce significant changes; the N-isopropyl derivative (No. 4) is a strong depressor agent. The corresponding derivatives, Nos. 11 and 16, are of very low potency and cause both pressor and depressor responses. Greatest pressor and depressor potency is found with those compounds containing an alcoholic hydroxyl. Among these, maximum excitatory action is obtained with the N-methyl derivative; maximum inhibitory action, with the N-isopropyl or N-t.-butyl derivatives.

TABLE 7

The effect of changes in the structure of the side chain on sympathomimetic potency



Compound No.	Structure		Relative activity (In terms of multiples of the effective dose of racemic epinephrine)	
	R	R'	Blood pressure*	Bronchioles*
1	H	H	E, 0.67 (149)	I, 104 (149)
2	CH_3	H	E, 1.00 (149)	I, 1.0 (149)
4	$CH(CH_3)_2$	H	I, 0.35 (149)	I, 0.5 (149)
18	H	CH_3	E, 12 (237), 2–6 (213)	I, 14.9 (240)
19	CH_3	CH_3	I/E, 1.0/40–80 (188, 238)	I, 14.7 (240)
20	H	C_2H_5	I/E, ± 50–500/1273† (187)	I, 80 (152)
21	CH_3	C_2H_5	I, (203)	
22	$CH(CH_3)_2$	C_2H_5	I, 3 (152)	I, 5.3 (152)

* E, excitation or pressor response; I, inhibition or depressor response.

† E value obtained in the isolated perfused cat leg.

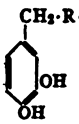
The size and shape of the group between the benzene ring and the nitrogen as well as of the alkyl substituent of the secondary amine influence excitatory and inhibitory potency. This is illustrated by the data in table 7. The addition of a methyl group to the side chain at R^1 (No. 18) causes a large reduction in pressor potency. The corresponding N-methyl derivative (No. 19) is predominantly depressor. Both Nos. 18 and 19 are more potent bronchodilators than No. 1 but distinctly less active than No. 2. An increase in length to an ethyl group in the R^1 position causes a further reduction in pressor and a simultaneous increase in depressor potency. No. 20 has a weak excitatory and a strong inhibitory effect. The N-isopropylbutanol derivative (No. 22) is a potent depressor and bronchodilator drug but less active than No. 4 in which R^1 is H. No. 20 is a more potent bronchodilator than No. 1 but somewhat less potent than No. 18. These data suggest that adrenergic excitatory action is diminished by

alkyl substitution on the second carbon of the side chain. Adrenergic inhibitory action is also diminished but less than excitatory action. Inhibitory action is dominant with those derivatives in which there is an N-alkyl substituent.

The effect of modifying the structure of the side chain is further illustrated by the compounds in table 8. Greatest activity, relative to No. 2, is obtained with No. 9. Nos. 8 and 25 appear to be of comparable activity, the additional methyl group of No. 25 not causing any significant difference in action over that of the unsubstituted compound, No. 8. Compound No. 26, wherein the amine group is on the terminal carbon, is distinctly less pressor than Nos. 24 and 25. When there is only one carbon between the ring and the amine group (Nos. 23 and 24), pressor potency is very low. In the case of the structural isomer of No. 25, 2-(3′,

TABLE 8

The effect of change in length of the side chain on pressor potency



Compound No.	Structure		RELATIVE PRESSOR POTENCY*	REFERENCE
	R	R′		
2			1	
23	—	H	800	243
24	—	CH_3	800	242
8	CH_2	H	35–100	149, 25
9	CH_2	CH_3	6.5	149
25	$CH \cdot CH_3$	H	50	24, 108, 219
26	CH_2-CH_2	H	150–191	24, 219

* Expressed in terms of multiples of the effective dose of racemic epinephrine.

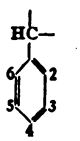
4′-dihydroxyphenyl)-3-methylaminopropane, pressor potency has been reported to be distinctly greater than that of either Nos. 25 or 26 (189).

The effect of hydroxyl substitution on the benzene ring depends upon the position and number of substituents (table 9). The greatest increase in pressor potency in the phenethanolamine series is obtained by substitution at the 3 and 4 positions (No. 1). Of these two, the 3-hydroxyl group (No. 28) appears to be of more importance inasmuch as the 4-hydroxyl derivative (No. 29) is no more potent than the unsubstituted compound (No. 27). Compound Nos. 30 and 31 are reported to have low pressor potencies. The addition of a third hydroxyl to the ring is not favorable for pressor action inasmuch as No. 32 is reported to be depressor and No. 33 ineffective.

The results obtained with the various phenethylamine derivatives make generalization difficult. It would seem that there is no great difference in pressor potency with Nos. 36–39 and No. 8. The unsubstituted compound (No. 34) and its 2-hydroxyl analog (No. 35) are of comparable potency and both are distinctly less potent than the above-mentioned compounds. It is interesting to note

TABLE 9

The effect of the number and position of the hydroxyls on the benzene ring of sympathomimetic amines



Compound No.	Structure 2	3	4	5	6	RELATIVE PRESSOR POTENCY*	REFERENCE
A. ETHANOLAMINES							
2						1	
27	H	H	H	H	H	100–124	61, 236
28	H	OH	H	H	H	10	147
29	H	H	OH	H	H	100	151, 178
30	OH	H	OH	H	H	weak	31
1	H	OH	OH	H	H	0.67–1.0	149, 179
31	OH	H	H	OH	H	weak	163
32	OH	OH	OH	H	H	depressor	163
33	H	OH	OH	OH	H	ineffective	163
B. ETHYLAMINES							
2						1	
34	H	H	H	H	H	183–500	25, 108, 238
35	OH	H	H	H	H	500	25
36	H	OH	H	H	H	70–100	24, 25
37	H	H	OH	H	H	70–105	24, 61, 108, 151
8	H	OH	OH	H	H	50	24, 25, 108
38	OH	OH	OH	H	H	100	25
39	H	OH	OH	OH	H	50	106

* Expressed in terms of multiples of the effective dose of racemic epinephrine.

TABLE 10

The effect of alkoxy substitution on the benzene ring of various sympathomimetic amines

Compound No.	Structure 1	2	3	4	RELATIVE PRESSOR POTENCY*	REFERENCES
2					1	
40	CH_3O	CH_3O	H	H	>400	81
41	CH_3O	CH_3O	H	CH_3	Weak	121
42	CH_3O	CH_3O	CH_3O	H	Ineffective	133
43	CH_3O	CH_3O	H	CH_3	Weak	121
44	H	CH_3O	CH_3O	CH_3	Weak	121
45	CH_3O	H	CH_3O	CH_3	Weak	121

* Expressed in terms of multiples of the effective dose of racemic epinephrine.

that No. 28 is much more pressor than No. 36. The alcoholic hydroxyl appears to be important for pressor action when the 3-hydroxyl group is present on the benzene ring and relatively unimportant in its absence (Nos. 27, 29, 34 and 35) or when there are three hydroxyl groups on the ring (Nos. 32, 33, 38 and 39).

The effect of substituting methoxyl for hydroxyl groups on the benzene ring is shown in table 10. In all instances sympathomimetic potency is greatly reduced, the resulting compounds having very little pressor activity. The 2,4-dimethoxyl analog of epinephrine has been reported to be predominantly depressor (238). The replacement of the 3-hydroxyl group on the benzene ring of epinephrine by a 3-amino group diminishes the effects on blood pressure, the non-gravid uterus and the denervated nictitating membrane of anesthetized cats (86a).

SUMMARY

The data presented here suggest that, with the exception of the action on the heart, the adrenergic excitatory action of epinephrine equals or exceeds that of other compounds described. It also has inhibitory actions and plays an important role in regulating autonomic activity. *l*-Arterenol appears to be somewhat less potent and its physiological significance less apparent. There is evidence that it is an intermediate in the synthesis of epinephrine. Maximum inhibitory potency is obtained by replacing the hydrogen atoms of the N-methyl group of epinephrine by other methyl groups, to give the corresponding isopropyl or *t*-butyl derivative. Derivatives of this type have not been obtained from biological material and there is no evidence at the present time that they are produced in the animal body. Physiological potency in excess of that obtained with epinephrine suggests the importance of these substances as tools in studying the mechanism of adrenergic inhibitory action. Other modifications in structure, discussed above, diminish both excitatory and inhibitory actions. Of the various modifications, substitution of a methyl or ethyl group on the second carbon of the side chain diminishes inhibitory action less than excitatory action. The structural requirements for adrenergic inhibitory action appear to be less specific than those for excitatory action.

The concept of the sympathins E and I as mediators of adrenergic nerve impulses seems to have outlived its period of usefulness. Various alternative hypotheses have been suggested. The suggestion of two mediators Sc (contracting substance) and Sr (relaxing substance) proposed more recently (101, 196) seems to be little more desirable than the original concept of the sympathins. The postulation of alpha and beta receptors (4) agrees somewhat better with the experimental data. However, this requires the assumption that stimulation of either receptor may cause either excitation or inhibition; that union with the cell receptor is determined by the structure of the sympathomimetic amine but the nature of the response elicited after union is determined by the organ. Thus, union with the alpha receptors induces contraction of the blood vessels in skeletal muscle and skin, and of the nictitating membrane and uterus, but induces relaxation of intestinal smooth muscle. On the other hand, union with the beta receptors may cause relaxation of blood vessels in skeletal muscle and in the coronary vas-

cular bed, relaxation of the uterus (rat, cat, dog and human) and the bronchioles, and stimulation of the heart.

If one assumes excitation or inhibition to result from stimulation of a specific receptor, it is difficult to explain the action of sympathomimetic amines on the heart. Cardiac effects do not correlate well with vascular effects. 'Isuprel' appears to be one of the most potent vasodepressor drugs and at the same time it is more stimulating to the heart than is epinephrine. In order of increasing cardiac stimulation we find No. 5 (N-propyl) < epinephrine < arterenol < No. 3 (N-ethyl) < 'Isuprel'. These observations suggest that a third receptor, specific for sympathetic action on the heart, may be involved; that there may be an adrenergic inhibitory receptor (Ac) involved in the contraction of smooth muscle, an adrenergic inhibitory receptor (Ar) involved in relaxation of smooth muscle, and a third receptor (Ae) concerned in cardiac excitation. The structure of epinephrine could be considered optimal for stimulation of Ac but considerably less than optimal for Ar. The primary amine, arterenol, is almost equal to epinephrine in its effect on Ac but distinctly less effective on Ar. 'Isuprel' or the *t.*-butyl analog (No. 6) appears to have the optimum structure for stimulation of Ar. The structural requirement for maximum effect on Ae needs further investigation. The present summary leaves it obvious that these oversimplified hypotheses describe rather than explain the mechanism of adrenergic transmission.

The last two decades have provided us with much detailed information on the factors influencing the activity of sympathetic nerves and their effectors. However, many points remain obscure. The substance or substances involved, the immediate precursor, the manner in which the active agent is liberated, the exact role of the known substances in this sequence of events, the effect of the level of activity of the effector on the resultant response and many other problems require clarification. Progress has been accelerating so that present research efforts can be confidently expected to lead soon to a more complete understanding of these problems. With this increase in knowledge, it is not too much to hope that there will be a correlative development of synthetic agents of great therapeutic importance.

REFERENCES

1. Abderhalden, E. and Gellhorn, E.: Das Verhalten des Herzstreifenpräparates (nach Loewe) unter verschudenen Bedingungen; Das Verhalten des Herzstreifenpräparates (nach Loewe) unter verschudenen Bedingungen. II. Mitteilung. Versuche über den Einflup von *l*-, *d*- und *d-l*-Adrenalin auf den schlagenden und nichtschlagenden Herzstreifen: Arch. f. d. ges. Physiol., 183: 303–332, 1920, 196: 608–628, 1922.
2. Abelin, J.: Die physiologische Tätigkeit der Harnblase und ihre Beeinflussung durch Produkte der inneren Sekretion und andere wirksame substansen: Ztschr. f. Biol., 69: 373–408, 1919.
3. Adler, L. Beitrage zur Pharmakologie der Beckenorgane: Arch. f. exper. Path. u. Pharmakol., 83: 243–256, 1918.
4. Ahlquist, R. P.: A study of the adrenotropic receptors: Am. J. Physiol., 153: 586–600, 1948.
5. Allen, W. J., Barcroft, H. and Edholm, O. G.: On the action of adrenaline on the blood vessels in human skeletal muscle: J. Physiol., 105: 255–267, 1946–47.
6. Alles, G.: The comparative physiological actions of dl-β-phenylisopropylamines. I. Pressor effect and toxicity: J. Pharmacol. Exper. Therap., 47: 339–354, 1933.
7. Alles, G. and Prinzmetal, M.: The comparative physiological actions of dl-βphenylisopropylamines. II. Bronchial effect: Ibid., 48: 161–174, 1933.
8. Amberg, S.: The toxicity of epinephrin (Adrenalin): Am. J. Physiol., 8: xxxiii-xxxiv, 1903.
9. Ambler, C. and Pick, E. P.: Über die Strophanthinkontraktur der gentrennten Kammerhälften des Kaltblüterherzens: Arch. f. d. ges. Physiol., 184: 62–78, 1920.

10. Anrep, G. V. and Stacey, R. S.: Comparative effect of various drugs upon the coronary circulation: J. Physiol., 64: 187-192, 1927-28.
11. Auerbach, M. E. and Angell, E.: The determination of arterenol in epinephrine Science, 109: 537, 1949.
12. Aumann, K. W. and Youmans, W. B.: Quantitative comparison of responses of isolated and of intact intestine to seven sympathomimetic amines: Proc. Soc. Exper. Biol. Med., 42: 111-112, 1939.
13. Bacq, Z. M.: Recherches sur la physiologie du système nerveux autonome; les propriétés biologiques et physico-chimiques de la sympathine comparées à alles de l'adrenaline Arch. internat. de physiol., 36: 167-246, 1933.
14. Bacq, Z. M. and Brouha, L.: Recherches sur la physiologie du systeme nerveux autonome. I. La transmission humorale des excitations nerveuses sympathiques: Ibid., 35: 163-195, 1932.
15. Bacq, Z. M. and Fischer, P.: Nature de la subetance sympathicomimetique extraite des nerfs ou des tissus des mammiferes.: Ibid., 55: 73-91, 1947.
16. Bacq, Z. M. and Henri, V.: Preuve Spectrographique de la formation de subetances par excitation des nerfs cardiaques· Compt. rend. Acad. de sc., 196: 135-137, 1933.
17. Bacq, Z. M., Henri, V. and Schepers, P.: Étude spectrographique des subetances formus au cours de l'excitation des nerfs cardiaques: Compt. rend. Soc. de biol. Paris, 112: 703-704, 1933.
18. Bainbridge, F. A. and Dale, H. H.: The contractile mechanism of the gall-bladder and its extrinsic nervous control: J. Physiol., 33: 138-155, 1905-06.
19. Bainbridge, F. A. and Trevan, J. W.: Some actions of adrenalin upon the liver: Ibid., 51: 460-468, 1917.
20. Barbour, H. G.: Die Struktur verschiedener Abschnitte des Arteriensystems in Beziehung auf ihr Verhalten sum Adrenalin: Arch. f. exper. Path. u. Pharmakol., 68: 41-58, 1912.
21. Barbour, H. G. and Prince, A. L.: The influence of epinephrin upon the coronary circulation of the monkey: J. Exper. Med., 21: 330-337, 1915.
22. Barcroft, H.: A study of the influence of adrenaline on the systemic blood flow: J. Physiol., 76: 339-346, 1932.
23. Barcroft, H. and Konzett, H.: Action of noradrenaline and adrenaline on human heart rate: Lancet, 256: 147-148, 1949.
24. Barger, G.: Organic Chemistry in Biology and Medicine, 1930, McGraw-Hill Book Co., New York.
25. Barger, G. and Dale, H. H.: Chemical structure and sympathomimetic action of amines: J. Physiol, 41: 19-59, 1910-11.
26. Battelli, F. and Taramasio, P.: La toxicité de la subetance active des capsules surrennales: Compt. rend. soc. biol., 54: 815-817, 1902.
27. Bauer, W., Dale, H. H., Poulsson, L. T. and Richards, D. W.: The control of circulation through the liver: J. Physiol., 74: 343-375, 1932.
28. Beauvallet, M.: Action des amino-alcools diphenoliques: adrenaline, isopropyladrenaline, dioxynorephedrine et dioxyephedrine sur l'intestin isolé: Compt. rend. Soc. biol., 140: 108-110, 1946.
29. Bercovitz, Z.: Studies on the visceral sensory nervous system. XII. The response of the isolated esophagus of the frog and the turtle to certain drugs: Am. J. Physiol., 60: 219-233, 1922.
30. Blaschko, H.: The activity of 2(-)-dopa decarboxylase: J. Physiol., 101: 337-349, 1942.
31. Boruttau, H.: Homologs of adrenine: Chem. Ztg., 36: 1111, 1914 (Chem. Abs., 8: 2152, 1914).
32. Bouchard, C. and Claude, H.: Recherches experimentales sur l'adrenaline: Compt. rend. Acad. de sc., 135: 928-931, 1902.
33. Bovet, D. and Bovet-Nitti, F.: Medicaments du Système Nerveux Vegetatif. Editions S. Karger S. A., Bale, 1948.
34. Brinkman, R. and van Dam, E.: Die chemische Übertragbarkeit der Nervenreiswirkung: Arch. f. d. ges. Physiol., 196: 66-82, 1922.
35. Brodie, T. G. and Cullis, W. C.: The innervation of the coronary vessels: J. Physiol., 43: 313-324, 1911-12.
36. Brodie, T. G. and Dixon, W. E.: Contributions to the physiology of the lungs. Part II. On the innervation of the pulmonary blood vessels, and some obeervations on the action of suprarenal extract: Ibid., 30: 476-502, 1903.
37. Brooks, C., McPeek, C. and Seymour, R. J.: Action of adrenaline on vasomotors and heart beats studied separately by the artificial control of blood pressure by means of the compensator: J. Pharmacol. Exper. Therap., 11: 168-169, 1918.
38. Bülbring, E. and Burn, J. H.: An action of adrenaline on transmission in sympathetic ganglia, which may play a part in shock: J. Physiol., 101: 289-303, 1942.
39. Bülbring, E. and Burn, J. H.: Liberation of noradrenaline from adrenal medulla by splanchnic stimulation: Nature, 163: 363, 1949.
40. Burton-Opitz, R.: The vascularity of the liver. XI. The motor reaction in the portal radicles of the liver: Quart. J. Exptl. Physiol., 7: 57-74, 1914.
41. Cameron, W. M., Crismon, J. M., Whitsell, L. J. and Tainter, M. L.: Analysis of circulatory actions of ethylnorsuprarenin: J. Pharmacol. Exper. Therap., 62: 318-332, 1938.
42. Cameron, W. M. and Tainter, M. L.: Comparative actions of sympathomimetic compounds; bronchodilator actions in bronchial spasm induced by histamine: Ibid., 57: 152-169, 1936.
43. Cameron, W. M., Whitsell, L. J., Crismon, J. M. and Tainter, M. L.: Further evidences on nature of vasomotor actions of ethylnorsuprarenin: Ibid., 63: 340-351, 1938.
44. Campbell, J. A.: The effects of certain animal extracts upon the blood vessels: Quart. J. Exper. Physiol , 4: 1-17, 1911.
45. Cannon, W. B.: Bodily changes in pain, hunger, fear and rage, 1929, Appleton-Century, New York.
46. Cannon, W. B. and Bacq, Z. M.: Studies on the conditions of activity in endocrine organs. XXVI. A hormone produced by sympathetic action on smooth muscle: Am. J. Physiol., 96: 392-412, 1930-31.

47. CANNON, W. B. AND DE LA PAZ, D.: Emotional stimulation of adrenal secretion: Ibid., 28: 64-70, 1911.
48. CANNON, W. B. AND GRIFFITH, F. R.: Studies on the conditions of the endocrine glands. X. The cardio-accelerator substance produced by hepatic stimulation: Ibid., 60: 544-559, 1922.
49. CANNON, W. B. AND HOSKINS, R. G.: The effects of asphyxia, hyperpnoea, and sensory stimulation on adrenal secretion: Ibid., 29: 274-279, 1911.
50. CANNON, W. B. AND LISSAK, K.: Evidence for adrenaline in adrenergic neurones: Ibid., 125: 765-777, 1939.
51. CANNON, W. B. AND LYMAN, H.: The depressor effect of adrenalin on arterial pressure: Ibid., 31: 376-398, 1912-13.
52. CANNON, W. B. AND ROSENBLUETH, A.: Studies on conditions of activity in endocrine organs. XXIX. Sympathin E and Sympathin I: Ibid., 104: 557-574, 1933.
53. CANNON, W. B. AND URIDIL, J. E.: Studies on the conditions of activity in endocrine glands. VIII. Some effects on the denervated heart of stimulating the nerves of the liver: Ibid., 56: 353-364, 1921.
54. CARLSON, A. J.: Studies on the visceral sensory nervous system. XIII. The innervation of the cardia and the lower end of the esophagus in mammals: Ibid., 61: 14-41, 1922.
55. CASTILLO, J. C. AND DE BEER, E. J.: The tracheal chain. I. A preparation for the study of antispasmodics with particular reference to bronchodilator drugs: J. Pharmacol. Exper. Therap., 98: 104-109, 1947.
56. CATTELL, McK., WOLFF, H. G. AND CLARK, D.: The liberation of adrenergic and cholinergic substances in the submaxillary gland: Am. J. Physiol., 109: 375-385, 1934.
57. CHANCE, M. R. A.: Aggregation as factor influencing toxicity of sympathomimetic amines in mice: J. Pharmacol. Exper. Therap., 87: 214-219, 1946.
58. CLARK, G. A.: The vaso-dilator action of adrenaline: J. Physiol., 80: 429-440, 1933.
59. CLEGHORN, A.: The action of animal extracts bacterial cultures, and culture filtrates on the mammalian heart muscle: Am. J. Physiol., 2: 273-290, 1898.
60. COW, M. A.: Some reactions of surviving arteries: J. Physiol., 42: 125-143, 1911.
61. CRISMON, C. A. AND TAINTER, M. L.: Comparative pressor efficiency of sympathomimetic amines in the normal state and in decerebrate shock: J. Pharmacol. Exper. Therap., 66: 146-170, 1939.
62. CRISMON, J. M. AND TAINTER, M. L.: Action of sympathomimetic amines on heart-lung preparation: Ibid., 64: 190-208, 1938.
63. CUSHNY, A. R.: The action of optical isomers. III. Adrenalin: J. Physiol., 37: 130-138, 1908.
64. CUSHNY, A. R.: Further note on adrenalin isomers: Ibid., 38: 259-262, 1909.
65. DAKIN, H. D.: The physiological action of synthetical substances allied to adrenalin: Ibid., 32: xxiv-xxvi, 1905.
66. DALE, H. H.: On some physiological actions of ergot: Ibid., 34: 163-206, 1906.
67. DALE, H. H. AND RICHARDS, A. N.: The vasodilator action of histamine and of some other substances: Ibid., 52: 110-165, 1918.
68. DALEY, I. DE B.: Reactions of the pulmonary and bronchial blood vessels: Physiol. Rev., 13: 149-184, 1933.
69. DAUTREBANDE, L., PHILIPPOT, E., CHARLIER, R., DUMOULIN, E., AND NOGAREDE, F.: Aerosols medicamenteux. IV: Arch. int. de pharmacodyn. et de therap., 68: 117-210, 1942.
70. DEROUAUX, G. AND ROSKAM, J.: Adrenal [redacted] sympathetic nerve stimulation: J. Physiol., 108: 1-8, 1949.
71. DETTINGER, B. L., BEAVER, D. C., AND LANDS, A. M.: Toxicity of 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride (Isuprel): Proc. Soc. Exper. Biol. Med., 68: 501-505, 1948.
72. DIXON, W. E. AND HAMILL, P.: The mode of action of specific substances with special reference to secretin: J. Physiol., 38: 314-336, 1909.
73. DRAKE, M. E., JOHN R., RENSHAW, F. AND THIENES, C. H.: The smooth muscle actions of epinephrine substitutes. VIII. Responses of denervated smooth muscles: Arch. int. pharmacodyn. et de therap., 61: 494-503, 1939.
74. DRINKER, C. K. AND DRINKER, K. R.: A method for maintaining an artificial circulation through the tibia of the dog, with a demonstration of the vasomotor control of the marrow vessels: Am. J. Physiol., 40: 514-521, 1916.
75. EDMUNDS, C. W.: Some vasomotor reactions of the liver: J. Pharmacol Exper. Therap., 6: 569-590, 1914-15.
76. EDMUNDS, C. W. AND ROTH, G. B.: The point of attack of certain drugs acting on the periphery. I. Action on the bladder: Ibid., 15: 189-199, 1920.
77. ELLIOTT, T. R.: On the action of adrenalin (preliminary report): J. Physiol., 31: xx-xxi, 1904.
78. ELLIOTT, T. R.: The action of adrenalin: Ibid., 32: 401-467, 1905.
79. EMILSSON, B.: Influence of sympathicolytics on action of adrenaline substitutes on isolated intestine; bee venom and ergotamine: Acta Physiol. Scand., 3: 335-350, 1941-42.
80. EMMERT, J.: Ueber die Wirkung subkutan einverleibten Adrenalins: Arch. f. path. Anat., 194: 114-121, 1908.
81. EPSTEIN, D., GUNN, J. A. AND VIRDEN, C. J.: The action of some amines related to adrenaline. I. Methoxy-phenylethylamines: J. Physiol., 76: 224-246, 1932.
82. ERB, W.: Experimentelle und histologische Studien über Arterienerkrankung nach Adrenalininjektionen: Arch. f. exper. Path. u. Pharmakol., 53: 173-212, 1905.
83. ERLANGER, J. AND GASSER, H. S.: Studies in secondary traumatic shock. III. Circulatory failure due to adrenalin: Am. J. Physiol., 49: 345-376, 1919.
84. EULER, U. S. V. AND HAMBERG, ULLA: l-nor Adrenaline in the suprarenal medulla: Nature, 163: 642-643, 1949.
85. EULER, U. S. V. AND SCHMITERLÖW, C. G.: Sympathomimetic activity in extracts of normal human and bovine blood: Acta Physiol. Scand., 13: 1-8, 1947.
86. FOLKOW, B., FROST, J. AND UVNÄS, B.: Action of adrenaline, nor-adrenaline and some other sympathomimetic drugs on the muscular, cutaneous and splanchnic vessels of the cat: Ibid., 15: 412-420, 1948.

86a. Foret, J., Cauwenberg, H. van and Bacq, Z. M.: Action sympathicomimétique de deux nouvelles amines: Comp. rend. Soc. de biol., 141: 534, 1947.
87. Franklin, K. J.: Actions of adrenaline and acetylcholine on isolated pulmonary vessels and azygos vein of dog: J. Physiol., 75: 471–479, 1932.
88 Freeman, H. and Carmichael, H. T.: A pharmacologic study of the autonomic nervous system in normal men. The effects of intravenous injections of epinephrine, atropin, ergotamine and physostigmine upon the blood pressure and pulse rate: J. Pharmacol. Exper. Therap., 58: 409–416, 1936.
89. Fröhlich, A.: Eine neue physiologische Eigenschaft des d-Suprarenins. Vorläufige Mitteilung: Zentralbl. f. Physiol., 23: 254–256, 1909.
90. Fuchs, R. T.: An initial depression of heart rate in response to epinephrine in human subjects: J. Pharmacol. Exper. Therap., 63: 143–152, 1938.
91. Führer, H. and Starling, E. H.: Experiments on the pulmonary circulation: J. Physiol., 47: 286–300, 1913.
92. Gaddum, J. H. and Schild, H.: A sensitive physical test for adrenaline: Ibid., 80: 9–10P, 1934.
92a. Gaddum, J. H., Peart, W. S. and Vogt, M.: The estimation of adrenaline and allied substances in blood: J. Physiol., 108: 467-481. 1949.
93. Goldenberg, M., Faber, M., Alston, E. J. and Chargaff, E. C.: Evidence for the occurrence of nor-epinephrine in the adrenal medulla: Science, 109: 534, 1949.
94. Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G. and Roh, C. E.: The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension: Am. J. Med., 5: 792–806, 1948.
95. Golla, F. L. and Symes, W. L.: The reversible action of adrenaline and some kindred drugs on the bronchioles: J. Pharmacol. Exper. Therap., 5: 87–103, 1913–14.
96. Gottlieb, R.: Ueber die Wirkung des Nebennierenextractes auf Herz und Gefasse: Arch. f. exper. Path. u. Pharmacol., 43: 286–304, 1899.
97. Grab, W., Janssen, S. and Rein, H.: Ueber die Grösse der Leberdurchblutung: Ztschr. Biol., 89: 324–331, 1929.
98. Grant, R. T. and Pearson, R. S. B.: Blood circulation in human limb; observations on differences between proximal and distal parts and remarks on regulation of body temperature: Clin. Sci., 3: 119–139, 1938.
99. Green, H. D., Schroeder, E. F. and Paschold, J. H.: Aortic blood flow curves: Am. J. Physiol., 129: 366–367, 1940.
100. Greene, H. D., Wegria, R. and Boyer, N. H.: Effects of epinephrine and pitressin on the coronary artery inflow in anesthetized dogs: J. Pharmacol. Exper. Therap., 76: 378–391, 1942.
101. Greer, C. M., Pinkston, J. O., Baxter, J. H., Jr., and Brannon, E. S.: Comparison of response of smooth muscle to arterenol, l-epinephrine and "liver sympathin." I. Responses of smooth muscle of iris and of vascular smooth muscle; Nor-epinephrine (β-(3,4-dihydroxyphenyl)-β-hydroxyethylamine) as a possible mediator in the sympathetic division of the autonomic nervous system: Ibid., 60: 108–109, 1937; 62: 189–227, 1938.
102. Griffith, F. R., Jr., Omachi, A., Lockwood, J. E. and Loomis, T. A.: Effect of intravenous adrenalin on blood flow, sugar retention, lactate output and respiratory metabolism of peripheral (leg) tissues in anesthetized cat: Am. J. Physiol., 149: 64–76, 1947.
103. Gruber, C. M.: A note on the effect of adrenaline upon strips of excised pregnant human uterus: Endocrin., 9: 407–409, 1925.
104. Gruber, C. M.: Autonomic innervation of genito-urinary system: Physiol. Rev., 13: 497–609, 1933.
105. Gruber, C. M. and Roberts, S. J.: XVI. The effect of adrenalin upon the coronary circulation: Am. J. Physiol., 76: 508–529, 1926.
106. Guggenheim, M.: Die biogenen Amine und ihre Bedeutung für die Physiologie und Pathologie des Pflanzlichen und tierischen Stoffwechsels; Nordeman, Karger.
107. Gunn, J. A. and Gunn, J. W. C.: The action of certain drugs on the uterus of the guinea pig and the rat: J. Pharmacol. Exper. Therap., 5: 527–538, 1913–14.
108. Gurd, M. R.: Physiological action of dihydroxyphenylethylamine and sympatol: Quart. J. Pharm., 10: 188–211, 1937.
109. Hall, H. L.: A study of the pulmonary circulation by the trans-illumination method: Am. J. Physiol., 72: 446–457, 1925.
110. Hamilton, W. F. and Remington, J. W.: Some factors in the regulation of the stroke volume: Ibid., 153: 287–297, 1948.
111. Handovsky, H.: Ueber die Wirkung des N-Methyl, diaethylaminoaethyl-Ephedrins auf Blutdruck und Bronchialwiderstand im Vergleich mit den entsprechenden Wirkungen des Ephedrins: Arch. int. pharmacodyn. et de therap., 51: 301–334, 1935.
112. Harries, F.: Das schlagend überlebende Herzstreifenpräparat: Ztschr. f. d. ges. exper. Med., 6: 301–326, 1918.
113. Hartman, F. A.: The differential effects of adrenin on splanchnic and peripheral arteries: Am. J. Physiol., 38: 438–455, 1915.
114. Hartman, F. A., Evans, J. I. and Walker, H. G.: The action of epinephrin upon the capillaries and fibers of skeletal muscle: Ibid., 85: 91–98, 1928.
115. Hartman, F. A., Evans, J. I. and Walker, H. G.: Control of capallaries of skeletal muscle: Ibid., 90: 668–688, 1929.
116. Hartung, W. H.: Epinephrine and related compounds; influence of structure on physiological activity: Chem. Rev., 9: 389–465, 1931.
117. Hartung, W. H.: Sympathomimetic agents; beta-phenethylamine derivatives: Ind. and Eng. Chem., 37: 126–137, 1945.

118. HEDBOM, K.: Ueber die Einwirkung verschiedener Stoffe auf das isolirte Säugethierherz: Skan. Arch. f. Physiol., 8: 147-222, 1898.
119. HEYMANS, C.: Au sujet de l'influence del'adrenaline et de l'ephedrine sur les centres vasoregulateurs: Arch. Int. de pharmacodyn. et de therap., 35: 307-313, 1928.
120. HJORT, A. M.: Some physiological properties of certain N-methylated-β-phenylethylamines: J. Pharmacol. Exper. Therap., 52: 101-112, 1934.
121. HJORT, A. M., DE BEER, E. J., RANDALL, L. O.: Experiences with the biological assay of several sympathicotonic substances including epinephrine: Ibid., 71: 105-113, 1941.
122. HOLTON, P.: Noradrenaline in adrenal medullary tumors: Nature, 163: 217, 1949.
122a. HOLTZ, P., CREDNER, K. AND KRONEBERG, G.: Uber das sympathicomimetische pressorische Prinsip des Harns ("urosympathin"). Arch. f. exper. Path. u. Pharmakol., 204: 228-243, 1947.
123. HOPPE, J. O., SEPPELIN, D. K. AND LANDS, A. M.: An investigation of the acute toxicity of the optical isomers of arterenol and epinephrine: J. Pharmacol. Exper. Therap., 98: 502-505, 1949.
124. HORWITZ, O.: Case of large overdose of epinephrine: Am. Heart J., 33: 102-106, 1947.
125. HOSKINS, R. G.: The sthenic effect of epinephrin upon intestine: Am. J. Physiol., 29: 363-366, 1911-12.
126. HOSKINS, R. G. AND GUNNING, R. E. L.: Effects of adrenin on the distribution of the blood. V. Volume changes and venous discharge in the intestine: Ibid., 43: 399-407, 1917.
127. HOSKINS, R. G., GUNNING, R. E. L. AND BERRY, E. L.: The effects on the distribution of the blood. I. Volume changes and venous discharge in the limb: Ibid., 41: 513-528, 1916.
128. HOSKINS, R. G. AND LOVELETTE, C. R.: The adrenals and the pulse rate: J. Am. Med. Assoc., 63: 316-318, 1914.
129. HUNT, R.: Vasodilator reactions. I.: Am. J. Physiol., 45: 197-230, 1917-18.
130. ISSEKUTZ, B. V., JR.: Die Wirkung von Gefässmitteln auf den lokalen Stoffwechsel des Muskels: Arch. f. exper. Path. u. Pharmakol., 197: 313-331, 1941.
131. JACKSON, D.: The peripheral action of certain drugs with special reference to the lungs; The action of certain drugs on the bronchioles: J. Pharmacol. Exper. Therap., 4: 291, 320, 1913; 5: 479-510, 1913.
132. JAEGER, E.: Pharmakodynamische Studie über Adrenalon. Gefäß verengernde Atem- und sekretorische Wirkung; Pharmakodynamische Studie über Adrenalon. Sitz der gefäß verengernden Wirkung, und Wirkung von Adrenalon bei Gegenwart verschiedener vasomotorisch Wirkender Mittel: Compt. rend. de la Soc. biol., 85: 433-433; 910-912, 1921.
133. JANSEN, M.: β-(2,4,5-Trimethoxyphenyl)-äthylamin, ein Isomeres des Mescalins: Rec. trav. chim., 50: 291-312, 1931.
134. JANUSCHKE, H. AND POLLAK, L.: Zur Pharmakologie der Bronchia muskulatur. (Zugleich ein Beitrag zur Lehre von der Lungenstarre): Arch. f. exper. Path. u. Pharmakol., 66: 205-220, 1911.
135. JOHNSON, V., HAMILTON, W. F., KATZ, L. N. AND WEINSTEIN, W.: Studies on the dynamics of the pulmonary circulation: Am. J. Physiol., 120: 624-634, 1937.
136. KAHN, R. H.: Über humorale Uebertragbarkeit der Herznervenwirkung: Arch. f. d. ges. Physiol., 214: 482-498, 1926.
137. KATZ, L. N., LINDNER, E., WEINSTEIN, W. AND ABRAMSON, D. I.: Effects of various drugs on the coronary circulation of the denervated isolated heart of the dog and cat. I. Observations on epinephrine, acetylcholine, acetyl-β-methylcholine, nitroglycerine, sodium nitrate, pitressin and histamine. Arch. int. de pharmacodyn. et de therap., 59: 399-415, 1938.
138. KATZ, L. N. AND RODBARD, S.: The integration of the vasomotor responses in the liver with those in other systemic vessels: J. Pharmacol. Exper. Therap., 67: 407-422, 1939.
139. KEHRER, E.: Physiologische und pharmakologische Untersuchungen an den überlebenden und lebenden inneren Genitalien: Arch. f. Gynäkol., 81: 160-210, 1907.
140. KLEE, P.: Beitrage zur pathologischen Physiologie der Mageninnervation. 3. Mitteilung: Zur Atropinfrage: Dtsch. Arch. f. Klin. Med., 133: 265-285, 1920.
141. KNAUS, H. H. AND CLARK, A. J.: The action of certain drugs and ions on the rat's uterus: J. Pharmacol. Exper. Therap., 26: 347-358, 1926.
142. KONZETT, H.: Neue broncholytisch hochwirksame Körper der Adrenalinreihe: Arch. f. Path. u. Pharmakol., 197: 27-40, 1940.
143. KONZETT, H.: Zur Pharmakologie neuer adrenalinverwandter. Körper: Ibid., 197: 41-57, 1940.
144. KONZETT, H. AND HEBB, C. O.: Vaso- and bronchomotor actions of noradrenaline (arterenol) and of adrenaline in the isolated perfused lungs of the dog: Arch. internat. pharmacodyn. et de therap., 78: 210-224, 1949.
145. KOUNTZ, W. B.: Studies on coronary arteries of human heart: J. Pharmacol. Exper. Therap., 45: 65-76, 1932.
146. KURODA, M.: Observations of the effects of drugs on the ileocolic sphincter: Ibid., 9: 187-195, 1917.
147. LANDS, A. M. AND GRANT, J. I.: To be published.
148. LANDS, A. M., LUDUENA, F. P., GRANT, J. I. AND ANANENKO, E.: To be published.
149. LANDS, A. M., NASH, V. L., DETTINGER, B. L., GRANGER, H. R. AND MCCARTHY, H. M.: The pharmacology of compounds structurally related to hydroxytyramine: J. Pharmacol. Exper. Therap., 92: 369-380, 1948.
150. LANDS, A. M., NASH, V. L., MCCARTHY, H. M., GRANGER, H. R. AND DETTINGER, B. L.: Pharmacology of N-alkyl homologues of epinephrine: Ibid., 96: 110-119, 1947.
151. LANDS, A. M., RICKARDS, E. E., NASH, V. L. AND HOOPER, K. Z.: Pharmacology of vasodepressor compounds structurally related to sympathomimetic amines: Ibid., 89: 297-305, 1947.
152. LANDS, A. M., SIEGMUND, O. H. AND ANANENKO, E.: Bronchodilator action of butanol derivatives: Fed. Proc., 8: 312, 1949.
153. LANGENDORFF, O.: Über die Innervation der Koronargefässe: Zentralb. f. Physiol., 21: 551-557, 1907.
154. LANGLEY, J. N.: Observations on the physiological action of the suprarenal bodies: J. Physiol., 27: 237-256, 1901-02.

155. LANE, A. B.: Über die Bildung einer adrenalinähnlichen Substans nach Reizung des Nervus sympathicus: Arch. Neerland. Sciences exact. nat., 12: 433–444, 1928.

156. LAUNOY, L. AND MENGUY, B.: Zahlenmäßige Angaben über r-Adrenalin, l-Adrenalin und über Adrenalon: Compt. rend. Soc. biol., 87: 1066–1068, 1922.

157. LESAGE, M. J.: Toxicite de l'adrenaline en injection intraveineuse pour le chien; Toxicite de l'adrenaline en injection intraveineuse pour le chat; Action generale de l'adrenaline en injection intra-veineuse ches le chien. Influence de la dose. Mecanisme de la mort; Action general de l'adrenaline en injection intra-veineuse ches le chat; Phenomenes d'accoutumance du coeur du chat a l'adrenaline: Compt. rend. Soc. biol., 56: 632–634; 665–666; 709–711; 754–756; 800–801, 1904.

158. LEVY, A. G.: Sudden death under light chloroform anesthesia; Ventricular fibrillation caused by stimulation of the cardiac accelerator nerves under chloroform: J. Physiol., 42: iii–vii, 1911; 44: xvii–xviii, 1912.

159. LEWANDOWSKY, M.: Wirkung des Nebennierenextractes auf die glattan Muskeln der Haut: Zentralb f. Physiol., 14: 433–435, 1900.

160. LIEB, C. C. AND MCWHORTER, J. E.: Action of drugs on the isolated gall bladder: J. Pharmacol. Exper. Therap., 7: 83–96, 1915.

161. LISSAK, K., MARTIN, J. AND ANGYAN, A: Mechanism of action of aleudrine (isopropyladrenaline): Orvosok Lapja Nepegeszegügy, 2: 129–132, 1946 (Chem. Abs., 42: 3074, 1948).

162. LOEWE, S.: Das schlagend überlebende Herzstreifenpräparat: Ztschr. f. d. ges. exper. Med., 6: 289–300, 1918.

163. LOEWE, S.: Über cyklische seitenkettenäthylamine. Die pharmakologischen Wirkungen einiger neuer Pyrogalloläthylamino-verbindungen: Skand. Arch. Physiol., 43: 214–243, 1923.

164. LOEWI, O.: Uebertragbarkeit der Herznervenwirkung: Arch. ges. Physiol., 189: 237–242, 1921.

165. LOEWI, O.: Ferrier lecture on problems connected with principle of humoral transmission of nervous impulses: Proc. Roy. Soc. London, s. B., 118: 299–316, 1935.

166. LUCAS, D. R. : Physiological and pharmacological studies of the ureter. III.: Am. J. Physiol., 22: 245–278, 1908.

167. LUDUENA, F. P.: Accion de algunas aminas simpaticomimeticas sobre el retractor del pene y la presion arterial del perro: Rev. soc. argentina. biol., 16: 417–431, 1940.

168. LUDUENA, F. P., ANANENKO, E., SIEGMUND, O. H. AND MILLER, L. C.: Comparative pharmacology of the optical isomers of arterenol: J. Pharmacol. Exper. Therap., 95: 155–170, 1949.

169. MACHIELA, J.: Studien am isolierten Herzstreifen (Loewe): Ztschr. f. d. ges. exper. Med., 14: 287–310, 1921.

170. MACHT, D. I.: The action of drugs on the isolated pulmonary artery: J. Pharmacol. Exper. Therap., 6: 13–37, 1914–15.

171. MACHT, D. I.: The pharmacology of the ureter. I. Action of epinephrine, ergotoxin and of nicotine: Ibid. 8: 155–166, 1916.

172. MACHT, D. I. AND GIU-CHING TING: Study of antispasmodic drugs on the bronchus: Ibid., 18: 373–398, 1921.

173. MACLEOD, J. J. R. AND PEARCE, R. G.: The outflow of blood from the liver as affected by variations in the condition of the portal vein and hepatic artery: Am. J. Physiol., 35: 87–105, 1914.

174. MARKWALDER, J. AND STARLING, E. H.: A note on some factors which determine the blood-flow through the coronary circulation: J. Physiol. 47: 275–285, 1914.

175. MARRAZZI, A. S.: Electrical studies on the pharmacology of autonomic synapses. II. The action of a sympathomimetic drug (epinephrine) on sympathetic ganglia: J. Pharmacol. Exper. Therap., 65: 395–404, 1939.

176. MARRAZZI, A. S.: Reduction of sympathetic synaptic transmission as index of inhibition at adrenergic junctions in general: Science, 104: 6–8, 1946.

177. MARRAZZI, A. S. AND MARRAZZI, R. N.: Chemical structure and the definition of sympathin E: Science, 106: 520–521, 1947.

178. MARSH, D. F. AND HERRING, D. A.: The comparative pharmacology of the N-alkyl-l-(p-hydroxyphenyl)-2-aminoethanols: Arch. int. de pharmacodyn. et de therap., 78: 489–498, 1949.

179. MARSH, D. F., PELLETIER, M. H. AND ROSS, C. A.: The comparative pharmacology of the N-alkylarterenols: J. Pharmacology Exper. Therap., 92: 108–120, 1948.

180. MAUTNER, H. AND PICK, E. P.: Über die durch Shockgifte erzeugten Zirkulationsstorungen. II. Das Verhalten der überlebenden Leber: Biochem. Ztschr., 127: 72–93, 1922.

181. MCGINTY, A. P. AND BAER, L. S.: Effect on heart of overdose of epinephrine; report of case: Am. Heart J., 33: 102–106, 1947.

182. MCGUIGAN, H. AND HYATT, E. G.: The primary depression and secondary rise in blood pressure caused by epinephrine: J. Pharmacol. Exper. Therap., 13: 59–69, 1918–19.

183. MCMICHAEL, J. AND SHARPEY-SCHAFER, E. P.: Cardiac output in man by direct Fick method; effects of posture, venous pressure change, atropine, and adrenaline: Brit. Heart J., 6: 33–40, 1944.

184. MEEK, W. J. AND EYSTER, J. A. E.: The effect of adrenalin on the heart-rate: Am. J. Physiol., 38: 62–66, 1915.

185. MELVILLE, K. I.: The antisympathomimetic action of dioxane compounds (F883 and F 933), with special reference to the vascular responses to arterenol and nerve stimulation: J. Pharmacol. Exper. Therap., 59: 317–327, 1937.

186. MEYER, O. B.: Über einige Eigenschaften der Gefäßmuskulatur mit besonderer Berücksichtigung der Adrenalinwirkung: Ztschr. f. Biology, 48: 352–397, 1906.

187. MORTON, M. C. AND TAINTER, M. L.: Effects of sympathomimetic amines on perfused blood vessels: J. Physiol., 98: 263–282, 1940.

188. MÜGGE, H.: Ein Beitrag zur Analyse der Wirkung des Ephedrins und einiger chemisch verwandter Substanzen: Arch. f. exper. Path. u. Pharmakol., 165: 230–243, 1932.

189. MUNCH, J. C., GATTONE, V. H. AND PRATT, H. J.: Chemistry and pharmacology of an analogue of epinephrine: J. Am. Pharm. Assoc., Sc. Ed., 30: 183–186, 1941.

190. NATHANSON, M. H. AND MILLER, H.: Effect of isopropylepinephrine on the rhythmic property of the human heart: Proc. Soc. Exper. Biol. Med., 70: 633–636, 1949.
191. NEU, M.: Bedeutung des Suprarenins für Geburtschülfe: Arch. f. Gynakol., 85: 617–711, 1908.
192. OGAWA, S.: Beitrage zur Gefäßwirkung des Adrenalins: Arch. f. exper. Path. u. Pharmakol., 67: 89–110, 1912.
193. OLIVER, G. AND SCHAFER, E. A.: On the physiological action of extract of the suprarenal capsules; The physiological effects of extracts of the suprarenal capsules: J. Physiol., 17: ix-xiv, 1895; 18: 230–276, 1895.
194. ORTH, O. S., LEIGH, M. D., MELLISH, C. H. AND STUTZMAN, J. W.: Action of sympathomimetic amines in cyclopropane, ether and chloroform anesthesia: J. Pharmacol. Exper. Therap., 67: 1–16, 1939.
195. PEDDEN, J. R., TAINTER, M. L. AND CAMERON, W. M.: Comparative actions of sympathomimetic compounds: bronchodilator actions in experimental bronchial spasm of parasympathic origin: Ibid., 55: 242–256, 1935.
196. PINKSTON, J. O., GREER, C. M., BRANNON, E. S. AND BAXTER, J. H.: Comparison of response of smooth muscle to arterenol, l-epinephrine and liver sympathin. I. Response of smooth muscle of iris and of vascular smooth muscle; II. Response of uterus, small intestine and nictitating membrane: J. Pharmacol. Exper. Therap., 60: 108–109; 115–116, 1937.
197. PITZORNO, P.: Effetti prodotti da sostanze adrenalinosimili sopra alcuni distretti vascolari: Arch. int. de pharmacodyn. et de therap., 47: 464–485, 1934.
198. PLUMIER, L.: Action de l'adrenaline sur la circulation cardio-pulmonaire: J. Physiol. et path. gen., 6: 655–670, 1904.
199. PUCCINELLI, E.: Sopra alcune modificazoni del deflusso venoso femorale per iniezione di adrenalina. Considerazioni sulla partecipazione del circolo femorale ad alcuni fenomeni vasomotori: Riv. di Pat. Sper., 12: 261–274, 1934.
200. QUITSCHAL, W.: Die inhalationstherapie bei Asthma bronchial und asthmoiden Zuständen bei der chronischen spastischen Bronchitis und Emphysem: Dtsch. Med. Wochenschr., 68: 942–944, 1942.
201. RANGER, H. A. AND BRADLEY, S. E.: Systemic and renal circulatory changes following administration of adrenin, ephedrine and paredrinal to normal man: J. Clin. Inv., 22: 687–693, 1943.
202. RAYMOND HAMET: l'adrenaline et son derive ethylamine peuvent provoquer a la fois de l'hypotension et de la vasoconstriction renale: Compt. rend. Soc. biol., 115: 512–515, 1934.
203. RAYMOND HAMET: Änderungen der physiologischen Wirkung der 3,4-Dioxyphenyl-β-aminobutanols bei Ersatz der Aminogruppe dieser Verbindung durch eine Methylaminogruppe: Compt. rend. ac. sc., 202: 690–692, 1936.
204. REMINGTON, J. W., HAMILTON, W. F. AND AHLQUIST, R. P.: Inter-relation between the length of systole, stroke volume and left ventricular work in the dog: Am. J. Physiol., 154: 6–15, 1948.
205. ROSENBLUETH, A. AND CANNON, W. B.: Studies on conditions of activity in endocrine organs. XXVI. A hormone produced by sympathetic action on smooth muscle: Ibid., 96: 392–412, 1932.
206. ROSENBLUETH, A. AND MORISON, R. S.: A quantitative study of the production of sympathin: Ibid., 109: 209–220, 1934.
207. ROSSLER, R. AND PASCUAL, W.: The coronary circulation in the isolated perfused heart: J. Physiol., 74: 1–16, 1932.
208. ROTHLIN, E.: Experimentelle Studien über die Eigenschaften überlebender Gefässe unter Anwendung der chemischen Reizmethode: Biochem. Ztschr., 111: 219–256, 1920.
209. RUBSAMEN, W. AND KLINGERMANN, N. R.: Pharmakologische Untersuchungen an der überlebenden menschlichen Uterus- und Tubenmuskulatur: Ztschr. f. Geburstschulfe. u. Gynakol., 72: 272–280, 1912.
210. RYLANT, P.: La "transmission humorale de l'action des nerfs cardiaques" de Loewi chez le mammifere: Compt. rend. Soc. de biol., 96: 1054–1056, 1927.
211. SCHAFER, E. A. AND MOORE, B.: On the contractility and innervation of the spleen: J. Physiol., 20: 1–50, 1896.
212. SCHAFER, E. S. AND LIM, R. K. S.: The effects of adrenaline on the pulmonary circulation: Quart. J. Exper. Physiol., 12: 157–198, 1919.
213. SCHAUMANN, O.: Über Oxy-Ephedrine: Arch. f. exper. Path. u. Pharmakol., 160: 127–176, 1931.
214. SCHAUMANN, O.: Pharmakologische Studien am Histaminasthma des Meerschweinchens: Med. u. Chem., 4: 229–247, 1942.
215. SCHAUMANN, O.: Zur Pharmakologie der optischen Isomeren des 3,4-Dioxynor-Ephedrin. Ein Beitrag zum Problem: Molekulare Asymmetrie, chemische Konstitution und physiologische Wirkung: 181: 137, 1936.
216. SCHMIDT, L.: Untersuchungen über die todliche Andrenalinwirkung am Meerschweinchen: Ztschr. f. d. ges. exper. Med., 9: 285–307, 1919.
217. SCHMIDT, J.: Beeinflussung von Druck and Stromvolumen in der Pfortader durch die Atmung und durch experimentelle Eingriffe: Arch. ges. Physiol., 126: 165–196, 1909.
218. SCHULER, W. AND WIEDEMANN, A.: Über die Adrenalinsynthese im Reagenzglase unter physiologischen Bedingungen: Hoppe-Seyler's Ztschr. f. physiol. Chem., 233: 235–256, 1935.
219. SCHULTE, J. W., REIF, E. C., BACHER, J. A., JR., LAWRENCE, W. S. AND TAINTER, M. L.: Further study of central stimulation from sympathomimetic amines: J. Pharmacol. Exper. Therap., 71: 62–74, 1941.
220. SCHULTZ, W. H.: Quantitative pharmacological studies: Adrenalin and adrenalin-like bodies: Bull. 55, Hyg. Lab. U. S. Public Health, 1909.
221. SCHULTZ, W. H.: Experimental criticism of recent results in testing adrenalin: J. Pharmacol. Exper. Therap., 1: 291–302, 1909–10.
222. SCHWARZ, O.: Untersuchungen über die Physiologie und Pathologie der Blasenfunktion. IV. Mitteilung. Zur Pharmakotherapie der Miktionsstorungen: Arch. f. Klin. Chir., 110: 286–308, 1918.
223. SEGAL, M. S.: Facts and fancies in the management of the seriously ill patient with bronchial asthma: Dis. Chest, 14: 795–823, 1948.
224. SEGAL, M. S. AND BEAKEY, J. F.: Management of bronchial asthma; use of 1-(3', 4'-dihydroxyphenyl)-2 isopropylaminoethanol: Ann. Allergy, 5: 317–336, 1947.

225. Siegmund, O. H., Granger, H. R. and Lands, A. M.: Bronchodilator action of compounds structurally related to epinephrine: J. Pharmacol. Exper. Therap., 90: 254–259, 1947.
226. Smith, M. L.: The action of the autonomic drugs on the surviving stomach: Am. J. Physiol., 46: 233–243, 1918.
227. Stehle, R. L. and Ellsworth, H. C.: Arterenol as a possible sympathetic hormone: J. Pharmacol. Exper. Therap., 59: 114–121, 1937.
228. Stewart, G. N.: Adrenalectomy and the relation of the adrenal bodies to metabolism: Physiol. Rev., 4: 163–190 1924.
229. Stoltzenberger-Seidel, M.: Klinische Untersuchungen zur Behandling des Asthma bronchiale: Klin. Wochenschr., 19: 1306–1310, 1940.
230. Stolz, F. and Flacher, F.: D. R. P., 157, 300 (Frdl., 7:689); U. S. Patent No. 862, 675; 930, 703.
230a. Stutzman, J. W. and Orth, O. S.: Studies of the actions of methyl-adrenaline: J. Pharmacol. Exper. Therap., 69: 1–12, 1940.
231. Swanson, E. E.: I. The action of ephedrine, pseudoephedrine and epinephrine on the bronchioles: J. Pharmacol. Exper. Therap., 36: 541–568, 1929.
232. Swanson, E. E., Scott, C. C. Lee, H. M. and Chen, K. K.: Comparison of pressor action of some optical isomers of sympathomimetic amines: Ibid., 79: 329–333, 1943.
233. Swanson, E. E. and Webster, R. K.: Action of ephedrine, pseudoephedrine and epinephrine on bronchiolar muscle of isolated lung: Ibid., 38: 327–342, 1930.
234. Tainter, M. L.: Comparative actions of sympathomimetic compounds; catechol derivatives: Ibid., 40: 43–64, 1930.
235. Tainter, M. L.: Comparative actions of sympathomimetic compounds: influence of cocaine and certain compounds upon the actions of a group of sympathomimetic amines: Quart. J. Pharmacol., 3: 584–598, 1930.
236. Tainter, M. L.: Pharmacological actions of phenylethanolamine: J. Pharmacol. Exper. Therap., 36: 29–54, 1929.
237. Tainter, M. L.: Comparative actions of sympathomimetic compounds: catechol derivatives and possible mechanisms of the sensitization-desensitization phenomena of cocaine: Arch. int. de pharmacodyn. et de therap., 41: 365–376, 1931.
238. Tainter, M. L.: Comparative actions of sympathomimetic compounds: phenyl and substituted phenyl derivatives, nonphenylic ring compounds and aliphatic amines: Ibid., 46: 192–232, 1933.
239. Tainter, M. L., Cameron, W. M., Whitsell, L. J. and Hartman, M. M.: Clinical actions of ethylnorsuprarenin: J. Pharmacol. Exper. Therap., 81: 269–277, 1944.
240. Tainter, M. L., Pedden, J. R. and James, M.: Comparative actions of sympathomimetic compounds: bronchodilator actions in perfused guinea pig lungs: Ibid., 51: 371–386, 1934.
241. Tainter, M. L. and Throndson, A. H.: Influence of vasoconstrictors on the toxicity of procaine anesthetic solutions: J. Am. Dent. Assoc., 25: 966–979, 1938.
242. Tiffeneau, M.: Thesis Diet. Med., Paris, 1910 Ref. cit. 33, (page 114).
243. Tiffeneau, M.: Titres et Travaux, Paris, 1922, Ref. cit. 33, (page 113).
244. Tiffeneau, R. and Beauvallet, M.: Etude des proprietes bronchodilatatrices de diverses aralcoylamines synthetiques: Compt. rend. Soc. biol., 139: 944–945, 1945.
245. Titone, F. P.: Ueber die Funktion der Bronchialmuskeln: Arch. ges. Physiol., 155: 77–91, 1913.
246. Trendelenburg, P.: Physiologische und Pharmakologische Untersuchungen an der isolierten Bronchialmuskulatur: Arch. exper. Path. u. Pharmakol., 69: 79–107, 1912–13.
247. Trendelenburg, P.: Adrenalin und adrenalinverwandte Substanzen: Handbuch der Experimentellen Pharmakologie, Heffter, 2.2: 1130–1293, 1924.
248. Trendelenburg, P. and Fleischhauer, K.: Ueber den Einfluss des Zuckerstiches auf die Adrenalinsekretion der Nebennieren: Ztschr. f. d. ges. exper. Med., 1: 369–396, 1913.
249. Trier, E. M.: Vaso-motor nerves in the lungs: J. Physiol., 48: 154–170, 1914.
250. Tullar, B. F.: The resolution of *dl*-arterenol: J. Am. Chem. Soc., 70: 2067–2068, 1948.
251. Tullar, B. F.: The separation of *l*-arterenol from natural U. S. P. epinephrine: Science, 109: 536, 1949.
251a. Verly, W.: Proprietes Pharmacologiques de la Dimethyl-noradrenaline: Arch. int. pharmacodyn. et de therap., 77: 375–382, 1948.
252. Warnant, H.: Recherches pharmacologiques sur le muscle bronchique des poumons isoles du cobaye normal et sensibilise: Arch. int. de pharmacodyn. et de therap., 37: 61–86, 1930.
253. Wegria, R., Essex, H. E., Herrick, J. F. and Mann, F. C.: Simultaneous action of certain drugs on blood pressure and on flow in right and left coronary arteries: Am. Heart J., 20: 557–572, 1940.
254. West, G. B.: Quantitative studies of adrenaline and noradrenaline: J. Physiol., 106: 418–425, 1947.
255. West, G. B.: The vasodepressor action of noradrenaline: Brit. J. Pharmacol., 4: 63–67, 1949.
256. Wiggers, C. J.: The action of adrenaline on the pulmonary vessels: J. Pharmacol. Exper. Therap., 1: 341–348, 1909.
257. Wiggers, C. J.: Studies in inaccessible internal hemorrhages. II. The ineffectiveness of adrenalin in pulmonary hemorrhage: Arch. Int. Med., 3: 360–367, 1909.
258. Woodbury, R. A., Hamilton, W. F. and Torpin, R.: The relationship between abdominal uterine and arterial pressures during labor: Am. J. Physiol., 121: 640–649, 1938.
259. Youmans, W. B., Haney, H. F., and Auman, K. W.: Relation of the groups of the adrenalin molecule to its cardioaccelerator action: Ibid., 130: 190–196, 1940.
260. Youmans, W. B., Karstens, A. I. and Aumann, K. W.: Effect of vagotomy and of sympathectomy on sensitivity of intestinal smooth muscle to adrenalin: Ibid., 137: 87–93, 1942.