PHARMACOLOGICAL REVIEWS
Vol. 22, No. 2

VASCULAR SMOOTH MUSCLE

II. PHARMACOLOGY OF NORMAL AND HYPERTENSIVE VESSELS[1,2]

A. P. SOMLYO AND A. V. SOMLYO

From the Departments of Pathology, Presbyterian-University of Pennsylvania Medical Center and the University of Pennsylvania School of Medicine

TABLE OF CONTENTS

[1] The authors' original studies and the preparation of this review have been supported by The Harrison Fund for Gynecological Research, National Science Foundation Grants GB7188 and GB5589, and National Institutes of Health Grant HE08226. Andrew P. Somlyo is recipient of U. S. Public Health Service Research Career Program Award K3-HE17,833.

[2] Address: Department of Pathology, Presbyterian-University of Pennsylvania Medical Center, 51 N. 39th St., Philadelphia, Pennsylvania 19104.

The responses of normal and hypertensive vascular smooth muscles to specific drugs and physical agents are the subject of the second part of this review, Part I (849) having dealt with general structural and biophysical properties. In presenting this survey we shall consider it axiomatic that there can be marked differences among the effects of drugs on different regional circulatory beds or consecutive and nonconsecutive vascular segments and indeed among different smooth muscle fibers within the same vessel. Therefore, we have not attempted to compile an encyclopedia of the drug effects on individual vascular beds among different species, but have preferred to emphasize the clinically and physiologically more important effects of drugs on blood vessels. The proceedings of a recent symposium on vascular neuroeffectors include additional information in this field (101).

The mechanisms of drug action, rather than the effects of drugs, were intended as our central theme. This decision inevitably led to the review of some studies *in vivo* in addition to our main subject, the investigations of isolated blood vessels. For the same reason, in exploring the mechanisms of drug interactions, we found

it desirable to consider the metabolism of the drugs discussed. In attempting to fit the mode of action of drugs on smooth muscle within the general framework of pharmacological mechanisms, a somewhat arbitrary selection of pertinent material has been unavoidable.

I. ANGIOTENSIN

Extensive reviews by Page and Bumpus (698) and by Peart (718) have dealt authoritatively with advances in this subject.

A. Species-specificity and the effect of structural variations

Angiotensin I is a decapeptide derived from a plasma globulin, angiotensinogen, by the hydrolytic action of the enzyme, renin (698, 718, 840). Renin is highly species-specific (840) and even the slight activity of hog renin on human angiotensinogen recently reported by Arakawa *et al.* (37) has been denied by Skeggs *et al.* (840). Modified, granular smooth muscle cells in the kidney are the major source of renin (Part I, section I F; 367, 698), but the enzyme also occurs in hog and rat aorta (367, 771). Renin is localized primarily to the outer media and adventitia in the hog abdominal aorta and its concentration in the whole aorta is about one thousandth of that in the hog kidneys (367). The parallel fall in rat aortic and plasma renin activity after bilateral nephrectomy (771) could indicate a renal source of the vascular enzyme.

Angiotensin I is converted to the biologically active octapeptide angiotensin II by the converting enzyme (698, 718, 840). Converting enzyme is present in plasma and has also been demonstrated in the aorta (698). Tissue converting-enzyme activity may be responsible for the occasional biological activity of angiotensin I on isolated tissues (698, *cf.* 916). Vane (916) found a high converting activity in the perfused pulmonary bed of the guinea pig but not in the systemic vascular beds investigated, and suggested that the lungs are the major sites of conversion of angiotensin I to angiotensin II (54a, 916).

The structure-activity relationships of various angiotensin analogues and derivatives have been discussed by Bumpus (153), Riniker and Schwyzer (754) and Skeggs *et al.* (840). The amino acid in the 5-position of angiotensin is isoleucine in the horse, hog (698, 718, 840), and man (36), and valine in the ox (698, 718, 840). The structural requirements for biological activity include (153, 475a, 840): 1) a free C-terminal carboxyl group and at least six amino acids from the C-terminus; 2) the aromatic groups in positions 4 and 8; 3) proline in position 7, possibly to maintain the reactive groups in the required position; and 4) the imidazole group, or an isosteric susbtituent that can have a markedly different pK than that of imidazole (30), in the 6 position. Structural alterations of the angiotensin molecule may also influence its biological activity indirectly, by making it more resistant to enzymatic breakdown. Thus, desamino-val-5-angiotensin II is resistant to attack by leucine aminopeptidase and also has prolonged rat pressor activity (754). Calcium is required for plasma angiotensinase A activity (153). It has been suggested, however, that tissue, rather than blood, enzymes account for the metabolism of angiotensin *in vivo* (54a). A technical con-

sideration relevant to experiments *in vitro* is the adsorption of very low concentrations of angiotensin to glass surfaces at neutral pH (698).

According to Helmer (410) on rabbit aortic strips asparginyl-1-valine-5-angiotensin II has only one-fourth the contractile effect of an equal pressor (cat) dose of the aspartyl-peptide (but *cf.* 501). Tachyphylaxis to the two peptides also appears to be different (this section B). Comparison of the pressor activity of isoleucine-5- with that of valine-5-angiotensin II produced conflicting results (698). A comparative study of the effects of the two peptides on isolated vascular smooth muscle of several species (hog, ox, horse) would be of great interest, in order to determine whether vascular receptors "show preference" towards the angiotensin of the same species. In this context, it may be noted that avian blood vessels are not contracted by valine-5-angiotensin II-amide (853). We have not found information on whether a renin-angiotensin system is present in birds, and will not exclude the possible existence of an avian angiotensin having an amino acid sequence slightly different from that of mammals and having avian vasoconstrictor activity.

B. Effect on veins, pulmonary vessels, and membrane potential; angiotensin tachyphylaxis

Since the review by Page and Bumpus (698) it has been shown that valine-5-angiotensin amide has, albeit limited, constrictor effect on certain veins. Strips of canine mesenteric and pulmonary veins (856) and of several rabbit veins (878) are contracted by valine-5-angiotensin amide. *In vivo* valine-5-angiotensin amide constricts small limb veins (272), small canine renal veins (988), and canine mesenteric veins (856). The development of tachyphylaxis to angiotensin by veins is very rapid (see below).

Pulmonary arteries of several mammals are constricted by angiotensin *in vitro* and *in vivo* (56, 122, 311, 477, I 555). Thus, although the hemodynamically demonstrable pulmonary vasoconstrictor effect may be minimal (698), mammalian pulmonary arterial and venous (856) smooth muscle is not totally insensitive to angiotensin.

The major effect of angiotensin is on peripheral resistance vessels (I 410) and isolated small arteries are also contracted by angiotensin (122, 907). The central artery of the rabbit ear is much less sensitive to angiotensin than the more distal arteries (230). Angiotensin also produces uterine vasoconstriction in ewes (373), and coronary vasoconstriction in dogs (257).

Angiotensin, like other excitatory agents, depolarizes vascular smooth muscle (851 and section XXII) and also has a contractile effect on vascular smooth muscle depolarized with potassium (I 557). Rabbit aortic strips while relaxing in spite of maintained high concentration (5×10^{-7} w/v) of angiotensin (tachyphylaxis) are also gradually repolarizing (858).

Tachyphylaxis to angiotensin has been observed to vary depending upon the source of vascular smooth muscle. It is particularly pronounced in veins (272, 501, 856, 878) and in arterioles of the hamster cheek pouch (261a) and also easily demonstrable in small arteries (125, 934) and in rat aortic strips (501, 934).

Khairallah *et al.* (501) concluded that angiotensinase is probably the plasma factor originally found by Page and Helmer (cited in 501) to reverse angiotensin tachyphylaxis. A plasma fraction rich in angiotensinase A (153) reversed tachyphylaxis due to aspartic-1- or asparagine-1-angiotensin (501). Tachyphylaxis to *beta*-aspartic-1-angiotensin, an analogue that is not attacked by angiotensinase, was not reversed by the plasma fraction, but could be reversed by adsorbing the peptide with Dowex 50. The reversal of tachyphylaxis to angiotensin by angiotensinase (501) was subsequently confirmed by two other laboratories (125, 582). In a third study (934) Dowex 50 did not reverse and renal extract only inconsistently reversed tachyphylaxis to angiotensin. Angiotensin amide is destroyed at a faster rate by angiotensinase A than is angiotensin (501). Tachyphylaxis to angiotensin amide in intact rats (887, 889) and in perfused rat hind limbs and kidney (889) has been demonstrated, and a recent conflicting report (789) requires further clarification.

In renovascular hypertension an association of increased plasma renin activity and increased resistance to the pressor effect of exogenous angiotensin have been reported (819, 834). The authors suggested that the angiotensin-infusion test is useful for the diagnosis of renovascular hypertension. Others either deny the inverse correlation between angiotensin-sensitivity and renin levels (898) or question the diagnostic reliability of the angiotensin infusion test (649, 688).

C. Effect of pregnancy, progesterone, Na, and antagonists

Normal pregnancy is associated with an increased tolerance to angiotensin (414, 623, 885) attributed to increased plasma angiotensinase activity (885). In rats progesterone treatment also reduces the pressor response to angiotensin (414), as do aminopeptidase and carboxypeptidase in spinal cats (512). Alloxan diabetic rats also show increased sensitivity to the vasoconstrictor effects of angiotensin and catecholamines (148).

Perfusion of rat tail arteries with low (72 mM) Na solution reduces the vasoconstriction elicited by single dose injections of angiotensin or vasopressin (422). Submaximal responses of perfused rabbit ears to angiotensin progressively decline when the Na concentration of the perfusate is increased or decreased by 40 mM (115). The somewhat greater responses to norepinephrine are not similarly affected. In contrast, acute reduction of Na (by 25%) in the bathing medium increases the response of rabbit aortic strips to angiotensin, while a similar increase of Na relaxes the angiotensin-induced contraction (670).

Inhibition of angiotensin-induced vasoconstriction by the vasodilator, cinnarazine, is nonspecific (356), despite earlier claims (801). The antagonism of several other drugs to angiotensin is also nonspecific (938), and we know of no truly specific angiotensin-antagonist.

D. Adrenergic interactions

Indirectly mediated effects of angiotensin have been dealt with in recent studies and implicated in the genesis of labile hypertension due to subpressor doses of angiotensin (624). Possible sites of interaction include the central nerv-

ous system, the adrenal medulla, adrenergic nerve endings, and smooth muscle cells.

Intracerebral injection of angiotensin into the lateral ventricle of cats elicits an acute pressor response (217, 825) that is inhibited by phenoxybenzamine and also by pronethalol (825). Inhibition by the *beta*-blockers, unless due to local anesthetic action (section IX K) suggests that the pressor response may be mediated partly by a centrally-evoked cardiac inotropic effect. Angiotensin (and also norepinephrine) injected into the vertebral artery of conscious rabbits elicit a greater pressor response than does intravenous injection (245). In anesthetized dogs vertebral artery injection of angiotensin does not evoke a rise in the resistance of cutaneous, renal or muscular bed (987) although it can elicit a rapid pressor response (fig. 4 in 987). Morrison and Pickford (654) recently measured the firing frequency of cervical sympathetic discharge and found it to be related to the level of blood pressure, independent of the nature of the pressor drug (angiotensin or norepinephrine), and abolished after section of the carotid sinus nerves, depressor nerves and cervical vagi. They suggested that the effects of centrally-injected angiotensin are reflex in origin and do not differ from the effects of norepinephrine.

The constriction of hand veins in man by angiotensin is due primarily to reflex neurogenic vasoconstriction (235). The effect of intravenous, but not of intra-arterial, angiotensin on human hand blood flow is inhibited by guanethidine or phenoxybenzamine (411, 818). The renal vasoconstrictor effect of intravenous angiotensin may also be neurally mediated (628, 629, but *cf.* 339), but renal intra-arterial injection has a direct vasoconstrictor effect (339, 533, 628). Neurally mediated reflex vasodilation is nonspecific and secondary to the pressor effect of angiotensin (221, 259, 987). The release of adrenal medullary catecholamines by angiotensin (290) shows positive correlation with its pressor activity in cats (864). In man catecholamines make little or no contribution to the pressor effect of angiotensin (818).

Sympathetic vasoconstriction is enhanced by angiotensin in dogs (626). Angiotensin also potentiates adrenergic vasoconstriction of cat mesenteric (707) and of canine cutaneous and renal vessels (987, 989). The physiologic significance of the minor potentiation of norepinephrine by angiotensin on human hand blood flow has been questioned (818). Angiotensin also potentiates the pressor response of the perfused rabbit ear (786 but *cf.* 222) and rat renal artery (413) to norepinephrine and to tyramine. Potentiation is not universal and the sympathetic vasoconstriction of the canine muscular bed and of the rabbit ear artery (222, 990) is reduced during infusion of angiotensin. Very high (2×10^{-5} w/v) concentrations of angiotensin inhibit the uptake of norepinephrine by rat arteries *in vitro* according to Palaič and Khairallah (699). Attempts to demonstrate inhibition of catecholamine-uptake by angiotensin *in vivo* have met with variable results and interpretations that do not support a predominantly cocaine-like effect of the peptide (703, 707, 786, 990). It has also been suggested that angiotensin may potentiate the effect of catecholamines by mechanically decreasing the series-elastic component in blood vessels (222, 702), by increasing catecholamine re-

lease (989), or *via* an effect on the smooth muscle (707). The effect of angiotensin on rat mesenteric vessels is potentiated by exogenous norepinephrine and nerve stimulation (631).

The effect of angiotensin on vascular strips is direct and not due to release of norepinephrine from nerve endings. Vascular preparations obtained from reserpinized animals remain sensitive to angiotensin (905) and may become supersensitive to the peptide (786). Cross tachyphylaxis does not occur in rat aortic strips between tyramine and angiotensin (700). Cocaine, in sufficient concentrations to block the effects of tyramine, does not block angiotensin (905). A contrary report (247) was based on experiments with very high (10^{-5}) concentrations of cocaine probably leading to nonspecific depression. Methylphenidate, an agent that also inhibits catecholamine uptake (section IX B), potentiates the response of rabbit aortic strips to angiotensin (612), but the relationship between the two effects is uncertain. Completely nerve-free placental (938) and, to a lesser extent umbilical (I 559)[3] vessels are also constricted by angiotensin.

II. NEUROHYPOPHYSEAL PEPTIDES AND ANALOGUES

The synthesis of a large number of neurohypophyseal peptide analogues, largely due to the laboratories of du Vigneaud, Boissonnas, and Rudinger (for reviews see 83, 126, 780) has spurred much interest in this field and created a unique opportunity for the study of structure-activity relationships. Several of the methods used in determining biological activity are assays *in vivo* (110, 871), and the potency of a given analogue under these conditions may be strongly influenced by its metabolism. Structure-activity relationships determined *in vivo* are not necessarily representative of the stereochemical relationships between the receptor and an agonist alone, and the evaluation of the effects of a given structural change on affinity or intrinsic activity may be difficult.

A. Clearance, inactivation, and binding

The enzymatic metabolism and clearance of neurohypophyseal peptides have been reviewed recently by Ginsburg (349), Lauson (548), and Tuppy (904). There are considerable variations in the inactivation of neurohypophyseal peptides among different species. Hepatic inactivation of arginine vasopressin accounts for a large proportion of the peptide cleared in rats, but apparently far less in dogs (548). The binding of neurohypophyseal peptides by circulating plasma proteins is also species-dependent (548). Kidney slices inactivate vasopressin (548), and skeletal muscle has oxytocinase activity (904), but similar data on inactivation by blood vessels are not available.

Enzymatic inactivation of neurohypophyseal peptides is subject to considerable substrate specificity. Trypsin inactivates vasopressin but not oxytocin (904). Chymotrypsin inactivates oxytocin and its derivatives but, if adequately purified, does not inactivate vasopressin (62, 904). During pregnancy a tissue oxy-

[3] References cited in Part I are not duplicated here; citation of these papers in the text is prefixed by Roman numeral I and followed by the numerical citation given in the References of Part I.

tocinase appears that cleaves the S—S bond of oxytocin (142, 182). Faster inactivation may account for the reduced depressor activity of oxytocin during pregnancy (149) although sensitization to the pressor effect (728) may also contribute.

An interesting observation of Chan and Wahrenburg (182) is that although oxytocin is nonspecifically bound to the myometrium, nonspecific binding of its deamino derivative is not detectable. Neither is deamino-oxytocin bound by the pituitary protein neurophysin (for review see 8), nor is it susceptible to leucine aminopeptidase (904) or serum (in contrast to tissue) oxytocinase (182).

It has been suggested that certain synthetic peptides, such as extended-chain neurohypophyseal peptide analogues (82) or vasopressin dimers (but *cf.* 798) may function as hormonogens that are broken down, by enzymatic action, to the active peptide. The activity and duration of action of these compounds will obviously depend on the presence of the "liberating" enzymes and the clearance of the active peptide. The unmodified extended-chain analogues may also act as specific antagonists to neurohypophyseal peptides (82) leading to more complex interactions than those modeled by simple drug-receptor kinetics.

The pronounced variations in the metabolism of different neurohypophyseal peptide analogues suggest that structure-receptor interactions of these peptides could be more clearly established in isolated preparations in which the metabolism and binding of peptides have been characterized. The relative vascular potencies of neurohypophyseal peptides and their analogues may be different *in vivo* and *in vitro*, as illustrated by the different vasoconstrictor potencies of (rat) equipressor concentrations of lysine-vasopressin and phenylalanine-2-lysine vasopressin on the rabbit ear (86). It is not known whether these and similar differences in peptide activity are related to site-specific variations of peptide metabolism or to differences in receptor structures.

B. Interactions with magnesium and its effects on biological activity

The vasoconstrictor action of every neurohypophyseal peptide analogue tested to date, including lysine- and arginine-vasopressin, phenylalanine-2-lysine-8-vasopressin, deamino-oxytocin, and vasotocin, is specifically potentiated by magnesium (and by manganese). This Mg-neurohypophyesal peptide interaction has been demonstrated in vascular smooth muscle of people (umbilical), dogs, chickens, and hagfish (I 560, 853, 857). Magnesium also potentiates the effects of neurohypophyseal peptides on the myometrium (181, 535, 804). The myoepithelial and intestinal (excitatory and inhibitory) effects of neurohypophyseal peptides are similarly Mg-dependent (I 560, 966).

The suggested mechanism of potentiating action of magnesium, based on indirect (kinetic) arguments, is that this cation (or manganese) increases the affinity of the receptors of vascular smooth muscle to neurohypophyseal peptides and their analogues by inducing a conformational change in the receptors (I 560, 853, 857). Similarly interpreted data have been obtained with uterine (78, 181, 535, 804) and with intestinal smooth muscle (966). The potentiation of neurohypophyseal peptides by magnesium has also been demonstrated in depolarized vascu-

lar (I 560) and uterine smooth muscle (535, 804). Schild (804) recently conducted extensive studies on potentiation of neurohypophyseal peptides by Co, Mn, Ni, Zn, Mg, and Fe in depolarized myometrium, and suggested that these metals form ternary coordination complexes with neurohypophyseal peptides and their receptors.

It has been suggested (78, 853) that, in a given biological system, neurohypophyseal peptides with relatively lower intrinsic activity will appear to be potentiated more by magnesium than would the more potent peptides. Vasopressin is less potent (ED50 higher) than oxytocin as a vasoconstrictor on avian (853) but more potent (ED50 lower) on mammalian (I 560) vascular strips. Magnesium increases the maximal response to vasopressin with avian (853) and to oxytocin (3-fold by 1.2 mM Mg) with mammalian (854) vascular strips. Chan and Kelley (181) and Krejčí and Poláček (535) found that the potentiation of oxytocic activity by magnesium, in a series of neurohypophyseal peptide analogues, was also inversely related to potency. It would therefore be anticipated that peptide analogues having very low oxytocic potencies (assayed in Mg-free solutions) would have somewhat higher activities in the Mg-containing assay-systems based on milk ejection or the avian depressor or rat pressor effect, and this is indeed found with many (139, 140, 143, 265, 291, 345, 441a, 442, 732, 814, 871) though not all (141, 291, 880a) analogues. It is clear therefore that this apparent dissociation of oxytocic from other activities cannot be interpreted as being due to intrinsic differences between, for example, vascular and myometrial receptors.

The decreased maximal response, in Mg-free solution, of the depolarized myometrium (804) and avian pulmonary artery (853) to vasopressin, and of canine iliac arteries to oxytocin (854) is in seeming contradiction to an effect of the cation being mediated by increased affinity of the respective peptides. It is possible that the intrinsic activity of the postulated Mg-receptor-peptide complex is greater than that of the (binary) receptor-peptide complex (804). Alternatively, the absolute number of receptors may be decreased in Mg-free media, the latter acting in the manner of an irreversible blocking agent, causing a decline in the maximal response to peptides having low intrinsic activities (few or no spare receptors). In any event, the critical observation that remains to be accounted for, in terms of drug-receptor interaction, is the parallel variation of the affinity and the intrinsic activity of peptides when tested in different biological systems. A direct experiment determining the effect of Mg on the binding of isotope-labeled peptides to tissues would be of great interest. The suggested classification of neurohypophyseal peptide receptors into Mg-dependent and Mg-independent groups is discussed elsewhere (this section E).

C. Chlorobutanol: the effect of an active preservative in peptide preparations

Chlorobutanol (0.5%) is used as a preservative in a number of commercial preparations of neurohypophyseal peptides and kinins. This simple compound is not biologically inert: it is a vasodilator and smooth muscle relaxant. It is difficult, therefore, to evaluate earlier studies in which preparations containing the preservative have been used without reporting its concentration. Further, it

should not be assumed that the action of preservatives is identical in different systems. For example alcohol, in the concentrations used to dilute Dibenamine, constricts human placental vessels (937).

Chlorobutanol accounts for the entire vasodepressor effect of commercial synthetic oxytocin in cats (492). In man, however, preservative-free oxytocin also has a hypotensive effect, though not nearly as pronounced as it is in birds (see below). Isolated canine and avian arterial smooth muscle (I 560, 853) and rabbit aortic (19) and human umbilical vein strips (854) are relaxed by chlorobutanol (10^{-5} to 10^{-4}) as are isolated intestinal and tracheal smooth muscle preparations (966). All these effects of the preservative are exerted at concentrations delivered by doses of neurohypophyseal peptides commonly used for experimental purposes. It is probable that the reported vasodilator action of vasopressin on umbilical vascular smooth muscle (I 559) and of phenylalanine-2-lysin-8-vasopressin on coronary arterial smooth muscle (16) was due to the preservative. The proportion of active peptide to preservative varies with different neurohypophyseal peptide analogues: the effects of the preservative would be most dominant in dilute preparations of peptides having low activities. All blood vessels may not be equally sensitive to chlorobutanol and the possibility cannot be ruled out that the results of Altura's and Hershey's (19) careful study on segmental microcirculatory responses to a large series of neurohypophyseal peptide analogues were influenced also by a selective effect of the preservative. Preferential vasodilation in some other circulatory beds may have been responsible for the reported (361) reduction of splanchnic blood flow by chlorobutanol. The positive interaction between chlorobutanol and oxytocin on the coronary circulation (308) indicates a possible additional complication in interpreting some results obtained with peptides in the presence of preservative.

Finally, it should be reemphasized that preservative-free neurohypophyseal peptides have vasodilator effects, of varying degrees (this section E), in several species. Further evaluation of these effects, and of the literature, will be greatly facilitated by the use of "pure" peptides or, if not available, by accurate control experiments with the solvent and preservative only.

D. Evolutionary aspects: species-specificity or structural specificity

The structural evolution of neurohypophyseal peptides from the most primitive vertebrates, Class Agnatha (hagfish, lamprey) to man have been reviewed recently by Acher (8) and Sawyer (795). The two predominant evolutionary lines are the isotocin, mesotocin, oxytocin series that contain a neutral amino acid (leucine or isoleucine) in the 8-position, and the vasotocin, vasopressin series that contain the basic amino acid arginine (in pigs lysine) in the 8-position (8, 795). Little attention has been directed heretofore to the species-specific differences in the potency of various neurohypophyseal peptide analogues, particularly as regards their vasomotor effects. Vasomotor sensitivity to these peptides has been considered to be a recent phylogenetic development in higher vertebrates (248, 793, 967). More recent work indicates that species-specificity of peptide-receptor interaction, rather than the basicity of the 8-position alone, determines

the vascular potency of a given peptide, and that pronounced vascular sensitivity to neurohypophyseal peptides appeared at the earliest stage of vertebrate phylogenesis.

Basicity of the 8-position, contrary to previous beliefs (for review, see 83) is not a necessary structural condition for the vasoconstrictor action of neurohypophyseal peptides. The commonly inferred generalization, that vasopressin-like activities are predominantly vasoconstrictor and oxytocin-like activities predominantly vasodilator may be an oversimplified extension of the species-specific responses of intact rats and birds to neurohypophyseal peptides. Oxytocin *in vitro* is a more potent vasoconstrictor than vasopressin in avian vascular smooth muscle (853) and in human umbilical vessels (I 559). Oxytocin also produces vasoconstriction in the isolated hind-limb of the frog, although its potency is less than that of vasotocin, whereas arginine vasopressin has no effect on this preparation (915). It seems significant that oxytocin is a more potent vasoconstrictor than vasopressin in those two classes in which not vasopressin but oxytocin (Aves) or its closely related analogue mesotocin (Amphibia) is also the native neurohypophyseal hormone (8). This species-specificity also extends to the vasodepressor effects of neurohypophyseal peptides: the avian depressor activity of oxytocin (450 U/mg) and of mesotocin (498 U/mg), is considerably greater than that of arginine (60 U/mg) or lysine (40 U/mg) vasopressin (83). In contrast, mammals produce both oxytocin and vasopressin and, with the above noted exception of umbilical vessels, mammalian blood vessels are more sensitive to the vasoconstrictor effects of the vasopressins (*e.g.*, 19, 20, I 200, I 560, 793). In classes (Amphibia and Agnatha) in which vasotocin is a native hormone (8, 9, 304, 794, 795) it also appears to be the most potent vasoconstrictor (853, 857, 915).

The ring structure rather than the side chain seems more crucial for amphibian (915) and avian vascular activity. Oxypressin, an analogue that has the side chain of oxytocin attached to the vasopressin ring, has very little avian depressor activity whereas arginine vasotocin (composed of an oxytocin ring and of an arg-8-vasopressin side chain) (83) is a more potent avian depressor.

The evolutionary mechanism of the species-specific vascular sensitivity to native neurohypophyseal peptides is a fundamental question to be answered. One possibility, the control of both the vascular receptor and the structure of neurohypophyseal peptides by a single genetic locus that produces simultaneous and parallel evolutionary changes, has little to recommend it beyond its teleological desirability. A more likely possibility is that receptors to neurohypophyseal peptides have at least an accessory locus that may be induced by a circulating hormone to which it conveys stereochemical specificity. Although speculative, this hypothesis can be experimentally tested. It would predict the vascular smooth muscle of the Brattleboro strain of rats congenitally lacking vasopressin (913) to be relatively less sensitive than normal to vasopressin as compared to oxytocin. Contrary to this expectation, aortic strips from these animals, like the strips from normal rats, were considerably more sensitive (ED50 and maximal response) to arginine vasopressin than to oxytocin (854).

Vascular smooth muscle of lower vertebrates can be exquisitely sensitive to neurohypophyseal peptides, as indicated by the contractile effects of very low (10^{-11} M) concentration of vasotocin on strips of ventral aorta of the hagfish (857). Vasotocin is a neurohypophyseal peptide native to cyclostomes (304, 794), descendants of the earliest stage in vertebrate evolution. In a preliminary comment, Sawyer (795) also indicated that vasotocin injected into intact lungfish elicits a pressor response. In view of the findings with the isolated hagfish vessels, (857) Sawyer's observation (795) probably represents a peripheral vasoconstrictor action of vasotocin, although the possibility of a cardiac action has not been formally ruled out. In giant Ceylonese frogs only relatively high concentrations of vasotocin have vasoconstrictor activity (915). Isolated pulmonary arterial smooth muscle of chickens is highly sensitive to the vasoconstrictor action (ED50 3×10^{-9} M) of oxytocin and, in view of the relatively specific sensitivity of this preparation to neurohypophyseal peptides, it has been recommended as useful for bioassay (853). It appears reasonable to conclude that species-specific preference to the peptides native to mammals is the characteristic acquired during evolution, but that vascular sensitivity to native (nonmammalian) neurohypophyseal peptides was already present at the earliest stage in vertebrate phylogenesis. The suggested physiological role of vasotocin in regulating the regional circulatory responses of the gills (857) or the kidneys (795) remains to be established *in vivo*. Furthermore, determination of the vascular effects of isotocin, mesotocin, glumitocin, and the (oxytocin-like) unidentified neurohypophyseal peptides of elasmobranchs (721) in the species in which they occur naturally, would help to differentiate the structural characteristics of neurohypophyseal peptides conveying vascular activity from those that are species specific. The recent studies of Maetz and Rankin (596a) have already revealed a great sensitivity of the perfused gills of fresh water eels to the vasoconstrictor action of isotocin (threshold 10^{-13} M).

E. Receptors serving relaxation and contraction, and their relationship to epithelial receptors; the neurohypophyseal peptide antagonists

The common characteristics of neurohypophyseal peptide-receptors mediating contraction of vascular, uterine, and intestinal smooth muscle, as well as myoepithelium, are their magnesium-dependence (this section B) and their susceptibility to blockade by the same type of inhibitors. These neurohypophyseal peptide inhibitors include methylated derivatives of neurohypophyseal peptides that act as competitive inhibitors of oxytocic, milk-ejecting (111), and rat pressor (534, 551) activities, and also inhibit the action of neurohypophyseal peptides on vascular smooth muscle *in vitro* (Vavra, Krejčí and Kupkova, cited in 778). Isoglutamine-oxytocin inhibits the rat pressor activity of vasopressin (748). It should be mentioned however, that although certain tyrosine-containing synthetic peptides inhibit the pressor effect of vasopressin in dogs and rabbits, as well as the avian depressor and the rat oxytocic effects of oxytocin *in vitro* there is little or no correlation between the inhibitory activities of the various tyrosine-contain-

ing peptides in the different assay systems (459). 1-Acetyl-8-lysine-vasopressin is an inhibitor of the rat pressor and the avian depressor activity of neurohypophyseal peptides, although it acts as a weak (less than 0.5% of the corresponding activities of vasopressin) agonist in the standard milk ejection and oxytocic assays *in vitro* (173, 780). Martin and Schild (603) pointed out that thioglycolate inhibits the effects of neurohypophyseal peptides on the rat uterus *in vitro* (in Mg-free solution) and on mammary strips, but not on the perfused rat hind limb nor on the rat uterus *in vivo*. It seems to us that the occasional failure of some inhibitors to block the effect of neurohypophyseal peptides on all sensitive contractile tissues may be due to differences of the assay systems rather than to different vascular, uterine, and myoepithelial receptors. For example, 2-O-methyloxytocin can act as either a weak partial agonist or as a competitive antagonist in the rat uterine bioassay, depending upon the Mg and Ca concentration of the medium (536). If both oxytocin and vasopressin can act on the same type of smooth muscle receptor, then the unresolved major question is the mechanism of the greater sensitivity of the myometrium to oxytocin and of vascular smooth muscle to vasopressin within the same species. Oxytocin is a less active vasopressor (approximately one hundredth) than vasopressin in the rat, and the latter peptide is also the more active topical vasoconstrictor (19, 20, 565). The three major possibilities are that: 1) rat myometrial and vascular receptors are structurally different at some critical site; 2) autoinhibitoin due to a vasodilator effect of oxytocin interferes with its vasoconstrictor action; and 3) local metabolism of the two peptides is markedly different in the uterus and in blood vessels. There is not enough evidence to choose among these possible mechanisms, and we must caution against the assumption that a fundamental difference has been conclusively documented among the receptors of different smooth muscles of a single species to neurohypophyseal peptides.

There is some evidence that the inhibitory receptors to neurohypophyseal peptides in contractile tissues are also closely related to, if not identical with, the receptors mediating vasoconstriction. Because magnesium specifically potentiates both the intestinal inhibitory and the various contractile effects of neurohypophyseal peptides (966), we have suggested that inhibitory and excitatory effects are mediated by a common receptor but different secondary messengers (853). Lloyd and Pickford (569) found that tyrosine-methyl^2-oxytocin blocked both the vasodepressor and vasopressor actions of oxytocin in rats, and they also suggested that the two effects are mediated by a common receptor. 1-L-Penicillamine oxytocin inhibits both the avian depressor and the rat oxytocic activity of oxytocin (813 but *cf.* 815). Calcium is probably the "messenger" mediating contraction due to drugs in general (section XXII; Part I, sections VI C and H). Direct studies bearing on the mechanism of the vasodilator action of neurohypophyseal peptides are hindered by the difficulty in demonstrating the avian vasodilator activity *in vitro* (853). Very high concentrations of oxytocin (without chlorobutanol) relax mammalian vascular strips (19, I 560), but the relationship of this observation to the slight mammalian vasodepressor action of

oxytocin *in vivo* is uncertain. High concentrations of 1-L-penicillamine oxytocin produce hypotension in rats (180), but whether this is due to a peripheral vascular action is not known.

The epithelial (natriferic, hydro-osmotic) receptors to neurohypophyseal peptides differ in some essential respects from the receptors of contractile tissues. Classifying neurohypophyseal peptide receptors on the basis of their magnesium dependence (966), epithelial (in contrast to contractile) receptors are Mg-independent: the effects of neurohypophyseal peptides on epithelial water and Na-transport are not potentiated by magnesium or by manganese (80). Marked dissociation of the rat pressor from the antidiuretic activity of desulfurized vasopressin (305) and of certain structural analogues of neurohypophyseal peptides (727, 873, 924; but *cf.* 731) also suggest a significant difference between the two types of receptor. The evidence, in our opinion, does not support Bentley's suggestion (81) that the natriferic receptors of the toad bladder are identical with smooth muscle receptors to neurohypophyseal peptides.

F. Major requirements for activity: carba-analogues, linear peptides, and selenium isologs

The presence of a disulfide bridge within the ring structure of neurohypophyseal peptides naturally led to speculations that hormone-receptor interactions are mediated through reaction of the peptide disulfide with a thiol group of the membrane (for review, see 778). This hypothesis was invalidated by the demonstration that carba-analogues, in which one or both sulfur atoms were replaced by methylene groups, retain biological activity (476, 779, 785). Decreasing the size of the ring, with (778) or without (466) removal of the disulfide bridge, leads to marked decrease in all biological activity. Enlargement of the ring, while retaining the disulfide bridge, leads to almost complete loss of activity (467). Desulfurized arginine vasopressin loses almost all antidiuretic, but retains some rat pressor and avian depressor activity (83, 305).

The question of the biological activity of the oxytoceine, the linear peptide obtained by reduction of the S—S bridge of oxytocin to —SH groups, is not resolved. Du Vigneaud and his associates (978) found that oxytoceine had significant (70 U/mg) avian vasodepressor activity, but they also indicated that oxytoceine may have been reconverted to oxytocin *in vivo*. Because of the ease with which oxidation of oxytoceine takes place even in NaCl solution bubbled with N_2 (978), assays of oxytoceine *in vitro* may also be equivocal. The slight activity of desulfurized acyclic peptides (83, 305) suggests that the ring structure may not be absolutely essential for vascular activity.

The reactivity of selenium is very similar to that of sulfur and it may be anticipated that selenium isologs (Se substituted for S in the molecule) would have biological activities similar to the S—S neurohypophyseal peptides (476). This expectation has been confirmed by synthesis of biologically active (including avian depressor) selenium isologs of oxytocin (83). Several deuterated derivatives of deamino-oxytocin also have activities identical with that of the parent peptide (116).

The most essential structural group of neurohypophyseal peptides is the carboxamide of the asparagine residue in the 5-position (379), removal of which leads to almost complete loss of both contractile and antidiuretic activity (85, 264, 379, 936).

It is possible to modify the relative activity of peptides on the epithelial and contractile tissues of the same species, and clinically useful analogues having high ratio of pressor activity to antidiuretic activity have been developed (83, 84, 86).

G. Interactions with steroids, catecholamines, and cyclic 3′,5′-AMP; vasopressin tachyphylaxis

Considerable evidence has been presented by Pickford and her associates, that estrogen and some other steroids influence the vascular activity of neurohypophyseal peptides in certain species. Rats are particularly susceptible to this action of steroids: estrogen (324, 568, *cf.* 660) or testosterone (429) convert the effect of normally vasodilator concentrations of oxytocin to a vasopressor one. Estrogen also converts to vasoconstriction the vasodilator action of oxytocin on the dog hind limb (568, but *cf.* 665) and on the human forearm (389). It is difficult to assess the influence, if any, of chlorobutanol on these experiments. However, "oxytocin-reversal" is associated also with increased sensitivity to the pressor action of vasopressin containing little or no chlorobutanol (432, 565). In contrast to the responses of some mammals, the avian depressor action of oxytocin is not reversed by sex steroids (185, 567).

The mammalian vasodilator activity is influenced also by the sympathetic nervous system. Lumbar sympathectomy eliminates the vasodilator action of oxytocin and converts it to vasoconstrictor on the dog and monkey limb preparations (390, 568, 570). Stimulation of the sympathetic trunk (390), or the infusion of epinephrine after sympathectomy (570) reestablishes the vasodilator activity of oxytocin. Treatment with reserpine or dihydroergotamine also produces oxytocin-reversal in dogs (390). The avian depressor activity of oxytocin is not modified by sympathectomy or reserpinization (567, 968), nor is the inconsistent avian vasodilator action of oxytocin *in vitro* enhanced by the addition of epinephrine to the bath (853).

The tachyphylaxis to the pressor action of vasopressin *in vivo* is diminished by pretreatment with reserpine (663, 672, 715). It has been suggested that this is a "pseudo-tachyphylaxis" due to secondary hemodynamic changes elicited by adrenergic discharge that is eliminated by reserpine (672, 715, 899). True tachyphylaxis to neurohypophyseal peptides occurs in several isolated smooth muscle preparations (I 559, 966).

Vasopressin potentiates the effect of catecholamines released during nerve stimulation (94) without apparently affecting the amine storage mechanisms (412). Vasopressin (673) and chlorobutanol-free oxytocin (492) also produce ethylnorepinephrine-reversal. The suggestion of Nash *et al.* (673), that these peptides have *beta*-blocking effects, merits further consideration although other mechanisms of ethylnorepinephrine-reversal (492) cannot be ruled out. Vaso-

pressin also potentiates the contractile action of norepinephrine on rat aortic strips (60) and microcirculation (19). The role of *beta*-adrenergic blockade in this phenomenon cannot be entirely excluded, since norepinephrine does have some vascular *beta*-adrenergic activity (section IX J). Externally added cyclic 3′,5′-adenosine monophosphate (cyclic 3′,5′-AMP, sections IX I and X) also potentiates the vasoconstrictor effect of norepinephrine on rat aortic strips, and this rather circumstantial evidence has been used to suggest that cyclic 3′,5′-AMP is the secondary messenger of vasopressin acting on vascular smooth muscle (61). However, when documented, a rise in intracellular cyclic 3′,5′-AMP has generally been associated with smooth muscle relaxation (758) and it is possible that cyclic 3′,5′-AMP mediates vasodilator action of neurohypophyseal peptides. The avian vasodepressor action of a synthetic oxytocin preparation was blocked by dichloroisoproterenol (931). The vasodilator action of synthetic oxytocin with preservative (chlorobutanol) on canine arterial strips is also blocked by *beta*-adrenergic blocking agents, although in this preparation the preservative-free peptide has only vasoconstrictor effects (I 560). The interesting observation of the oxytocin-blocking effects of dichloroisoproterenol (931) deserves further exploration with a preservative-free oxytocin preparation.

H. Regional circulatory effects: uterine, umbilical, gastrointestinal, coronary, pulmonary, adenohypophyseal, and renal vascular responses to neurohypophyseal peptides

Comprehensive reviews on the circulatory effects of neurohypophyseal peptides have been published by Pickford (728) and by Saameli (784). We shall briefly survey here only the recent work on specialized vascular beds that are relevant to the clinical pharmacology of neurohypophyseal peptides. The majority of these studies deal with the effects of neurohypophyseal peptides on arterioles, but venular smooth muscle is also contracted by neurohypophyseal peptides (19, 20, 178, 243).

The uterine blood flow of rabbits is decreased only by very large doses of vasopressin (172). Isolated human uterine arteries are not contracted by oxytocin, although they contract in response to the (not neurohypophyseal peptide) oxytocics ergonovine and sparteine (205). Isolated human umbilical vessels are very sensitive to the contractile effects of oxytocin (I 560), although they develop tachyphylaxis (I 559). Perfused placental beds are also constricted by oxytocin (514, 599). Corbit (200) demonstrated a decrease in umbilical venous oxygen saturation after the (maternal) injection of oxytocin into patients undergoing caesarian section. Whether the latter effect is caused by an umbilical vasoconstrictor action of oxytocin *in vivo* remains to be determined.

Vasopressins constrict the gastrointestinal blood vessels of several species, including man (*e.g.*, 826, 890). This splanchnic vasoconstrictor effect of vasopressin has been used for the treatment of bleeding esophageal varices (83, 232, 295, 686, 784, 903). The vasoconstrictor effects of neurohypophyseal peptides on the splanchnic microcirculation have been suggested to improve the survival rates of experimentally shocked rats (19, 20).

Vasopressin constricts coronary blood vessels of several species (*e.g.*, 409, 609, 663, 784). The possibility that impairment of ventricular dynamics by the coronary vasoconstrictor action may account for pseudotachyphylaxis to vasopressin (672) has been mentioned. Preservative-free oxytocin constricts the perfused canine coronary vascular bed, while the combination of peptide and preservative dilates it (308). The earlier reported relaxant effect of 2-phenylalanine-8-lysine vasopressin on isolated bovine coronary vessels (16), was subsequently shown to be due to the preservative-diluent employed (19). The umbilical vasodilator activity of the diluent-preservative of oxytocin has been mentioned (this section C). The thoracic aorta of dogs is insensitive to vasopressin and the aortic response to vasopressin increases caudally (I 554).

The pulmonary vascular effects of neurohypophyseal peptides, in normal man, are variable (751). Vasopressin is a pulmonary vasoconstrictor in patients with diffuse tuberculosis (752). There is an interesting preliminary report of experimental pulmonary thromboarteriopathy produced in rabbits by vasopressin (Yano, cited in 975). The authors seemed to attribute this to the general pressor action of the peptides rather than to a specific pulmonary vascular activity. Main pulmonary artery strips of dogs are not contracted by vasopressin or oxytocin (I 555), whereas those of chickens are extremely sensitive to neurohypophyseal peptides (this section D). The possibility of neurohypophyseal peptide-controlled circulatory changes in the gills (857) still remains to be established *in vivo*, but is supported by observations on perfused gills (596a).

Lysine vasopressin, which is not the native peptide of this species, has been shown by Yates *et al.* (980) to produce only a minor decrease in the pituitary blood flow of rats.

Renal vasodilation can be elicited by very low doses of vasopressin in cats (57; but *cf.* p. 555 in 784). Phenylalanine-2-lysine-8-vasopressin, in very low concentrations, has a similar vasodilator action in man (195). Higher concentrations of vasopressin have a renal vasoconstrictor effect (784) and may possibly reduce blood flow through the renal vasa recta (309, but *cf.* 48).

It seems appropriate to conclude this section by noting that the role of neurohypophyseal peptides *in vivo* (19, I 560, 728, 762a, 950) in regulating physiological and pathological hemodynamics deserves further impartial evaluation. The specific antagonism of the rat pressor and avian depressor actions of the vasopressins by their 1-acetyl-derivatives (173, 870) would render the analogues useful tools, as blocking agents, for determining masked hemodynamic effects of neurohypophyseal peptides. One may expect to reverse with 1-acetyl-8-arginine vasopressin those hemodynamic consequences of hemorrhagic shock that are considered to be (950) due to elevated levels of circulating vasopressin.

III. PLASMA KININS AND RELATED HYPOTENSIVE POLYPEPTIDES

The plasma kinins, linear polypeptides liberated from plasma pseudoglobulins (kininogens) by a variety of agents including kallikrein, Hageman factor, low pH, plasmin, and trypsin, have been reviewed in detail by Erdös (274). Bradykinin formed by the action of trypsin on pseudoglobulin is a nonapeptide; kallidin

formed by the action of the enzyme kallikrein is a decapeptide, lysyl-bradykinin; and a third plasma kinin is the undecapeptide, methionyl-lysyl-bradykinin, released from pseudoglobulin by acidification (274, 729).

The undecapeptides eledoisin, physalaemin, and phyllokinin, the first two from molluscan venom, the third from the skin of South American tree frogs, were isolated and characterized by Erspamer *et al.* (26) and reviewed, together with wasp kinins, by Pisano (730). In addition to being linear polypeptides, the substances isolated from venoms have actions like those of kinins, and in particular are highly potent hypotensive agents. Caerulein, an amphibian decapeptide, has a hypotensive action that varies considerably among different species (97).

A. Effects on isolated blood vessels, perfused organs, and blood pressure

Several types of larger arteries and veins are constricted by kinins and eledoisin. These include sheep coronary arteries (530) and ductus arteriosus (531), bovine pulmonary arteries (515), human umbilical arteries (I 136, 270), canine femoral and mesenteric veins (237), cat inferior vena cava, and normal and reserpinized rabbit aorta (906). Bradykinin also constricts normal and denervated rabbit ear veins (117, 378, 434). High concentrations (10^{-5} w/v) of bradykinin contract rabbit mesenteric vein strips (878) but low concentrations (5×10^{-8} to 10^{-7} w/v) transiently inhibit the spontaneous activity of this preparation (854). Canine large coronary arteries are not contracted by bradykinin (33, 530), but the peptide has considerable vasodilator activity on the total perfused coronary bed (35, 611, 662). Dimethothiazine antagonizes some of these vascular and myotropic effects of bradykinin, but also those of histamine and serotonin (436). Bradykinin (5×10^{-8} to 10^{-6} w/v) relaxes strips of small (0.5 mm diameter) rabbit mesenteric arteries contracted by norepinephrine (854).

Pulmonary vasoconstrictor effects of kinins have been reported in rabbits (406, 552), guinea pigs (515, 645), and, perhaps on the venous side, dogs (451). The pulmonary hemodynamic effects of bradykinin in man are thought to be secondary to the action of bradykinin on the systemic circulation (224). The inhibition of the vasoconstrictor effects of bradykinin by various anti-inflammatory agents is nonspecific (863). Pulmonary artery strips of chickens are not contracted by bradykinin or eledoisin (853), and incidentally, while bird plasma contains kininogens, it is lacking in Hageman factor, which in mammals would initiate kinin formation (276). The effect of the higher molecular weight (6000 to 6500) kinins of birds, ornitho-kinins (953, 954), on isolated avian vessels remains to be investigated. In general, as in the case of other drugs, vascular sensitivity to kinins and related peptides varies among different species and vascular beds.

Profound peripheral vasodilation is perhaps the most characteristic generalized response of mammalian cutaneous, muscular, and splanchnic beds, to bradykinin, kallidin, eledoisin, and physalaemin (38, 88, 89, 112, 189, 271, 277, 294, 315, 453, 511, 523, 559, 661, 662, 692, 701). The vasodilator action of these peptides is primarily direct and also occurs in denervated vascular beds (315), after sympathetic blockade or atropine (566, 605, 769), *beta*-adrenergic blocking agents (189,

843, 844), and reserpinization (638). The hypotensive action of caerulein is reduced by atropine (97). The cellular mechanism of the direct vasodilator action is not known. Whether these peptides act solely by inhibiting spike-electrogenesis or also by pharmacomechanical inhibition (a relaxant effect not due to hyperpolarization or a decrease in the frequency of action potentials, [section XXII; Part I, section VI H]) could be readily determined in vascular beds perfused with depolarizing concentrations of potassium. It should be noted that several of the available kinin preparations contain chlorobutanol as the preservative (274, 853, see also section II C) and the diluent itself may cause vasodilation at high infusion rates (511).

The physiologic role of plasma kinins in mediating functional vasodilation has not been fully clarified. Evidence has been marshalled both for (418, 419) and against (70, 797, 843, 844) the idea that kinins mediate functional vasodilation in some exocrine glands. Vasodilation has been observed in glands depleted of kallikrein (70). Carboxypeptidase B, which abolishes the vasodilation produced by exogenous bradykinin, does not abolish the vasodilation elicited by chorda tympani stimulation (843). It is generally agreed that kinins do not play a significant role in functional vasodilation of skeletal muscle (418, 942).

In addition to the vasoconstrictor effects of bradykinin *in vitro* discussed earlier, both venodilator and venoconstrictor effects may be observed *in vivo* in different regions of the venous circulation (378, 523, 667, 774, 945). The suggestion that kinins produce selective constriction of arteriovenous shunts in man (236) has been questioned (701). The very interesting observations of Majno *et al.* (597, 597a), are indicative of active contraction of venular endothelium by bradykinin (see also section VIII). Some of the cutaneous venoconstrictor responses to kinins in men are blocked by guanethidine and are, like those of angiotensin (section I D), neurally mediated (605).

B. Interaction with the adrenergic system and serotonin

Bradykinin, like angiotensin, releases adrenal catecholamines in cats (290). The avian hypertensive response to kinins and to physalaemin is indirectly mediated through the release of catecholamines (277, 278, 872). The same mechanism appears to produce the pressor component of the diphasic response to bradykinin in rats (638), and it has been suggested that in cats a centrally mediated sympathetic mechanism is also participating (544). Neurogenic venoconstriction by bradykinin was discussed in the preceding section.

Zweifach (995) found that bradykinin potentiated the venoconstriction of the rat mesenteric microcirculation by serotonin: after preconstriction of the microcirculatory bed with serotonin, the application of a normally vasodilator dose of bradykinin evoked intensive venular constriction (945, 995). The reason why eledoisin does not interact with serotonin (945) remains to be determined. The potentiation of the hypotensive effects of bradykinin by a component of *Bothrops jararaca* venom is thought to be caused by inhibition of kinin catabolism (25). Sulfhydryl compounds potentiate, *via* an unknown mechanism, some effects of kinins on smooth muscle (46, 274, 275).

C. Structure-activity relationship

Many kinin analogues have been synthetized and the attempts at establishing structure-activity relationships have been reviewed recently (274, 812, 866). As in the case of neurohypophyseal peptides, kinin activity may also be influenced by susceptibility to degrading enzymes (866), and the observable effect of molecular changes is not necessarily due to changes in complementarity between peptides and receptor. For example, bradykinin is inactivated much faster by guinea pig serum than is eledoisin (872).

It has been pointed out by Stewart and Woolley (867) that alterations of the carboxyl end of biologically active peptides result in far greater loss of activity than alterations of the amino end. This interesting observation may require some modification (866) with the discovery of phyllokinin (26), a highly active undecapeptide that in effect is bradykinin elongated at the carboxyl end.

Substitution of lysine for arginine in the 9-position of bradykinin leads to decrease in activity (275) reminiscent of the effect of this substitution in vasopressin. Substitution of D-arginine in either the 1 or the 9 position produced what may be total loss of activity (683). Detailed information about the effects of substitution of different amino acids may be found in several publications (274, 776, 812, 866, 867). The biological effect of a given structural change depends on the substituent as well as the substituted amino acid (583, 812) and is rarely predictable (316).

Extension of the amino end of bradykinin yields some highly active peptides (811), but these peptides, and possibly also phyllokinin (866), may function as kininogens. Shortening of the amino end of eledoisin yields active hexapeptides (316).

IV. PROSTAGLANDINS

Prostaglandins were discovered in seminal fluid by Goldblatt and von Euler and characterized largerly through the efforts of Bergström and his associates at the Karolinska Institute. Major reviews of the subject have been published recently by Bergström *et al.* (92) and by Horton (438).

Prostaglandins are 20-carbon, unsaturated fatty (prostenoic) acids, the PGF series differing from the PGE series only in having a hydroxyl, rather than a ketone, group in position 9 (92, 790). The primary prostaglandins are differentiated by subscripts indicating the number of double bonds within the fatty acid chain (92, 790).

Arachidonic acid is a biological precursor of prostaglandins (92, 790) and is also reported to have hypotensive and visceral smooth muscle stimulating activity (454, 455). It has been suggested (415, 929), however, that peroxide formation, the biosynthetic pathway of prostaglandins, may account for the apparent activity of arachidonic acid.

PGE_1 is a potent vasodilator of the systemic and pulmonary circulation in practically every species examined, and this effect is not abolished by *beta*-adrenergic blocking agents (92, 93, 218a, 407, 425, 664, 668, 946). The PGA prostaglandins are also potent hypotensive agents (943). The hypotensive effects

and the stimulation of visceral smooth muscle vary to some extent, according to the particular prostaglandin and the animal species employed (92).

The circulatory responses to $PGF_{1\alpha}$ and $PGF_{2\alpha}$ are complicated by species-specific variations, reviewed in detail by Bergström *et al.* (92). Some of these differences may be related to indirect, neurally mediated pressor effects of prostaglandins. The venoconstrictor component of the response to $PGF_{2\alpha}$ in rats is abolished by acute lumbar sympathectomy and reestablished by stimulation of the cut sympathetic, although the pressor effect of $PGF_{2\alpha}$ in rats is not blocked by pentolinium or reserpinization (258). $PGF_{2\alpha}$ also produces pulmonary vasoconstriction in cats (32) and in dogs (258, 452) and the latter effect is partially inhibited by phenoxybenzamine (258). It should be noted that although PGE_1 does not measurably release catecholamines in cats (437) it does release adrenal medullary catecholamines in dogs, which cause an indirect, pressor response (493).

Rabbit aortic strips are contracted by PGE_1 and by $PGF_{1\alpha}$ (503, 868), and in this preparation the contractile threshold is lower (10^{-10} *vs.* 10^{-9} w/v) for PGE_1 than for $PGF_{1\alpha}$ (868). Subthreshold concentrations of PGE_1 increase the (submaximal) contractile effects of angiotensin and serotonin on rabbit aortic strips (503).

Strips of small (200 to 1000 μ) canine mesenteric, renal, and muscular arteries exhibit a biphasic dose-response curve to prostaglandins (868). Low concentrations of PGE_1 or $PGF_{1\alpha}$ relax and higher concentrations contract these strips, with reversal of action at a prostaglandin concentration of about 10^{-6}. The relaxant effects are not abolished by a *beta*-adrenergic blocking agent (MJ 1999), nor the contractile effect by phentolamine. Skeletal muscle arteries and veins are contracted by $PGF_{2\alpha}$ in a concentration (10^{-6} w/v) that produces relaxation with PGE_1 (372), but the effect of lower concentrations of $PGF_{2\alpha}$ has not been tested. Intra-arterial injection of $PGF_{2\alpha}$ causes vasodilation in cats (32) and vasoconstriction (664) or a diphasic effect (372) in dogs. The observations of Strong and Bohr (868) clearly indicate that without comparisons over the entire dose-response range in several species it is difficult to categorize qualitative differences between the vascular effects of the PGE and the PGF series.

It has been suggested that hydroxy-fatty acids may function as Ca^{++}-carriers (868, 929), but an attempt to demonstrate facilitation of Ca^{++}-transport from aqueous into lipid phase by PGE_1 was unsuccessful (726).

Interest in prostaglandins has been fostered by their occurrence in a number of tissues, particularly lung and renal medulla (92, 478, 553). Human umbilical vessels contain at least four prostaglandins, three (PGE_2, $PGF_{1\alpha}$, and $PGF_{2\alpha}$) of which contract and one (PGE_1) that relaxes the umbilical artery (487). Because the prostaglandins in this study were not tested over an entire dose-response curve, the possibility of a dual, concentration-dependent effect similar to that observed with somatic vessels (868) cannot be excluded. Since prostaglandins can be released from various tissues by electrical stimuli (for review see 92), one may also speculate whether the delayed contractile component of electrically stimulated umbilical vessels (I 551) is mediated by prostaglandins.

V. VASOACTIVE SUBSTANCES IN TISSUES AND BODY FLUIDS

The chemically identified vasoactive substances of the vessel wall, such as catecholamines (section IX) and prostaglandins (section IV), have been discussed elsewhere. In this section we shall be concerned primarily with vasoactive substances of uncertain chemical identity obtained from biological materials. Some caution must be exercised in interpreting these studies and the physiological significance of the substances described. Vasoactivity of tissue or plasma extracts can be enhanced by preparatory processes and also may be due to a combination of several known substances, rather than to a single, previously unknown compound. A large proportion of the vasoconstrictor material found in rabbit plasma is histamine and serotonin (972; but *cf.* 40, 41), the former potentiating the latter's action on rabbit aortic strips (974). Angiotensin has been identified with reasonable certainty in stable human plasma solutions (914).

In spite of the most stringent precautions, vasoactive substances may be produced as the result of the extraction process. For example, Schachter (796) has shown that simple dilution of serum will lead to the production of kinins. Prolonged incubation of plasma at normal pH at 37°C may also lead to formation of vasoactive substances (759). Khairallah and Page (500) observed formation of a probably lipid vasopressor substance during extraction of human blood. Vascular activity may also be due to contaminants, such as norepinephrine in partially purified gangliosides (757), or the still unidentified, histamine-like hypotensive contaminant of thyrocalcitonin (860). The artifactual production of an isoproterenol-like substance (section IX J) during acid extraction of epinephrine for chromatography has been observed (756).

Release of vasoactive materials within the blood vessel wall, or interaction with these substances, may be responsible for some local indirect actions (I 200) of drugs. In addition to the renin-like material (234, and section I A), a hypotensive peptide that contracts visceral smooth muscle has also been isolated (547) from blood vessels. Placental extracts also contain renin-like (423, 985) and kinin-like (837, 838) substances.

In carefully controlled cross-perfusion experiments in which denervated rabbit ear artery was the biological indicator (40, 41) struggling and hemorrhage were associated with the appearance of circulating vasoconstrictor substances, probably epinephrine. Stringent precautions were necessary to prevent the formation of serotonin. The dilated state of the denervated ear circulation in animals at rest (40) seems to preclude the presence of high concentrations of circulating unbound vasoconstrictors in normal blood.

Clotting of blood may release, in addition to serotonin (41), vasoactive peptides. The production of kinins by Hageman factor has been mentioned (section III). Enzymatic hydrolysis of fibrinogen by thrombin yields fibrinopeptides, some of which are vasoactive. Bovine fibrinopeptide B and human fibrinopeptide A are pulmonary vasoconstrictors in rabbits, dogs, and lambs (68). Bovine fibrinopeptide B also constricts rabbit carotid artery strips (351) and produces a prolonged, oscillatory pressor response in rats (197). The rapid rate of release of human fibrinopeptide A (888) is at least compatible with the idea (68) that this

substance may mediate some of the hemodynamic effects of pulmonary embolism. Thrombin itself, interacting in a yet undefined manner with the cellular elements in blood, has a vasodilator effect (693).

The vasoconstrictor activity of kinekard, an inotropic human plasma factor studied by Nayler *et al.* (249, 678, 679), is blocked by phenoxybenzamine. This compound, as well as another vasoactive factor (or factors) in dog plasma (123, 124, 907) and in human plasma (433) have not been characterized chemically. L-Arginine increases the contractile frequency of bat veins, but is ineffective on rat portal veins (129).

The vasoconstrictor extracted from colostrum was identified as a mixture of glucose and galactose esters of uridine diphosphate (955). Kininogen is also present in bovine colostrum (652). It has been reported recently that a feline salivary protein or glycoprotein selectively constricts intestinal blood vessels (651). Further vasoactive substances of uncertain character have been reported to occur in eel serum (465), cerebrospinal fluid (740), and coronary sinus blood of severely stressed hearts (879). It should also be mentioned that albumin, although not vasoactive, in relatively low concentrations potentiates the effect of norepinephrine (see also section IX H) on rabbit aortic strips (970).

VI. CHOLINERGIC AGENTS AND BLOCKERS AND CHOLINESTERASE INHIBITORS

A. Direct and indirect cholinergic vasoconstriction, cholinesterase inhibitors

Vasoconstriction of certain types of isolated vascular preparation, for example rabbit aortic strips, by cholinergic agents is due to a direct effect of the drug on vascular smooth muscle (I 200). It has been suggested that in other instances, the vasoconstrictor action of acetylcholine may be mediated through the release of catecholamines. In the material reviewed by us (*e.g.*, 105, 252, 313) we found no evidence for an *obligatory* cholinergic step in vascular adrenergic transmission (for reviews see 293, 528). The inhibition of acetylcholine release by catecholamines (928) in guinea pig ileum indicates the possibility of a presynaptic inhibitory adrenergic-cholinergic interaction. The latter type of mechanism may contribute to the inhibition of cholinergic vasodilation by vasoconstrictor nerve activity (127).

The contribution of an adrenergic component to cholinergic vasoconstriction varies among different species. In dogs, the renal vasoconstrictor effect of acetylcholine can be eliminated with reserpine and adrenergic blocking agents (198, 441, 727) and the general pressor response to systemic acetylcholine has been ascribed to stimulation of the adrenal medulla and sympathetic ganglia (213). The venoconstrictor (accessory cephalic vein) action of acetylcholine is probably due to both a direct and an indirect action (753). Caution must be exercised in interpreting data obtained with blocking agents (*e.g.*, Dibenamine) that may affect muscarinic as well as *alpha*-adrenergic receptors (328) and seem to have a depressant effect on Ca^{++}-permeability that varies among different types of blood vessel (section XIV). Atropine cannot only block, but also reverse the vasoconstrictor effect of acetylcholine in pig coronary artery strips (881).

Acetylcholine also decreases blood flow through the ductus arteriosus, but the

mechanism responsible for this observation *in vivo* is uncertain (846). The electrical excitatory effects of acetylcholine have been discussed in Part I (section VI F) of this review (see also this section B).

The cholinesterase inhibitors diisopropyl fluorophosphate and physostigmine contract rabbit aortic strips. This effect is elicited only by very high concentrations of the drugs and is probably unrelated to cholinesterase inhibition (266). The major portion of the rabbit aortic enzyme is a pseudocholinesterase (266, *cf.* 770). Variations in the distribution of vascular cholinesterase have been discussed previously (Part I, section II C). The ultrastructural distribution of cholinesterase is discussed in the following section.

Certain lipid-soluble quaternary ammonium compounds (noracetylcholine 12, norcholine 12) inhibit the contractile effects of several agonists in the following order: acetylcholine > serotonin, histamine > KCl, norepinephrine (266).

B. Vasodilator (and diphasic) effects of cholinergic agents

The predominant peripheral effect of cholinergic stimuli is vasodilation (I 15, I 410, 608, 634, 909). Circulatory control mechanisms mediated by cholinergic vasodilator fibers, operating primarily on the terminal vasculature of skeletal muscle, have been reviewed in detail by others (I 410, 909). Atropine-sensitive, cholinergic fibers have been demonstrated in several species, but Uvnäs (909) has recently questioned their existence in primates. Duling and Berne (261a) observed a propagated vasodilator response of the hamster microcirculation to acetylcholine and suggested that this effect was neurally mediated.

The sensitivity of the guinea pig uterine artery to its cholinergic vasodilator innervation increases during pregnancy, and is accompanied by a spread of cholinesterase activity over the smooth muscle plasma membrane facing cholinergic endings (75). In the arteries of nonpregnant animals cholinesterase-staining appears limited to the pinocytotic vesicles (75).

Several large blood vessels are constricted by acetylcholine *in vitro* (I 200, 402) but, in some instaces at least, the absence of a demonstrable vasodilator action may be due to an absence of resting tone. Preconstricted rabbit aortic chains (468) and strips (854) are relaxed by lower concentrations of acetylcholine (10^{-9} to 10^{-7} w/v) than those producing vasoconstriction, but in canine saphenous veins only the vasoconstrictor effect is demonstrable (194). The concentration of acetylcholine and the perfusion pressure employed, as well as seasonal variations (in Japanese toads) are some of the other variables that determine whether vasoconstriction, dilation, or a diphasic response is elicited by a cholinergic agent (401). The umbilical vasoconstrictor and vasodilator effects of acetylcholine are blocked by atropine (360). Of some interest to anesthesiologists is the reported vasodilator effect of succinyl choline (930).

The cellular mechanisms of acetylcholine action have not been established in vascular smooth muscle. We have adopted a general model (section XXII) according to which excitatory drugs act by a common mechanism of gradedly increasing the permeability of the membrane to Ca^{++} and other ions. There is massive evidence showing the effect of acetylcholine on end-plate permeability

(I 156, 491), and in intestinal smooth muscle the association of cholinergic excitation with an increase in monovalent-ion permeability has also been clearly demonstrated (130, 154, 262, I 295). Burgen and Spero (154) found that Dibenamine shifts the carbachol dose-contractile-response curve of intestinal smooth muscle before depressing the maximal response, whereas it produces an immediate, absolute depression of the cholinergically increased permeability to rubidium. It is interesting to compare these results to those of Furchgott and Bursztyn (328) who, also by using Dibenamine as the cholinergic blocking agent, found that a 100% contractile response is elicited by activation of only 6.2% of the available receptors. Both sets of observations (154, 328) suggest that measurement of monovalent-ion permeabilities gives a more direct indication of drug-receptor combination than the contractile response. The existence of "spare receptors" as determined by the contractile response may merely indicate that the actomyosin-troponin system saturates with only a 6 to 10% increase in Ca^{++} permeability. It would be obviously desirable to relate Ca^{++} flux, rather than only monovalent-ion fluxes, to contraction.

The mechanism of vasodilator action of acetylcholine is not known. In intestinal smooth muscle (130, 154, 262, I 295) cholinergic agents increase K^+-permeability, and in some invertebrate tissues (457, 497) the Cl-permeability. Under appropriate conditions of E_K and E_{Cl} either of these effects could lead to the hyperpolarization elicited by acetylcholine in certain types of vascular smooth muscle (I 197, I 199). It was tempting to suggest that vasodilation by acetylcholine may be mediated through hyperpolarization (852). Recent experiments (854), however, showed a relaxant effect of acetylcholine (10^{-8} to 10^{-7} w/v) on depolarized rabbit aortic strips. Polarized guinea pig uterine arteries are also relaxed by acetylcholine in the absence of detectable hyperpolarization (76). Acetylcholine, like *beta*-adrenergic amines (sections IX I and XXII) can apparently relax vascular smooth muscle by both electromechanical and pharmacomechanical mechanisms.

VII. SEROTONIN

Serotonin (5-hydroxytryptamine, 5-HT) was reviewed by Page (696), who more recently published a monograph on this subject (697). Serotonin antagonists were reviewed by Gyermek (380), and an extensive survey of the effects of serotonin on the regional vascular beds of several species has been compiled by Garattini and Valzelli (332).

The dual, excitatory and inhibitory action of serotonin, and the existence of specific excitatory serotonin receptors were recognized in the earliest studies (I 200). More recent work reemphasized the vasoconstrictor effects of serotonin on the larger canine systemic arteries (1, 382, I 560, 625) and veins (194, 856, 859) and on pulmonary vessels of several mammals (50, 151, 312, 711, I 555, I 557) and birds (853). The microcirculatory constrictor effect of serotonin, in rats, is predominantly on the venules (I 15, 945, 948). Monkey cerebral arteries (488) and rabbit aortic strips (I 200, 969) are also constricted by serotonin. Maengwyn-Davies *et al.* (595) observed the progressive development of tachyphylaxis to

serotonin by guinea pig aortic strips. The human umbilical vessels, relatively insensitive to norepinephrine, are highly sensitive to the excitatory effects of serotonin (45, I 136, I 559).

The excitatory effects of serotonin on the membrane potential of vascular smooth muscle are similar to those of other agonists: depolarization and, in spike-generating vascular smooth muscle, an increased spike-frequency (Part I, section VI, I 557, 859). The quantitative differences between the depolarization (and contraction) produced by serotonin and by other agents will be discussed with the general mechanisms of drug action (section XXII).

Serotonin antagonists, structurally related to lysergic acid, inhibit the vasoconstrictor action of serotonin (I 15, 45, 151, 312, I 200, 380, 488, 933, 945) and even reverse serotonin-induced cerebral vasoconstriction (488). High concentrations of antiserotonin compounds may produce vasoconstriction (45, 194, 969). *p*-Tosylarginine methylester inhibits the contractions of rabbit aortic strips elicited by serotonin, and also those due to catecholamines and histamine (947).

Some *alpha*-adrenergic blocking agents, including phentolamine (194), also antagonize the vasoconstrictor effect of serotonin (45, I 200, 312, 380, 945, 969). The fact that several types of vascular smooth muscle (*e.g.*, umbilical vessels and small pulmonary arteries) that are insensitive to norepinephrine, are highly sensitive to serotonin, however, indicates the existence of distinct *alpha*-adrenergic and serotonin receptors.

The claim that specific serotonin receptors appeared only recently in vertebrate phylogenesis (747), in our opinion, requires more support than has been presented. The inability of a fixed dose of methysergide, present over an unspecified exposure time, to block the branchial vasoconstrictor action of serotonin in the hagfish need not imply the absence of a specific serotonin receptor. The degree of blockade with lysergic acid derivatives varies with duration of exposure and even among mammalian species (380). Furthermore, since LSD-sensitive serotonin receptors are already present in molluscs (380) it would seem unnecessary to assume their more recent origin among vertebrates.

The primary vasoconstrictor effect of serotonin is due to a direct action on vascular smooth muscle, as indicated by its persistence after reserpinization (151, 312, 696) or denervation (951). It is also observed in the inherently nerve-free umbilical preparations. Laverty (549), however, found a decreased response to serotonin in rat hind-limb preparations after reserpine treatment; this raises the possibility of some indirect action of serotonin due to catecholamine release.

Cocaine sensitizes to the pressor action of serotonin (696) and also potentiates its effect on the canine saphenous vein (194) and on the rat fundus strip preparation (689, 956). Discussion of mechanisms of serotonin release by tyramine, reserpine, and other agents, and the possibility of its action as a "false transmitter" is beyond the scope of this review (155, 696).

A vasodilator action of serotonin is observed in certain vascular beds, particularly in small arteries of dogs. Vasodilator effects have been demonstrated in canine limb (382, 625, 951), mesenteric (625), and coronary circulation (398). In the human forearm cutaneous vasoconstriction and muscular vasodilation are elicited by serotonin (933).

The mechanism of the vasodilator action of serotonin remains to be fully clarified. In the dog, sympathetic stimulation or the infusion of epinephrine enhance the vasodilator action of serotonin and the latter effect can be diminished by dichlorisoproterenol (625). High concentrations (3 to 5 $\times$ 10^{-6} w/v) of propranolol inhibit the vasodilator effects of serotonin on branchial vessels of hagfish (747). On the other hand in the human forearm the vasodilator effect of serotonin is not blocked by propranolol and can be elicited in sympathectomized subjects (933). In the canine hind-limb preparation antihistamines, hypoxia (951), and sympathectomy (625, 951) each inhibit the vasodilator response to serotonin, whereas atropine is ineffective (625). In contrast to the above observations with dogs, serotonin has a purely vasoconstrictor action on the rat hind limb (312) although this effect is still enhanced by nerve section (549).

Nonspecific sensitization of the rabbit ear artery to several vasoconstrictors by serotonin has been described by De La Lande *et al.* (225, 227), but is no longer demonstrable after depolarization of the artery. Thyroxine pretreatment sensitizes the rat hindquarter to the vasoconstrictor action of serotonin (705), but the effect is probably not specific (section IX G).

VIII. HISTAMINE AND ANTIHISTAMINES

The dual, vasodilator and vasoconstrictor, action of histamine (I 200) has been further documented in more recent studies (244). The contractile effects are readily demonstrable in large veins and arteries (I 200, 344, 869) as are the electrical excitatory effects of histamine (Part I, section VI F). Histamine, like other agonists, can contract depolarized blood vessels (I 557) but also relaxes depolarized smooth muscle (852), and its vasodilator effect persists in microcirculatory vessels perfused with high K^+-solutions *in situ* (15).

Ultrastructural studies of Majno *et al.* (597a) revealed deformations of rat vascular endothelial nuclei, suggestive of *endothelial* contraction, under the influence of histamine. They observed similar endothelial effects of bradykinin and serotonin, and suggested that these agents stimulate active endothelial contraction leading to the pulling apart of venular endothelium with the consequent increase in venular permeability (597, 597a). Endothelial gap formation due to the hydrostatic effect of constriction of larger veins under the influence of histamine, bradykinin or serotonin has been previously considered to be the mechanism whereby these agents increase vascular permeability (774), but a hydrostatic effect does not seem to be compatible with the changes in endothelial ultrastructure (597a).

The possibility of a histaminergic vasodilating mechanism operating *in vivo* (147, 803) has been reviewed by others (24, I 410). It has been pointed out by Altura and Zweifach (18, 21–24) that certain antihistamines have direct vasoconstrictor effects and also sensitize the rat microvasculature to catecholamines. These authors point out that the vasoconstrictor action of topically applied antihistamines is not necessarily due to removal of histaminergic vasodilator mechanisms and should not be taken as conclusive evidence for the existence of the latter. Antihistamines also produce pulmonary vasoconstriction in rats (405).

A cocaine-like effect of some antihistamines (*e.g.*, diphenhydramine, chlor-

pheniramine) on catecholamine-uptake mechanisms has been demonstrated and is thought to account for the potentiation of the pressor effect of norepinephrine by these agents (458, 472).

A catecholamine-releasing action of histamine has been suggested to be present in certain nonvascular smooth muscle preparations (281, 592). The uptake, metabolism, and chemistry of histamine have been reviewed by Green (371). The volume edited by Rocha e Silva (761) covers the general pharmacology of histamine.

IX. ADRENERGIC PHARMACOLOGY OF VASCULAR SMOOTH MUSCLE

The formidable efforts devoted by pharmacologists to adrenergic agents foredoom to failure any attempt at a comprehensive review of this field. To omit this section from a review of vascular smooth muscle would be tantamount to ignoring what certainly has been the quantitatively major area of experimentation with isolated vascular preparations. The section on adrenergic pharmacology is, therefore, presented as a compromise between the impossible and the unavoidable.

The general pharmacology of adrenergic agents has been the subject of a relatively recent symposium (10). The major topic of recent interest to vascular pharmacology has been the action of vasoactive agents on the neuronal uptake, storage, and release of adrenergic transmitters and false transmitters. Specific reviews of these subjects include those by Iversen (461), Muscholl (658), Trendelenburg (900), and Zaimis (983).

A. Sympathomimetic amines: tyramine, ephedrine, amphetamine

From studies of the nictitating membrane, Trendelenburg *et al.* (901) pointed out that there is a gradual transition among agents having greater or lesser degrees of, respectively, direct and indirect activity, rather than a sharp and absolute dichotomy. This conclusion is also valid in the case of vascular smooth muscle.

Burn and Rand (157) produced convincing evidence in studies of perfused dog hind leg, rabbit ear, and aortic strips, that tyramine and related agents stimulate blood vessels in a large measure through the release of catecholamines from local stores. A marked diminution of the vasoconstrictor response to tyramine in catecholamine-depleted preparations, restoration of this response with exogenous norepinephrine, and inhibition of the effects of tyramine in normal preparations by cocaine (see below) were the major arguments favoring a mechanism of action of tyramine, amphetamine, and ephedrine *via* catecholamine release. The release of catecholamines by tyramine and other "indirectly-acting" amines has been directly demonstrated in several tissues (330, 658) including blood vessels (577, 911). There is also a large body of unanimous evidence that reserpinization, sympathectomy, and cocaine inhibit the vasoconstrictor effects of catecholamine-releasing agents (sympathomimetic amines and others) in perfused vascular beds (157, 165, 230, 331, 589, 675, 724, 882). The indirect effect of tyramine is not considered to be mediated by action potentials of adrenergic nerves as it is not blocked by tetrodotoxin (73, 880).

The effect of any drug acting on the neuronal uptake and release of catecholamines will be influenced by the access of the drug to adrenergic nerve endings and by the density of adrenergic innervation in a given blood vessel. In view of the predominantly adventitial and adventitio-medial distribution of adrenergic nerves in many, though not all, blood vessels (Part I, section II D; 103, 615) it may be anticipated that the indirect effect of tyramine would be more prominent with the amine applied to the adventitia. By ingenious use of the rabbit ear artery De La Lande and Waterson (230) demonstrated the greater effect of extraluminal than of intraluminal tyramine. They also found that the difference in effect of the two routes of application was abolished by denervation and by cocaine, and they suggested that the indirect phase of the biphasic response to intraluminal tyramine (282) was due to extraluminal escape of the amine.

Depletion of endogenous catecholamine stores is considered to be the major mechanism responsible for tachyphylaxis to the indirect action of tyramine and related agents (331, 593, 594). Anatomical removal of the adrenergic plexus of the rabbit aorta also reduces its sensitivity to tyramine (106, 615). The reduction in the norepinephrine content of cold-stored rabbit aorta is associated with more pronounced tachyphylaxis to tyramine (912). In view of the variable catecholamine content of different blood vessels (279, 340, 619, 739) it may be anticipated that indirect adrenergic responses would be subject to regional variations.

Inorganic ions may facilitate or inhibit adrenergic release and uptake mechanisms. The uptake mechanism appears to require sodium (119, 346, 509), and the amount of norepinephrine released by sympathetic nerve stimulation or by depolarization with potassium increases as a function of extracellular calcium concentration (133, 283, 509). The release of norepinephrine (from cat iris) by tyramine requires both Na and K^+, and is abolished at 4°C (893). These local effects of ions and temperature on catecholamine storage mechanisms should be considered in designing and evaluating experiments dealing with ionic modifications of the responses of vascular smooth muscle to catecholamines.

A direct effect of tyramine on vascular smooth muscle, in addition to the indirect effect, is now supported by unequivocal evidence. The probability of a direct effect was suggested by the residual response of reserpinized vascular smooth muscle to high concentrations of tyramine (331, 537, 882) although the persistence of a reserpine-fast but tyramine-sensitive catecholamine site in these preparations could not be ruled out. Conclusive evidence for a direct action of tyramine and mephentermine was obtained with the demonstration of the contractile response of nerve-free umbilical vessels to these amines (I 559, 882). The general significance of the results obtained with umbilical vascular smooth muscle was confirmed with more common preparations, the denervated rabbit aortic strip (106) and the ear artery (230).

There is some question whether the direct effect of tyramine and other "indirectly-acting" amines is mediated through *alpha*-adrenergic or through tryptamine receptors. The sensitivity of human umbilical vessels to both tyramine and norepinephrine is low, although the same preparations are quite sensitive to serotonin (I 559, 882). Tyramine (537) and amphetamine (65) protect the *alpha*-adrenergic receptors from blockade with Dibenamine, whereas an active serotonin

blocking agent is relatively ineffective in antagonizing amphetamine (518). The above findings suggest an action of tyramine mediated by *alpha*-adrenergic receptors. On the other hand bovine coronary arteries are relaxed by norepinephrine but contracted by high concentrations of tyramine (34). It is possible that direct effects of "indirectly-acting" amines may be mediated by more than one type of receptor. The structural and quantitative aspects of relative indirect and direct activity of a large series of amines described in the literature (*e.g.*, 165, 394, 518, 502, 546, 658, 738, 901) are outside the scope of this review. *Alpha*-methyl-norepinephrine is of some special interest among these amines, since it is a metabolite of the antihypertensive agent α-methyl-dopa (529). *Alpha*-methyl-norepinephrine is a potent directly acting amine, and the antihypertensive action of its precursor, α-methyl-dopa, remains unexplained (529, 643, 724).

The maximal contractile effect of "indirectly acting" sympathomimetic amines is low, and may in some cases be less than 20 % of the maximal response to norepinephrine (65, 331, 394, 518, 546, 738). It seems probable that these inequalities of maximal contraction, which includes the component due to the direct effect of these drugs on smooth muscle (see above), are due primarily to differences in the intrinsic activity of these compounds or, as we would suspect, their unequal efficiency of increasing the permeability of the membrane to calcium (section XXII; Part I, section VI H). However, because *beta*-blockers were not used in the studies cited above, *beta*-adrenergic autoinhibition (section IX J) may also have contributed to the depression of the maximal contractile response to certain sympathomimetic amines. The relatively low maximal contractile effect of isoproterenol on rabbit aortic strips (618) is most probably due to this type of autoinhibition. In comparing the effects of norepinephrine with those of isoproterenol for estimating "spare receptors" the authors did not consider the possibility of autoinhibition of isoproterenol. For this reason, we are not prepared to accept the conclusion (618) that there are no spare *alpha*-receptors in the rabbit aorta.

A direct vasodilator effect of tyramine, not blocked by cocaine, was already noted by Burn and Rand (157). Ephedrine also has a direct vasodilator effect, which can be blocked by propranolol (317).

Finally, it should be noted that an indirect vasopressor action, mediated through the release of endogenous catecholamines, is not limited to sympathomimetic amines. Such an indirect effect can also be elicited by other agents affecting uptake and storage mechanisms, such as cocaine (596), guanethidine (2, 334, 614, 617), and bretylium (506).

B. Cocaine, desipramine, and phencyclidine

The "cocaine paradox," sensitization to the effects of norepinephrine but desensitization to those of tyramine and other "indirectly acting" amines (157), has been largely resolved by recognition of the effects of cocaine on catecholamine uptake and storage mechanisms. It is generally agreed that cocaine inhibits the indirect action of tyramine by preventing its uptake into, and the consequent release of norepinephrine from, adrenergic neurones (331, 658).

The mechanism of potentiation of catecholamines by cocaine is thought by many to be due to inhibition of amine uptake mechanisms (331, 461, 658) although the possibility of postsynaptic potentiation has received increasing support. The major argument favoring presynaptic potentiation is the unequivocal evidence that cocaine inhibits catecholamine uptake across the adrenergic neurone membrane. Also, De La Lande *et al.* (226) found that the response of the central artery of the rabbit ear to a fixed concentration of norepinephrine applied extraluminally was increased several-fold by cocaine, while the effect of intraluminally applied norepinephrine was only slightly augmented by it. They also found that, although intraluminal and extraluminal cocaine both tended to increase the effect of extraluminal norepinephrine, this action was less marked with intraluminal than with extraluminal cocaine and the former, in some experiments, even depressed the response to intraluminal norepinephrine. They concluded that cocaine enhanced the constrictor action of norepinephrine by inhibiting the uptake of the catecholamine into neuronal sites at the adventitial border. Bevan and Verity (106) found that cocaine did not potentiate the action of norepinephrine on acutely denervated aortic strips (median effective dose) although this effect was observed with controls. They suggested that this finding indicates some potentiation through inhibition of uptake. Haeusler *et al.* (383a) found that, in rat mesenteric arteries, cocaine and surgical denervation produced the same degree of potentiation to norepinephrine suggestive of a common presynaptic mechanism of supersensitivity.

A more direct potentiation of norepinephrine by cocaine, perhaps at the vascular smooth muscle membranes, has been suggested by Maxwell *et al.* (614–616). This argument has received some further support by the demonstration that impairment of the catecholamine-retaining activity of rabbit aortic strips through cold storage did not abolish the potentiating effect of cocaine (483, 923). In the latter studies the possibility remained that only intraneuronal binding, but not neuronal uptake and intraneuronal inactivation, of norepinephrine was abolished by cold storage, and cocaine could still exert its effect through the uptake mechanism. The possibility of a potentiating action of cocaine that is independent of its effect on uptake is also suggested by its ability to increase the *maximal* response of the denervated aortic strip (106) and of the vas deferens partially blocked by phenoxybenzamine (669) to norepinephrine. Further evidence of "facilitating" action of cocaine on smooth muscle, independent of an effect on neuronal stores, is the demonstration (489) that cocaine increases the maximal response of the vas deferens to acetylcholine and angiotensin and similarly potentiates the contractures evoked by Ca^{++} and depolarizing concentrations of K^{+}. The potentiation of methoxamine by cocaine also indicates an interaction unrelated to uptake mechanisms (483). The published data do not permit quantitative assessment of how much of the observed potentiation is due, respectively, to inhibition of uptake or to postsynaptic potentiation. In any event the major mechanism of potentiation may vary in different vessels and under different experimental conditions. Miller and Lewis (639) suggested that cocaine may increase the maximal response of denervated aortic strips to

norepinephrine by eliminating autoinhibition. Previous attempts at demonstrating a *beta*-blocking action of cocaine against isoproterenol as the agonist were unsuccessful (614), but neither did cocaine in these experiments increase the maximal response to norepinephrine. A reinvestigation of the effects of cocaine on *beta*-adrenergic responses of vascular strips would be of interest, although it is clear that potentiation of agonists other than adrenergic agents (489) cannot be due to a *beta*-adrenergic mechanism.

It has been suggested that desipramine (441) and phencyclidine (687) potentiate the vasoconstrictor action of norepinephrine through a cocaine-like mechanism. The onset of potentiation is slower with desipramine than with cocaine (441). Desipramine also has a direct, depressant effect on vascular smooth muscle (816, 829). Cocaine-like effects on vascular catecholamine uptake can also be elicited by tyramine (331) and by guanethidine and methylphenidate (612, 616). Methylphenidate (10^{-6} M) potentiates the response of rabbit aortic strips to norepinephrine, whereas higher concentrations depress the responses to histamine, serotonin, and norepinephrine (612). As in the case of cocaine the potentiating action of guanethidine and methylphenidate may not be due solely to interference with catecholamine uptake (616).

C. Reserpine and denervation supersensitivity

It is well known that reserpine depletes tissue catecholamine stores, and the drug is extensively used for this purpose in experimental pharmacology (this section A and B). As indicated earlier, this action accounts for the decreased sensitivity of reserpine-treated blood vessels to "indirect-acting" amines *in vivo*. Reserpine blocks the Mg-ATP dependent uptake of catecholamines, although not the Mg-ATP independent uptake of metaraminol (for review see 586).

Sensitization of reserpinized vascular smooth muscle to norepinephrine was described by Burn and Rand (157) and confirmed by others working with canine and rabbit vascular preparations (64, 169, 170, 331, 444, 584, 589, 882). Sensitization to catecholamines is influenced, in addition to the regimen of reserpine treatment employed, by the age of the rabbits (170). In cats the sensitivity to norepinephrine is decreased by reserpine given in concentrations sufficient (1 mg/kg) to induce circulatory failure (882, 963). An interesting observation of Nash *et al.* (675) is that the normal depressant effect of hypercapnia (section XVII A) is reversed after reserpine treatment of cats: in perfused hind-limbs of these animals the vasoconstrictor response to norepinephrine is accentuated. This effect of acidosis may be due to depression of monoamine oxidase and catechol-O-methyl transferase since the latter are probably the rate-limiting factors in the removal of catecholamines in reserpinized preparations.

Nonspecific supersensitivity of blood vessels to vasoactive agents other than catecholamines can also result from reserpine treatment (23, 444, 675, 859). The calcium content of the arteries of dogs, rats, and young rabbits is decreased after reserpine treatment (170). The response of depolarized rabbit vascular strips to Ca^{++} is less readily depressed by Dibenamine after reserpine treatment than in control preparations (859). Further and more direct proof will be required to

determine whether the general permeability (170) and the specific permeability of vascular smooth muscle membranes to Ca^{++} (859) is increased after reserpine treatment. An additional effect of reserpine treatment on spike-generating vascular smooth muscle is an increase in conducted spontaneous electromechanical activity (445, 859).

The mechanisms of denervation supersensitivity, based primarily on studies of the nictitating membrane, have been discussed by Trendelenburg (900) and may be applicable to vascular smooth muscle. He distinguished two components of supersensitivity, presynaptic and postsynaptic. Presynaptic supersensitivity, due to inhibition of uptake and storage mechanisms, is probably responsible for the specific increase in sensitivity to catecholamines after denervation or reserpine treatment. Nonspecific sensitization by reserpine to peptides, Ca^{++}, and other agents not taken up by adrenergic nerves may be due to vascular "postsynaptic" denervation supersensitivity, (859) rather than to a direct action of reserpine on vascular smooth muscle. The decreased effectiveness of phenoxybenzamine on denervated nictitating membranes (545) may be analogous to the decreased depressant effect of Dibenamine on reserpinized vascular smooth muscle discussed earlier. However, the general and massive physiological disturbances created by "reserpinization," emphasized by Zaimis (963, 983) preclude a precise determination of the events leading to Ca^{++} depletion and nonspecific sensitization of vascular smooth muscle.

The effects of reserpine on vascular smooth muscle *in vitro* have not been widely investigated. A general depressant effect of reserpine or its solvent (427) on vascular strips has been reported (28, 427, 508). Reserpine is a phosphodiesterase inhibitor (426), and a direct vasodilator action could be related to this effect. The absence of a vasoconstrictor response to acute reserpinization has been attributed to the release of inactive deaminated metabolites, rather than norepinephrine, when no monoamine oxidase inhibitors are administered (527).

The vessels of the denervated bat wing (957) and of the dog hind-limb after lumbar sympathectomy (749) are supersensitive to epinephrine. Grant (369) suggested that denervation supersensitivity to catecholamines is more pronounced in cutaneous than in skeletal muscle blood vessels. Surgical denervation produces only presynaptic, but not postsynaptic, supersensitivity in the mesenteric blood vessels of rats (383a). It would be of interest to explore further the possibility of postsynaptic sensitization to other agonists in other anatomically denervated blood vessels.

D. Nicotine

An indirect vasoconstrictor effect of nicotine, mediated by the release of stored catecholamines, is well documented (*e.g.*, 73, 157, 297, 589, 824). According to one report (3) this catecholamine-releasing action of nicotine is inhibited by tetrodotoxin, but others (384a) found that tetrodotoxin did not block the catecholamine-releasing action of acetylcholine on the nicotinic receptors of adrenergic nerves. The indirect vasoconstrictor effect of nicotine on rabbit aorta, although not mediated through ganglia, is inhibited by the ganglionic blocking

agent, hexamethonium (824). The mechanism of coronary vasoconstrictor action of nicotine on reserpinized animals (767) remains to be determined.

A direct vasodilator effect of nicotine, apparently independent of innervation, has also been demonstrated (297, 589, 642). The vasodilator effect is not blocked by propranolol or by cholinergic blocking agents (297, 589). The bell-shaped dose-response curves of the rabbit aorta to nicotine (641) may be due to autoinhibition by the vasodilator effect.

E. Adrenergic-neurone-blocking and ganglion-blocking agents

The neuroactive properties of adrenergic-neurone-blocking agents (*e.g.*, guanethidine, bretylium) have been reviewed by others (134, 529, 656). In addition to inhibiting neurally stimulated release of catecholamines, adrenergic-neurone blocking agents also produce indirect (tyramine-like) vasoconstriction (2, 617, 445, 529, 656). A direct vasoconstrictor action of high concentrations of a guanidine derivative and of guanethidine, blocked by phentolamine, has also been suggested (617). Guanethidine potentiates the response of rabbit aortic strips to, and inhibits the uptake of, norepinephrine (this section B; 613, 616). Acute administration of guanethidine potentiates microcirculatory responses to catecholamines (23, 986) whereas the effects of chronic guanethidine treatment are variable (23).

The vasodilator effect of guanethidine has been demonstrated in reserpine-treated hind leg preparations (2) and in rabbit aortic strips (614). Antihistamines and atropine do not block the vasodilator effect of guanethidine, and dichloro-isoproterenol only partially inhibits it (2). Maxwell *et al.* (617) suggested that the vasodilator effect may mask the vasoconstrictor action of guanethidine. The mechanism of vasodilator action of the adrenergic-nerve blocking agents may be related to their local anesthetic (*e.g.*, 741) properties (section XIII).

The inhibition of nicotine-induced catecholamine release by hexamethonium has been mentioned earlier (this section D; 578). Hexamethonium also blocks the acetylcholine-induced release of norepinephrine (384). Tetraethylammonium and mecamylamine potentiate, nonspecifically, the responses of cat carotid artery (585) and rabbit aorta (495) to vasoconstrictor amines and to angiotensin. High concentrations of ganglionic blocking agents depress the contractile response of these preparations. Microcirculatory responses to epinephrine are increased after ganglionic blockade with pentolinium (54).

F. Alpha-adrenergic receptors and blocking agents

The excitatory effects of *alpha*-adrenergic activation on vascular smooth muscle have been universally confirmed. In general, it may be assumed that the response of a given vascular bed to a sympathomimetic amine will be determined, respectively, by a) the relative sensitivity of the vascular smooth muscle to *alpha*-adrenergic (excitatory) and to *beta*-adrenergic (inhibitory) activation, and b) the relative *alpha/beta*-adrenergic activity of a given amine. The activity of epinephrine, relative to norepinephrine, on rabbit aorta can be enhanced by *beta*-

adrenergic blockade (102). The relative potency of various amines on different blood vessels may also vary in a manner independent of *beta*-blockade (102). These differences in potency may be due to different rates of inactivation, binding, or uptake (see also p. 164 in 461) or to the activity of these amines on tryptamine receptors, and we would hesitate to consider them as evidence of several types of *alpha*-receptors. The decreased sensitivity of certain tumor vessels to epinephrine has been used as a diagnostic aid in renal angiography (7, 479).

According to the model adopted in this review, *alpha*-adrenergic and other types of excitation are mediated primarily by an increase in the permeability of the membrane to ions (section XXII; Part I, sections VI F to H). Evidence of an *alpha*-adrenergic increase in the Na-permeability and depolarization of the membrane have been discussed earlier (Part I, section VI A and F). In spike-generating vascular smooth muscle excitation leads to an increase in action potential frequency (Part I section VI F, 106a). A most intriguing question relates to the nature of the difference between vascular and intestinal *alpha*-receptors. In the two tissues the affinity of the receptors to *alpha*-blocking agents appears to be identical (417). In intestinal smooth muscle activation of *alpha*-receptors increases the permeability of the membrane to potassium (469) and inhibits contractile activity (14, 326, 966). It is probable that, as suggested by Jenkinson and Morton (469), inhibitory and excitatory *alpha*-activation differ primarily by the latter's producing an increase in Na- and Ca^{++}-permeability, while the former affects only the potassium channels. The mechanism responsible for these differential effects of *alpha*-adrenergic agents on the permeability of different membranes is one of the more challenging problems of membrane pharmacology.

Alpha-adrenergic excitation increased the K^+-efflux from the rat aorta (I 505), but these experiments were conducted on polarized vascular smooth muscle. Hence it is uncertain whether the depolarizing action of norepinephrine (Part I, section VI F) or a primary increase in K^+-permeability caused the increase in efflux. It would be of interest to know whether *alpha*-adrenergic excitation also increases the K^+-permeability of depolarized vascular smooth muscle. A significant cancellation of depolarization due to increased Na-permeability could occur if an excitatory drug also increased K^+-permeability under conditions when E_K is more negative than the resting potential (Part I, section VI). This type of cancellation accounts for the incomplete depolarization of the motor end-plate by a cholinergic stimulus (pp. 125–126 in 491) and may also be the reason why norepinephrine produces only incomplete depolarization of vascular smooth muscle (851, 859).

A very interesting observation of Brecht's laboratory (143a, 521) concerns the effects of rapid, small (6 to 10 mM) increments of potassium concentration on the contractile response of bovine facial arteries to norepinephrine. Under the influence of such potassium-transients the contractures elicited by relatively high concentrations (5×10^{-6} w/v) of norepinephrine are relaxed. The mechanism of this phenomenon has not been established.

Regional and species-specific variations in the response of vascular smooth muscle to *alpha*-adrenergic stimulation are now implicitly accepted and require no further detailed documentation. Reviews and recent studies of the general systemic (772, I 410), coronary (95, 285, 601, 773, 800), pulmonary (50, 298, 450), intestinal (932), cerebral (370, 385, 393, 847), and retinal (27, 650) vasculature describe in detail regional and segmental responses to endogenous and exogenous catecholamines. The adrenergic responses of large feeding arteries and small resistance vessels of a given region often differ (805), as has been clearly shown in comparative studies of isolated mammalian coronary (994) and avian pulmonary vessels (853, 855).

Age-related changes in sensitivity to *alpha*-adrenergic agents have been reported, although *alpha*-receptors appear relatively early in fetal life. In chick embryos a pressor response to norepinephrine, which can be blocked with phenoxybenzamine, appears by the seventh day (350). In fetal mice of approximately 13 days gestation topical norepinephrine elicits vasoconstriction of the middle cerebral artery *anlage* (191). Not only is the newborn calf sensitive to catecholamines, but also its autonomic mechanism mediating asphyxial reflex vasoconstriction is fully operative (640). The threshold level to norepinephrine in mesoappendical vessels is higher in adult than in young rats (443). The sensitivity of human umbilical and placental vessels to norepinephrine is variable, but generally low and blocked by haloalkylamines (193, 360, 704, I 559).

Identification of *alpha*-receptors through labeling them with tritiated halogenoethylamines (*alpha*-blockers) has been attempted (246, 560, 647, 981) but appears to have been unsuccessful. Earlier claims of localizing aortic *alpha*-receptors to a phospholipid fraction (246) have been subsequently questioned on methodologic grounds (560). The major technical difficulty is, as in the case of intestinal cholinergic receptors (717), the extensive labeling of nonreceptor binding sites (647). In view of the nonadrenergic effects of halogenoalkylamines on the permeability of the membrane to calcium (section XIV), at least some of the "nonspecific" binding sites may represent functional groups of the plasma membrane.

Alpha-blocking agents inhibit, at least equally, the action of endogenous, neurally released catecholamines and of exogenous amines, according to recent studies (3, 93, 556). In the perfused hind-leg of the dog the small veins are more susceptible to blockade by phenoxybenzamine than are the arteries (3). In isolated blood vessels, however, the greater depressant effect of haloalkylamines on veins than on certain large arteries is relatively nonspecific (section XIV). Small veins are more sensitive to *alpha*-adrenergic blockade by dihydroergocristine than the rabbit aorta (300).

The effects of haloalkylamines that are not directly related to their *alpha*-blocking activity are discussed elsewhere (section XIV). Attention is called here to the observation that, at least under certain experimental conditions, Dibenamine in concentrations commonly employed for *alpha* blockade (1.5×10^{-6} w/v) may produce significant nonspecific depression of particularly sensitive (*e.g.*, rabbit mesenteric vein) vascular smooth muscles (859, section XIV).

G. Thyroxine and related compounds

The interaction of thyroid with adrenal medullary compounds has been the subject of frequently conflicting reports (396). Thyrotoxicosis has been reported to enhance the response of the vessels of the canine gracilis muscle to *alpha-* and *beta*-adrenergic agents (318) but also to depress the response of the perfused hindquarter of rats to norepinephrine (517). Aortic strips obtained from hyperthyroid rabbits exhibit a lesser maximal response to norepinephrine than normals (588). Since *beta*-blockers were not used in this study the possibility of *beta*-adrenergic sensitization by thyrotoxicosis (318) with consequent depression of the vasoconstrictor response (section IX J) cannot be ruled out. The responses of the aortic strips of thyrotoxic rabbits to nicotine and tyramine are reduced or absent, and only the response to nicotine can be restored with norepinephrine (588).

The potentiating effect of thyroxine and of L-3,3',5-triiodothyronine on the responses of rabbit aortic strips to low concentrations of catecholamines *in vitro* depends critically on the presence and binding of contaminating metal ions (828, 833). Attention is called to the very instructive observation that physiological salt solutions prepared from commercial reagents contain sufficient copper (6.6 μg/l) to decrease the peak and shorten the duration of the response to low concentrations of catecholamines and therefore "pseudoenhancement" of the response to epinephrine can be produced by any agent (*e.g.*, EDTA) that can chelate copper (833).

H. Vascular metabolism of catecholamines

The general aspects of catecholamine metabolism, largely reflecting the properties of adrenergic nerves, have been summarized in a recent monograph by Iversen (461). We shall review here only a few studies pertinent to experimentation with isolated vascular smooth muscle.

Metal-ion catalyzed auto-oxidation of catecholamines *in vitro*, in particular the effects of copper contamination in commercial reagents (833), and the elimination of these effects with chelating agents (331, 833) have been discussed in the preceding section. Metal-catalyzed auto-oxidation can limit not only the contractile response of vascular smooth muscle to catecholamines (331, 833) but also the uptake of tritiated norepinephrine into vascular adrenergic storage sites (681). Autooxidation of catecholamines in solution is more pronounced in the absence of tissues than in their presence (386). The protective effect of tissues, and of plasma albumin (section V) may be due to chelation of metal ions. The neuronal uptake of norepinephrine is influenced by extracellular Na and K^+ concentrations (119). It may be necessary to re-evaluate the influence of extracellular cations on the vasoconstrictor responses to catecholamines in terms of indifect effects related to vascular catecholamine metabolism (see also this section A).

Uptake of norepinephrine into vascular smooth muscle of rabbit ear arteries has been demonstrated with the fluorescence method by Avakian and Gillespie

(49). Demonstrable uptake required perfusion with high concentrations ($\geq 10^{-5}$ w/v) of norepinephrine, and uptake was depressed by concentrations of phenoxybenzamine well in excess of those depressing the contractile response. The authors concluded that uptake into smooth muscle was not mediated by *alpha-* or *beta*-adrenergic receptors. They also suggested that the delayed relaxation of contractions produced by very high concentrations of catecholamines is due to the slow leakage of amines previously taken up into smooth muscle. At high concentrations (10^{-4} M) most of the norepinephrine taken up by rabbit aorta is extraneuronal (682). The endogenously released norepinephrine concentration in the neurally-stimulated rat portal vein is estimated to be about 2×10^{-5} M (564) and in the rabbit pulmonary artery about 10^{-6} M (100a) and suggests that uptake of endogenous catecholamines by vascular smooth muscles may occur *in vivo*.

Oil-immersion of rabbit aortic strips, preventing the escape of water-soluble agonists, has been used by Kalsner and Nickerson (481, 482, 484) to correlate the time-course of relaxation with the concentration of active agonist in the biophase (I 200). Under these conditions iproniazid, a monoamine oxidase inhibitor, slowed the relaxation of phenylephrine-induced contractions. This finding is compatible with phenylephrine catabolism being the rate-limiting reaction in the relaxation process. The experience with the oil-immersion method, however, is too recent for a complete evaluation of the conclusions derived from it, and it is not within the scope of this review to evaluate the relative contributions of monoamine oxidase and catechol-O-methyl transferase to vascular catecholamine metabolism. We would caution, however, that the relaxation rate of vascular strips cannot be taken as a general index of the elimination of an agonist from the biophase. Under certain experimental conditions either tachyphylaxis or the activity of the smooth muscle relaxing system may be the rate-limiting parameter of relaxation.

Iproniazid given to rabbits decreases the responsiveness of their aortic strips to norepinephrine (52). Tranylcypromine, a monoamine oxidase inhibitor, contracts rabbit aortic strips, but other monoamine oxidase inhibitors do not share this activity (403).

I. Beta-adrenergic mechanisms

The general concept that in most tissues cyclic 3′,5′-AMP is the secondary messenger mediating *beta*-adrenergic effects has been pioneered by Sutherland *et al.*, who recently reviewed this topic (758, 877). It has been suggested that adenyl cyclase, the membrane-bound enzyme that catalyzes the conversion of ATP to cyclic AMP and is stimulated by *beta*-adrenergic agents, may be part of the *beta*-receptor (877). The cyclic nucleotide is catabolized to 5-AMP by phosphodiesterase (758, 877). It is generally suggested, although not specifically proved for vascular smooth muscle, that the biological effects of phosphodiesterase inhibitors (*e.g.*, theophylline, caffeine) are due to local accumulation of endogenous cyclic AMP.

Several diverse vasodilators, in addition to the methyl xanthines, inhibit

phosphodiesterase. These phosphodiesterase inhibitors include the phenothiazines and reserpine (426) and the benzothiazides (section XII).

Relaxation and variable membrane potential changes are the principal effects of *beta*-adrenergic activation of vascular smooth muscle. The relaxant effect, a common action on other smooth muscles and on avian slow muscles, can be elicited in several systems without hyperpolarization and inhibition of spike electrogenesis (215, 242, 469, I 529, 850). This pharmacomechanical inhibitory action of *beta*-adrenergic activation is assumed (section XXII) to be due to the lowering of cytoplasmic calcium ion concentration (Part I, sections VI C and H) mediated by either a decrease in the permeability of the plasma membrane to Ca^{++} or an increased active extrusion or reticular uptake of Ca^{++} (469, I 529, 850). The experimentally unsupported assumption that *beta*-adrenergic relaxation of the avian mesenteric artery is due solely to hyperpolarization and inhibition of spike electrogenesis (128) is not consistent with a large body of evidence on *beta*-adrenergic inhibition. Rasmussen and Tenenhouse (742) suggested regulation of membrane permeability to calcium as a general mechanism of action of cyclic AMP. It should be noted, however, that in order to relax vascular smooth muscle the nucleotide would have to decrease cytoplasmic Ca^{++}, producing an opposite effect to the one that would cause positive cardiac inotropism (877) or stimulus-secretion coupling (254). Ca^{++}-efflux from the perfused rat liver is increased by cyclic AMP and by certain substances (norepinephrine, glucagon) that increase its formation (321), but similar studies on vascular smooth muscle are lacking. The difficulty of interpreting the mechanical effects of exogenous cyclic AMP are discussed elsewhere (section X). Schild (I 529) made the very interesting observation that trace amounts of calcium are required for the myometrial relaxant effect of isoproterenol.

The response of the membrane potential of vascular smooth muscle to *beta*-adrenergic agents varies with the potassium concentration of the medium. This possibility was suggested previously (Part I, section VI F) on the basis of work on avian slow muscle, and has since been verified in experiments on the rabbit main pulmonary artery (851). This preparation is hyperpolarized by isoproterenol (2×10^{-7} w/v) in 1.0 mM K^+ and depolarized by the amine in 10.0 mM K^+ solution. In the presence of 5.9 mM K^+ the electrical response is minimal and variable. The suggested mechanism responsible for this phenomenon, *beta*-adrenergic stimulation of the Na pump with the Na/K^+ coupling ratio (and hence electrogenicity of the pump) determined by external K^+ concentration, have been discussed elsewhere (Part I, section VI; 850). The possibility that the depolarizing effect in high K^+ medium is due to an *alpha*-adrenergic effect has not been ruled out, however. Compatible with *beta*-adrenergic stimulation of the vascular Na-pump is the decrease in the Na-content of the rat aorta after injection of isoproterenol (211) and the inhibition of *beta*-adrenergic hyperpolarization by the Na,K^+-ATPase inhibitor, olygomycin (858a). An important contribution to the interpretation of adrenergic mechanisms was made by Jenkinson and Morton (469), who found that in intestinal muscle passive permeability changes, indicated by K^+-efflux, were associated with *alpha*- but not with *beta*-

adrenergic stimulation, an observation that was extended to uterine smooth muscle by Daniel *et al.* (215). The latter authors also suggested an alternative mechanism of action of isoproterenol on the membrane potential, mediated by a decreased Na-permeability. The electrophysiological studies of Bülbring and Tomita (152) on taenia coli also showed that the increase in membrane conductance produced by catecholamines is mediated by *alpha*-receptors, whereas *beta*-adrenergic activation has no demonstrable effect on membrane conductance. In the presence of theophylline (4.0 mM) a low concentration of isoproterenol, which by itself would have no detectable effect on the membrane potential, hyperpolarizes the rabbit main pulmonary artery (858a). Dibutyryl cyclic AMP (0.5 to 1.0 mM), particularly in conjunction with theophylline (4 mM), also hyperpolarizes (10 mV in a 1.0 mM K^+-Krebs solution) rabbit main pulmonary strips (858). These findings suggest that *beta*-adrenergic hyperpolarization is mediated by cyclic AMP. Adenosine monophosphate (1 mM), under similar experimental conditions, does not hyperpolarize the rabbit main pulmonary artery (858).

The identity of vascular *beta*-receptors with those of other tissues has recently been questioned and the possibility of several subtypes of *beta*-receptor has been suggested (326, 543, 557, 959). We agree with the conservative views of Furchgott (326) that a multiplicity of drug-tissue interactions may lead to apparent differences between *beta*-responses of different tissues without variations in the molecular structure of the *beta*-receptor. Interpretation of results obtained with different blocking agents is difficult, because the latter may also have adrenergic or nonspecific effects to which different tissues need not respond in the same manner. In comparing the potency ratios of several amines on different receptors, it is particularly important to recall that the intestinal inhibitory action of catecholamines is due to both *alpha*- and *beta*-effects (13, 326, 469, 966).

J. Beta-adrenergic action of norepinephrine; sympathetic vasodilation in veins and in coronary and umbilical vessels

A relaxant action of norepinephrine on the rabbit aortic strip, unmasked by *alpha*-blockade of the contractile effect, has been described by Furchgott (I 200, 326). After intensive *alpha*-blockade, reversal of the vasoconstrictor action of exogenous or endogenous norepinephrine to vasodilation has also been demonstrated *in vivo* (72, 144). More recent studies (see below) also indicate that even in the absence of *alpha*-blockade in certain blood vessels norepinephrine can exert a vasodilator effect that is abolished by *beta*-blocking agents.

Beta-adrenergic autoinhibition of the vasoconstrictor action of norepinephrine leads to a lesser maximal contractile effect than that produced by the amine when the *beta*-receptors are blocked. This has been demonstrated in pulmonary arterial strips of chickens, although it was not seen with sciatic artery strips of the same species (966). Similar observations on the rat aorta, an increase in the maximal contractile effect of norepinephrine by propranolol treatment, were reported subsequently but interpreted in a different manner (719). We fail to be

convinced by the latter author's argument that propranolol was not acting as a *beta*-blocker because its effects were partly mimicked by changes in ambient temperature.

Beta-adrenergic depression of the *alpha*-adrenergic action of norepinephrine action *in vivo* has also been demonstrated by the increased vasoconstriction that follows *beta*-blockade (353). In certain vascular beds, such as the coronary arteries of several species, *alpha*-receptor density seems low. Coronary vessels therefore are frequently, though not always, dilated by norepinephrine and epinephrine, although the response can vary with the initial tone (63) or size (994) of coronary arteries studied. Coronary vasodilation by exogenous or neurally released catecholamines can sometimes be converted to vasoconstriction by *beta*-blockade (255, 542, 883). The coronary vasodilator action of norepinephrine and of adenosine (section X) is potentiated by dypiridamole (400).

Autoregulatory escape, partial vasodilation during prolonged sympathetic stimulation (I 410), may in some instances occur as a manifestation of a delayed *beta*-adrenergic vasodilator action of norepinephrine, since in canine femoral arteries this phenomenon is partially inhibited by *beta*-blockade (341). The vasodilator action of norepinephrine administered during sympathetic stimulation is also blocked by dichloroisoproterenol (496). The diminished vasoconstrictor response of rabbit aortic strips to epinephrine after exposure to high concentrations of the amine (709) may also have been due to persistent *beta*-adrenergic effects, although other mechanisms cannot be ruled out.

Veins, it is now clearly established (4, 194, 694, 856, 878, 993), are also dilated by *beta*-adrenergic activation. The venoconstrictor effects of isoproterenol are due to its *alpha*-adrenergic action (194, 856, 878). Phenylephrine converts the effect of subcontractile doses of isoproterenol in rabbit aortic strips to a contractile one (591).

Human umbilical vascular smooth muscle is not relaxed by isoproterenol (360, I 559). In one report relaxation of longitudinal strips of human umbilical arteries by isoproterenol is mentioned (642) without description of experimental methods or specific data. In view of the relationship suspected between phosphodiesterase inhibitors and *beta*-adrenergic mechanisms (see preceeding section), it is interesting that caffeine (I 557) and theophylline (360) relax umbilical vascular strips under conditions in which isoproterenol is ineffective. A lack of vasodilator effect of isoproterenol on vascular strips of certain lower vertebrates has also been described (158). A possible *alpha*-adrenergic inhibitory action of catecholamines on umbilical vessels has also been reported (360). It would be of interest to determine whether this effect, like the one in intestinal muscle (469), is mediated through hyperpolarization due to an *alpha*-adrenergic increase in K^+-permeability, unaccompanied by increased Na^+ and Ca^{++}-permeability. Unlike the umbilical vessels, the vasculature of the perfused placenta is dilated by isoproterenol (192).

In view of the *beta*-adrenergic vasodilator properties of norepinephrine there is no reason to doubt that, under appropriate conditions (927), it can act as an

autonomic vasodilator transmitter. An isoproterenol-like substance may be formed as an artifact during chromatographic processing of biological materials (756) but there is no evidence for its natural occurrence.

K. Beta-blockers: local anesthetic and other nonspecific effects; interaction with alpha-adrenergic responses

Extensive studies of *beta*-adrenergic blocking agents, including specific blocking and nonspecific actions, have been reviewed by Ahlquist (13) and compiled in the proceedings of a recent symposium (648). A particularly important side effect of agents of the type of pronethalol and propranolol is their local anesthetic action, equivalent to or exceeding that of procaine (558). The local anesthetic effect (see section XIII) may be the mechanism of nonspecific vasodilator action of these agents (114, 473, 667, 827). The local anesthetic and nonspecific vasodilator effects are equally prominent with the racemic *beta*-blockers and with the (+)-isomers that have very little *beta*-blocking activity (473, 558, 827). The adrenergic-neurone blocking action of propranolol and pronethalol (223, 306) and their effect on lipid-facilitated calcium transport (680) may also be related to their local anesthetic action.

There have been reports of *beta*-blockers inhibiting the vasodilator action of some agonists that are generally not considered to be *beta*-adrenergic agents. In the single report of pronethalol and propranolol inhibiting the vasodilator action of histamine on the canine hind leg (47) the concentration of the blockers used was very high, in comparison with that required to block the effects of isoproterenol in this preparation (667). Inhibition of the peripheral vasodilator action of hydralazine by propranolol has been demonstrated but the possibility of an indirect, adrenergically-mediated effect has not been ruled out (150). The vasodilator actions of pheniprazine (644) and of nylidrin (600) are also partially inhibited by *beta*-blockers.

The relationship of the blockade of the canine vasodilator action of chlorobutanol-oxytocin mixtures by pronethalol (section II C) and of the mechanism of catecholamine-oxytocin vasodilator interaction (section II G) to *beta*-adrenergic mechanisms remains to be established.

Alpha-adrenergic blocking effects and protection of *alpha*-receptors from irreversible blocking agents have also been ascribed to *beta*-blockers, but the depression of the responses of certain vascular strips to norepinephrine by pronethalol or propranolol (176, 376, 519, 620, 855) could be largely due to a nonspecific local anesthetic effect with perhaps a small contribution (376) due to interaction with *alpha*-receptors. The depressant effect of dichloroisoproterenol on rabbit aortic strips is not specifically directed to *alpha*-agonists (376, 737, 973) although it satisfies the kinetics of competitive inhibition. The apparent protection of the *alpha*-receptors of aortic strips from phenoxybenzamine by *beta*-blockers (519, 620, 691, 977) is probably due largely to unmasking of residual (unblocked) *alpha*-receptors inhibited by the *beta*-adrenergic action of norepinephrine (326, 977). Some of the protecting effects, however, may be unrelated to *beta*-blockade, since the weak *beta*-blocker (+)-isomers were equally active

in protection studies of the vas deferens (714). The effect of *alpha*-blockers on the slight contractile effect of pronethalol on venous strips (856, 878) has not been determined.

X. ADENINE NUCLEOTIDES AND DIPYRIDAMOLE

A dual, excitatory and inhibitory, action is characteristic of the vascular effects of adenine nucleotides. In the rabbit aortic strip (I 200, I 202) ATP produces a contractile or a relaxant effect, depending upon the initial tone of the preparation. Relaxed strips are contracted and contracted strips relaxed, whereas the response of partially contracted strips is diphasic. Vasoconstrictor effects of ATP are pronounced in the rabbit pulmonary bed (587), although in the vasoconstricted (with serotonin) canine pulmonary circulation the vasodilator effect of ATP predominates (781). Strips of human umbilical veins (858) are contracted by ATP (6×10^{-5} to 6×10^{-4} w/v, lower concentrations not tested). The mechanism of the contractile effect of ATP is not known, but it is certainly not due to intracellular penetration of this charged nucleotide. *Alpha*-adrenergic blocking agents do not inhibit the vasoconstrictor effect of ATP on the rat renal artery (440). Although ATP did not contract the depolarized rat renal artery artery (440), Daniel and Irwin (212) found that the depolarized myometrium was contracted by the nucleotide. It remains to be determined whether the contractile responses of vascular smooth muscle to ATP are due to depolarization alone. ATP also contracts some striated muscles (850). The hyperpolarizing effects of cyclic-AMP and the potentiation of the hyperpolarizing action of isoproterenol by theophylline were discussed elsewhere (Section IX, I.).

The vasodilator and hypotensive effects of nucleotides on certain types of vascular smooth muscle are not limited to ATP, but are also exerted by ADP, AMP, cyclic 3′,5′-AMP, and adenosine (31, 322, I 200, I 202, 399, 934). Adenosine was found to have a vasoconstrictor and ATP a vasodilator effect on the perfused dog kidney (399).

The mechanism of the vasodilator action of adenosine is not known. Relaxation of canine vascular strips by adenosine is not inhibited by adrenergic blocking agents (934), but AMP inhibits the relaxant effect of subsequently added ATP on rabbit aortic strips (I 202). The activity of substituted adenosine derivatives that are not readily phosphorylated, such as 5′-chloro-adenosine, suggests that the adenosine structure itself is vasodilator (463). Cyclic 3′,5′-AMP also has a vasodilator effect on certain vascular beds (399, 934). Uridine nucleotides may dilate (UTP, UDP) or constrict (UMP) the canine coronary bed (399). Because of the relative lack of structural specificity for the vasodilator action of nucleotides, the vasodilator effect of externally added cyclic 3′,5′-AMP is not useful in establishing whether this nucleotide is the *beta*-adrenergic vasodilator messenger (see section IX I). Adenine nucleotides relax the K^+-contractures of smooth muscle and slow striated muscle (51, 850), and on taenia coli the pharmacomechanical relaxant potency of adenine is greater than that of ATP (51). It has been suggested, on the basis of studies of glycerinated gizzard myofibrils (428), that intracellular accumulation of AMP and inorganic phosphate during

anoxia may be sufficient to inhibit actomyosin ATPase and thus have a relaxant effect. While this, as well as earlier (I 554) speculations regarding the existence of contractile regulators in addition to Ca^{++} deserve further exploration, their applicability to normal vascular smooth muscle remains uncertain (see also section XXII). Some parallelism between the vasodilator activity of certain nucleotides and their ability to inhibit ADP-induced platelet-aggregation has been noted (132). ADP itself is a vasodilator, however, and under special experimental conditions *in vivo* both vasodilator and platelet-aggregating effects may contribute to its depressor action (475). The vasodilator action of adenine nucleotides is not limited to mammals: both ATP (931) and AMP (799) are potent depressors in the chicken.

Dipyridamole potentiates the vasodilator effects of adenine nucleotides in the coronary and other vascular beds, and some of this effect is thought to be caused by interference with adenosine catabolism (11, 95, 135, 399, 526, 538, 810). Dipyridamole itself, however, is also a vasodilator (11, 399, 934), and its potentiating action, as well as that of another vasodilator, lidoflazine (12), may involve multiple mechanisms. The vasodilator action of dipyridamole on vascular strips is not inhibited by adrenergic blocking agents (934). The effect of blocking agents on the vasoconstrictor effect of dipyridamole on the canine renal circulation (399) and portal vein (934) has not been explored.

A metabolic vasodilator function of adenosine released during exercise and anoxia has been suggested. Berne (95) has persuasively argued the possibility that adenosine functions as a coronary vasodilator. His laboratory (777) recently demonstrated the appearance of adenosine in coronary venous effluent during postanoxic hyperemia, and so considerably strengthened the case for a pathophysiological function of this nucleotide. The possibility of a vasodilator function of adenine nucleotides in skeletal muscle has been thoroughly reviewed by Haddy and Scott (383), who considered this possibility unlikely because of the rapid inactivation of adenosine to inosine. Dipyridamole did not potentiate hypoxic vasodilation of canine hind-limb, as may have been expected if vasodilation was due to adenine nucleotides (526). The authors properly cautioned, however, that their findings may not be applicable to more severe hypoxia than produced in their experiments. The recent demonstration of ATP release from exercising frog nerve-skeletal muscle preparations (136), not accomplished in earlier studies (383, 841), may reopen the question of an adenine-nucleotide-induced component of vasodilation in skeletal muscle. Hughes and Vane (445) suggested that the nonadrenergic neurogenic vasodilation (section XVIII) described by them may have been mediated by ATP.

The vascular biochemistry of adenine nucleotides was discussed in the first part of this review (Part I, section IV D; 29, 657).

XI. STEROIDS

Steroid hormones, except in very high concentrations, have no direct effects on the contractile properties of vascular smooth muscle, but can modulate the

effects of vasoactive agents. Chronic administration of steroids affects the morphogenetic function (Part I, section I C) of vascular smooth muscle.

Adrenal steroids *in vitro* (98, 120, 310, 435, 768) or applied *in vivo* either topically to the microcirculation (17, 745) or systemically (87, 206, 348, 554, 706, 806–808) potentiate the activity of peptide and amine vasoconstrictors. The potentiating activity of systemic glucocorticoid steroids on vasopressor responses may not be demonstrable (554, 602) except after ganglionic blockade (807). In a careful study of the effects of hydrocortisone on rabbit aortic strips, Besse and Bass (98) found that this steroid (3×10^{-5} M) potentiated the contractile effect of catecholamines in normal, cocaine-treated, or reserpinized preparations and also potentiated the relaxant effect of isoproterenol. The authors suggested that the steroid increased the affinity between catecholamines and vascular receptors. This suggestion is consistent with the parallel displacement of epinephrine dose-response curves by hydrocortisone, but other mechanisms, such as steroidal effects on metabolism or extraneuronal binding of catecholamines, cannot be ruled out. Steroidal inhibition of catechol-O-methyl transferase may be one of these mechanisms (480), but it does not account for the potentiation of peptide and noncatecholamine agonists.

High concentrations of corticosterone, progesterone, methyl testosterone, estradiol, and other steroids have inhibitory effects on vascular and visceral smooth muscle (408, 541, 555, 802). The specificity of these effects and their dependence on a particular hormonal structure is doubtful. Schatzmann (802) observed competitive inhibition by corticosterone of the oubain-induced contractures of rat aorta.

Pregnancy tends to decrease the pressor response to angiotensin (187, 414), and this effect, in rats, can be reproduced by exogenous progesterone (414). Progesterone also inhibits the renal vascular effects of angiotensin in unanesthetized women (188). The mechanism of the inhibitory action of pregnancy and progesterone is not known, but may involve increased inactivation of angiotensin (section I C). The cholinergic vasodilation of guinea pig uterine arteries is accentuated during pregnancy (74). Estradiol increases venous distensibility in women (363). Estrogens have also been reported to shorten the prolonged vasoconstrictor effects of norepinephrine in ovariectomized dogs (992). In hibernating male toads estrogens produce hypertension associated with arteriolar thickening (820). The vascular interaction of steroids with neurohypophyseal peptides has been discussed elsewhere (section II G).

Structural alterations in blood vessels can be induced by steroids experimentally or as the result of pregnancy (I 22, 209, 366, 561) and may also be reflected by changes in chemical composition (177, 579, 580, 736). Since steroids used for contraception also affect vascular architecture (209), the long-term effects of their use in people deserve careful and continual evaluation. Several studies of the effects of sex steroids on vascular chemistry and morphology, with particular reference to the relationship to atherogenesis, have been reviewed in Zemplényi's recent monograph (984) and other parts of this review (Part I, sections II C, III B, and IV B).

XII. DIGITALIS GLYCOSIDES AND DIURETICS

Digitalis glycosides in relatively high concentrations produce contracture of vascular strips and vasoconstriction of perfused vascular beds (145, 460, 555, 650, 802). The ouabain-induced contractures of the rabbit aorta require Ca^{++} in the bathing medium and are associated with increased Ca^{45} uptake (145). Depolarization of rabbit mesenteric veins by ouabain, observed by Matthews and Sutter (I 402), is presumably due to inhibition of the Na-pump (355), although an effect of ouabain on Na-permeability, as suggested by Casteels (175) in a study of taenia coli, cannot be excluded. Corticosterone inhibits the ouabain contracture of rat aortic strips and the antagonism is competitive (802). Lower concentrations of cardiac glycosides, insufficient to produce contracture, potentiate the magnitude and prolong the relaxation phase of rabbit carotid artery contractions elicited by a.c. electrical stimulation (555). The response to a.c. stimulation, however, includes a large indirect component secondary to the release of adrenergic neurotransmitter (section XVIII). Therefore, the potentiation of electrically-induced contractions by cardiac glycosides could be due to inhibition of catecholamine uptake, a direct effect on smooth muscle, or a combination of both mechanisms. Bohr *et al.* (123a) found that ouabain also enhanced the (submaximal) responses of rabbit mesenteric artery strips to norepinephrine. Direct vasoconstrictor effects of high concentrations of cardiac glycosides on human blood vessels *in situ* have been described (352, 604).

Diuretics may influence the reactivity of blood vessels *in vivo*, but the present discussion will be limited to their effect on isolated preparations. Hydrochlorothiazide has been reported to inhibit the response of rabbit aortic strips to catecholamines and serotonin (201), but others reported negative results (214). Neither has there been agreement regarding the effect of hydrochlorothiazide on vascular sodium content *in vitro* (337, 214). Hydrochlorothiazide is only poorly soluble, and furthermore dimethylformamide used as a solvent increases the inhibitory effect on the rabbit aorta (201). High concentrations of hydrochlorothiazide also inhibit intestinal smooth muscle (637).

Diazoxide, a nondiuretic benzothiadiazine, also has a nonspecific relaxant effect on vascular smooth muscle (214, 775, 964). The canine peripheral vasodilator effect of diazoxide is not abolished by *beta*-adrenergic blocking agents (677). Acetazolamide dilates and, in higher concentrations, constricts the blood vessels of the perfused canine hind limb and the frog preparation (713) and also the vasculature of the cat iris (590).

Inhibition of phosphodiesterase is a property common to benzothiadiazines, acetazolamide, and several other diuretics (646, 823), and may account for their vasodilator activity. Methyl xanthines, perhaps the best known group of phosphodiesterase inhibitors, are also among the best known vasodilators (section IX I). The critical information still lacking is whether phosphodiesterase inhibition *per se* is sufficient to cause relaxation of vascular smooth muscle and, if so, whether the vasodilator action of benzothiadiazines is simply a consequence of decreased cyclic AMP breakdown by phosphodiesterase.

XIII. LOCAL AND GENERAL ANESTHETIC AGENTS

A. Procaine and ethyl alcohol

The general pharmacology of local anesthetics has been reviewed by Ritchie and Greengard (755). For more recent work on nonvascular muscle the reports of Bianchi and Bolton (108) and Feinstein *et al.* (287, 289) may be consulted. There is considerable evidence that in a number of systems local anesthetics interfere with transmembrane fluxes of ions including Ca^{++}, possibly competing with the latter for membrane "stabilizing" sites.

The contractions of rabbit aortic strips induced by norepinephrine, histamine, and acetylcholine (44) are relaxed by procaine and other local anesthetic agents in concentrations of 1 to 3 mM (44, I 290, 676). It has been reported (I 290) that procaine does not relax the K^+-contracture of rabbit aortic strips, and this finding has been used as supporting evidence for the suggestion that K^+ and norepinephrine mobilize qualitatively different pools of Ca^{++} (I 290). In contrast, we have found (859), under slightly different experimental conditions, that procaine (0.5 to 5.0 mM) relaxed the K^+-contractures of rabbit aortic strips. Procaine (5.0 mM) shifts to the right the Ca^{++} dose-response curves of depolarized rabbit aortic and portal-mesenteric vein strips by approximately one log unit (851). Feinstein (287) also described a competitive interaction between the effects of local anesthetics and extracellular calcium on the depolarized myometrium. While our findings do not provide direct evidence against the existence of separate K^+- and norepinephrine-labile Ca^{++} pools, they do negate arguments (see also 859) based upon *qualitatively* differential effects of procaine on the two types of contracture.

Lidocaine and tetracaine in low concentrations can, like cocaine (section IX B), potentiate the responses of rabbit aortic strips to catecholamines (44, 676).

The indirect effect of local anesthetics on blood vessels is due to inhibition of vasomotor nerves. Procaine blocks the vasoconstriction of rabbit ear arteries evoked by periarterial nerve stimulation (78, 229), and cocaine (10^{-5} w/v) has a similar effect on rabbit mesenteric veins (445). The coronary vasodilation elicited by procaine in dogs subjected to coronary artery ligation may also be due to an action on nerves (848). It has been suggested that procaine also blocks pressor responses to acetylcholine mediated *via* carotid chemoreceptors (6). Procaine also inhibits the reflex vasodilation of canine muscular blood vessels that follows intravenous injection of norepinephrine (251). In dog hind-limb preparations procaine also has a direct vasodilator action (562).

Vasoconstriction elicited by procaine has been observed in the rabbit ear artery (229). In the hind limb of spinal cats (791) when basal tone is high, procaine produces vasodilation; when basal tone is low, procaine produces vasoconstriction that is not blocked by phenoxybenzamine (791). Procaine also has a dual effect on rabbit mesenteric veins: it relaxes the K^+-contracture but contracts vein strips in Krebs' solution (792, 854).

Ethyl alcohol injected intra-arterially constricts the blood vessels of the human forearm and this effect is not blocked by phenoxybenzamine; orally-ingested

alcohol elicits a neurally-mediated vasodilation (296). This finding may suggest to some the advantages of oral ingestion. The permeability changes induced, in intestinal smooth muscle, by ethanol were studied by Hurwitz *et al.* (448), who found them to be different from those produced by local anesthetics. There are no comparable data available on vascular smooth muscle. Ethyl alcohol, used also as a solvent for Dibenamine, contracts human placental vessels (192, 937).

The Ca^{++}-uptake of rat aortic strips is decreased by tetracaine in a concentration that also inhibits the contractures evoked by Ca^{++} and depolarizing concentrations of K^{+} (685). It was also reported in this study that certain agents (indomethacin and desipramine) inhibit the contractures of rat aorta without inhibiting Ca^{++}-influx. These findings may be compared with Feinstein's (287) observation on the rat uterus that among several myometrial relaxants (tetracaine, caffeine, and epinephrine) only tetracaine also inhibited transmembrane Ca^{++}-fluxes (see also section XXII).

B. Halothane, cyclopropane, and other general anesthetic agents

Cyclopropane, thiopental, and chloroform contract rabbit aortic strips, whereas the effect of halothane varies from contraction to relaxation (735). The response to norepinephrine is depressed by halothane (735). Halothane produces vasodilation and inhibits the vasoconstrictor action of norepinephrine on the human limb (113) and on canine skeletal muscle vessels (202, 203). It is probable that the peripheral vascular effects of halothane are due to a direct action on smooth muscle (155a, 202, 273). The bronchodilator action of halothane is inhibited by the *beta*-blocking agent MJ 1999 (513), but we have found no analogous studies related to vascular smooth muscle. Cyclopropane enhances the contractile effects of catecholamines, angiotensin, histamine, and serotonin on the rabbit aorta (735). Cyclopropane also potentiates vasoconstriction of the human forearm (621) and the rat microcirculation by catecholamines (53). Intra-arterial thiopental has a vasoconstrictor effect on rabbit ear vessels that is abolished after reserpinization, but potentiated by cocaine (156).

An indirect vasoconstrictor effect of halothane, mediated probably by the release of vasopressin, and a direct effect of cyclopropane have been well documented in a study of the perfused gracilis muscle of the dog (202). In this preparation cyclopropane produced vasoconstriction that was not abolished by *alpha*-adrenergic blockade.

Diethyl ether and methoxyflurane, administered by inhalation, produce vasodilation of the rat microcirculation (53) and dog hind limb (606). The decrease in human forearm-flow caused by ether is thought to be due to the release of catecholamines (622). The general circulatory effects of anesthetic agents have been dealt with in a monograph (734), and the effects of anesthesia on the electrical activity of blood vessels have been discussed previously (Part I, section VI).

XIV. HALOALKYLAMINES, CHLORPROMAZINE, CINNARAZINE, AND MANGANESE

The property relating the diverse agents included in this section is their ability to depress the contractures evoked by Ca^{++} and depolarizing concentrations of

K^+ and the contractile responses to drugs of vascular smooth muscles. There is a strong resemblance between the action of these muscle depressants and local anesthetics. Judging from the mainly indirect evidence available on vascular smooth muscle, and by analogy from more direct observations in other tissues, the smooth muscle depressants to be discussed seem to inhibit the transmembrane influx of calcium. The chemistry of haloalkylamines has been reviewed recently (343).

The depressant effect of very high concentrations (1.1×10^{-5} w/v) of phenoxybenzamine on the K^+ -contractures of rabbit aortic strips first indicated that haloalkylamines can affect vascular smooth muscle in a manner that is not directly related to their action as *alpha*-blocking agents (104). A less pronounced inhibition of the contractile effect of angiotensin has also been observed (104); the inability of other workers (831) to demonstrate this antagonism could have been due to differences in experimental conditions (*e.g.*, pH 7.0). It has been reported that high concentrations of Dibenamine (10^{-4} M) and phenoxybenzamine (10^{-4} M) inhibit the stimulated Ca^{45} influx into rabbit aorta (831) and guinea pig taenia coli (832). The observation reported, that the blocking agents inhibited the contractions of taenia coli but not the increased Ca^{45} uptake stimulated by angiotensin (832), is difficult to reconcile with the assumption that the Ca^{45} influx measured reflects intracellular free calcium ions. The measurements of total tissue calcium content in 12.0 mM Ca^{++} solution (832) may reflect primarily the high calcium content of extracellular fluid and these data, as presented, do not indicate drug effects. Nevertheless, in view of the extensive indirect evidence, interference by haloalkylamines with transmembrane calcium fluxes is a plausible mechanism of their inhibitory action.

Dibenamine in considerably lower concentrations (1.5 to 3.0×10^{-6} w/v) also inhibits the contractures elicited by Ca^{++} and depolarizing concentrations of K^+ in normal and reserpinized vascular smooth muscle (850, 859; see also Part I, sections VI C and F). The rabbit mesenteric vein is more sensitive to this effect of Dibenamine than the main pulmonary artery, and this difference has been related to the different electrophysiological properties (859). The depressant effect of chlorpromazine and of cinnarazine varies inversely with vessel diameter in rabbit mesenteric arteries (357). Lidoflazine, chlorpromazine, and cinnarazine, at a given concentration, also have a more pronounced effect on the canine mesenteric than on the pulmonary artery (I 216a). We have suggested that there is a correlation among the electrical properties of the vascular smooth muscle membrane, its (time-dependent) permeability to Ca^{++} in the depolarized state, and its sensitivity to agents that depress the transmembrane flux of calcium (Part I, section VI C and H; 850, 859). The indirect studies cited bear out these suggestions, but the confirmatory evidence of more direct experiments will be required before they can be accepted. A determination of the effect of haloalkylamines on the Ca^{++}-spikes of *Balanus nubilis* (388) would be of interest.

Other properties of haloalkylamines that may affect certain experimental parameters include the irreversible inhibition of acetyl-cholinesterase (69) and the inactivation of vasopressin (386). Both of these actions were observed in the

absence of intact tissues *in vitro* and the concentrations used for inactivation of vasopressin were extremely high. In general these activities are due to the ethyleniminium ion of Dibenamine (69, 386). Euler and Lishajko (280) found that in adrenergic nerve granules haloalkylamine *alpha*-blockers and also local anesthetic *beta*-blockers inhibited the release and uptake of norepinephrine. Phenoxybenzamine has also been employed to block catecholamine uptake in intact neurovascular preparations (101).

Manganese (0.3 to 3.0 mM) inhibits the contractile responses of vascular smooth muscle to several agonists, and this inhibition is antagonized by elevation of extracellular calcium (874, 876). Hagiwara and Nakajima (388) found that manganese inhibited the Ca^{++}-spikes of barnacles and concluded that a decrease in Ca^{++}-conductance is produced by Mn. The Ca^{++}-channels of this invertebrate, however, were not blocked by procaine (388) and so differed in this respect from those of mammalian smooth muscle (289). Furthermore, the action potentials of the taenia coli generated in Ca^{++}-free solution and probably carried by sodium are also abolished by manganese (362). Therefore, the general applicability to mammalian smooth muscle of the evidence regarding the mechanism of Mn action on the barnacle is open to question. Lanthanum inhibits transmembrane Ca^{++}-fluxes in several systems and depresses the contractile responses of rabbit aortic strips (913a).

The interaction of Mn with neurohypophyseal peptides has been discussed elsewhere (section II B).

XV. TETRODOTOXIN AND BACTERIAL TOXINS

The pharmacology of tetrodotoxin has been reviewed by Kao (I 317). The toxin, obtained from the puffer fish, is an extremely potent neurotoxin that abolishes spike electrogenesis in a number of biological systems. Although tetrodotoxin is generally more effective in abolishing Na-spikes than spikes due to other ion-currents, its action is not ion-selective nor universal, but is directed towards a given membrane channel through which several ions may travel (671). Keatinge (I 326), for example, found that the Na-spikes of sheep carotid arteries were not blocked by tetrodotoxin. Therefore, resistance to tetrodotoxin should not be accepted as sole evidence against Na being the charge carrier in a given system (I 317). In any event, the great variability of action potentials in different vascular smooth muscles and the possibility of early inward currents being carried by several ions (Part I, section VI; 859) suggests that there is not a unique carrier of these spikes.

The indirect vascular effect of tetrodotoxin is vasodilation secondary to removal of neurally-controlled vasomotor tone. This effect has been shown in dog and cat hind-limb (288, I 317, 486, 562), perfused rabbit ear (187), mesenteric vein (445), and pulmonary artery nerve-muscle preparation (874). This indirect, axonal-blocking action of tetrodotoxin resembles some effects of local anesthetic agents (section XIII A), and probably accounts for the major part of its hypotensive effect in intact animals.

Evidence has been presented recently (562) for a direct vasodilator effect of

tetrodotoxin on the canine hind-limb preparation. The vasodilator effect persisted after denervation, reserpinization, *beta*-adrenergic blockade, and atropine. In feline hind-limb, however, tetrodotoxin had no direct effect (288). It would be of interest to know whether the direct effect of tetrodotoxin in the dog is due to inhibition of myogenic spike electrogenesis in resistance vessels. The vasoconstrictor effect of norepinephrine is not inhibited (288, 874) nor are the spontaneous contractions of bovine facial arteries abolished by tetrodotoxin (388).

Endotoxin (*Escherichia coli*) does not contract rabbit aortic strips but potentiates the contractile effect of serotonin (948). Staphylococcal α-toxin elicits a slow, irreversible contracture in rabbit aortic strips (971). In rabbit vena cava the contracture is followed by relaxation, at which time the vessel no longer responds to epinephrine (891). The vascular effects of systemic injections of endotoxin and enterotoxin are influenced by the release of endogenous vasoactive substances (925) that are outside the scope of this review. Anaphylatoxin produces pulmonary vasoconstriction in cats and this effect is not abolished by adrenergic or cholinergic blocking agents (118).

XVI. MISCELLANEOUS VASOACTIVE AGENTS

A. Fluorides, iron, salicylates, intermediate metabolites, nitrite, substance P, and parathormone

Fluorides, in particular SnF_2, produce acute vasodilation in dog hind-leg preparations (109). Sodium salicylate is also a vasodilator and, when used as a solvent, contributes to the reported coronary vasodilator action of Khellin preparations (809, 908). Succinate, other Krebs intermediate metabolites, and acetate dilate the dog fore-limb vasculature (323).

The reported selective celiac vasodilator effect of purified parathormone preparations may indicate vascular activity of the hormone itself, but the possibility of contamination with a vasodilator peptide cannot be ruled out (183, 184). Substance P, a polypeptide isolated from brain and gut, is a potent systemic and pulmonary vasodilator (610). Pancreatic secretogogues (*e.g.*, pancreozymin, secretin) also increase pancreatic blood flow (250).

Ferric ion and ferritin dilate perfused canine mesenteric vessels (190). Sodium nitrite, although generally a vasodilator, produces vasoconstriction in the perfused canine hepatic bed (342) but the possibility of an indirect mechanism of action remains to be explored.

B. Cadmium, mercury, and lead

Cadmium (1.6×10^{-5} M) constricts the perfused vessels of the rat hind-leg (722) but does not contract rabbit aortic strips (723). The contractile responses of rabbit aortic strips to mercury and to epinephrine are antagonized by cadmium (10^{-4} M) whereas the effect of angiotensin is less inhibited (723). Cadmium also induces pathologic changes in testicular and placental vessels, but these may be due to endothelial damage and specific involvement of smooth muscle has not been demonstrated (377, 710).

Lead-cysteamine (10^{-4} M) contracts rabbit aortic strips (374).

XVII. HYDROGEN AND OXYGEN

There is an extensive body of work dealing with local P_{O_2} and pH as possible mediators of circulatory control mechanisms. Some of these studies have been reviewed by others recently (383, I 410), and therefore we shall limit our review of this field to a few illustrative examples. The specialized questions of the influence of pH and P_{O_2} on the ductus arteriosus and the pulmonary vasculature will be treated in separate sections. The effect of pH on the solubility and ATPase activity of contractile proteins has been discussed earlier (Part I, section IV A). More recently Murphy (656a) observed, in a carefully controlled study of the pH dependence of vascular actomyosin, optimum ATPase activity at pH 5.2 and a second, small peak at pH 7.5. The activity of the isolated enzyme is relatively constant between pH 6 and pH 7 (656a). In reference to the following discussion on pH it should be borne in mind that, judging from evidence obtained in other tissues, alterations of extracellular P_{CO_2} produce much greater changes in intracellular pH than those produced by a comparable change in extracellular pH with bicarbonate or hydrochloric acid (929a).

A. pH.

An increase in hydrogen ion concentration has a dual, indirect and direct, effect on the circulation of man, intact animals, and perfused organs. The *indirect* effect is an adrenergically (medullary and neurogenic) mediated *vasoconstriction* (160, 383, 525, 563, 952) and the *direct* effect is *vasodilation* (160, 218, 299, 383, 525, 526, 563, 630). *Beta*-adrenergic blocking agents do not inhibit the vasodilator response to hypercapnic acidosis (525, 952). The vasodilator effect of CO_2 on the nerve-free human umbilical vessels (704) also indicates that this effect is not neurally mediated. The cerebral vasodilator effects of CO_2 have been emphasized and employed clinically (284). Recently, however, it has been reported that intracerebral vessels are constricted by hypercapnia and the dilator response involves predominantly the pial blood vessels (633), and therefore the effect of increased total cerebral blood flow elicited by CO_2 on cerebral oxygenation may have to be reevaluated. Hypocapnia increases the vascular resistance of the limb in dogs, but this effect is detectable only after phenoxybenzamine treatment and is opposite to that observed in man (524).

Isolated femoral artery segments of dogs are dilated when the ambient pH is lowered with CO_2 or other acids from pH 7.4 to 7.1, but similar vasodilation is also elicited by mild (pH 7.5 to 7.68) increase in pH (168). CO_2 also relaxes bovine coronary artery strips (695), and canine mesenteric arteries (766). More marked increases in hydrogen ion concentration (pH 2 to pH 5) produce contractures in mammalian (I 555) and in amphibian (505) vascular smooth muscle.

The vasoconstrictor response to exogenous catecholamines is decreased by acidosis (*e.g.*, pH 7.2) and increased by alkalosis (160, 464, 630, 674, 766). Depression of norepinephrine-induced contractions by acidosis *in vitro* could be demonstrated in rat (896) but not in rabbit (962) aortic strips. Electrically stimulated contractions of canine veins are also inhibited by acidosis (917, 918).

In view of the stimulus parameters used in the latter studies, we would suspect that catecholamine release was the major mechanism mediating the contractions elicited by electrical stimulation and being modulated by pH. Acidosis decreases the neurogenic vasoconstriction of canine mesenteric arteries (766) and pulmonary arteries (this section D). Therefore, it is somewhat surprising that reflex sympathetic (160) and tyramine-induced vasoconstriction (161) are reportedly not inhibited by acidosis. The vasoconstrictor effect of angiotensin in cats is also inhibited by acidosis (160). A decrease in pH also inhibits the activation of striated muscle and hepatic phosphorylase by epinephrine (750), the responses of intestinal smooth muscle to several spasmogenic agents (392, 447, 762), and in general the metabolic effects of catecholamines (758). Acidosis may play a role in the reduction of the vasoconstrictor effect of norepinephrine by tetanization of skeletal muscle (464). There is some evidence that, as least in intestinal smooth muscle, the pH-dependence of histamine action is partly due to the effect of hydrogen ion on histaminase (762).

In reserpine-treated cats hypercapnia potentiates the vasoconstrictor effect of norepinephrine on the hind-limb (675). In view of the ion-dependence of catecholamine storage mechanisms (section IX H) an indirect effect of hydrogen ions on these systems may participate in the alterations of vascular sensitivity to catecholamines.

The effects of pH on the membrane properties of vascular smooth muscle remain to be explored. In other systems marked lowering of pH affects predominantly the Cl-permeability of the membrane, but the direction of change varies among different species (for review see 387).

The multiphasic changes in pH that are associated with vascular smooth muscle contraction have been followed with the glass electrode and are qualitatively similar to those of skeletal muscle (540). A particularly large, late component of acidification elicited during K^+-contractures is due to glycogenolysis and can be dissociated from the contraction with monoiodoacetate (540).

B. Oxygen: general effects

Oxidative metabolism and its relationships to glycolysis and phosphorylation have been considered in Part I of this review (Part I, sections IV B to D). Methods of calculating O_2 diffusion in tissues have been summarized by Forster (307). We shall concern ourselves here with the effects of alterations of P_{O_2} on vascular function and responses to drugs.

Anoxia usually produces, in addition to the indirect effects of sympathetic discharge, local vasodilation in mammalian systemic blood vessels (95, 179, 220, 383, I 410). The indirect, *alpha*-adrenergic effect of systemic hypoxia may oppose the local vasodilator effect (179). An indirect *beta*-adrenergic effect, such as that observed in the canine coronary bed (303) may contribute to anoxic vasodilation. The local vasodilator effect of anoxia on systemic blood vessels of intact animals and perfused extremities may be mediated by local metabolites rather than by the direct action of P_{O_2} on vascular smooth muscle (95, 383, I 410; section X).

Large decreases in P_{O_2} generally produce a modest fall in the resting tone of

isolated systemic vascular smooth muscle preparations (171, 764). Oxygenation of the anoxic perfused rabbit ear and the cat and rat aorta leads to considerable vasoconstriction (845). The ductus arteriosus (this section C) and umbilical and placental vessels (704) are particularly sensitive to the vasoconstrictor effects of oxygen.

Sudden oxygenation of anoxic rabbit aortic strips preconstricted with 20 mM K^+ or drugs produces relaxation or a diphasic response (375). A rise in temperature from 30°C to 37°C abolished the contractile, but not the relaxant, effect of oxygen. At the concentrations of inhibitors tested, cyanide blocked preferentially the relaxation and dinitrophenol the contraction. Phenoxybenzamine and atropine did not influence the effects of O_2.

Acute anoxia may lead to modest decrease of the contractile response to drugs, but the majority of studies agree that glycolysis can support contraction for several hours (I 125, I 200–202, 507, I 375, 830; Part I, sections IV B to D). The response of anoxic strips of rabbit aorta (supported by glucose in the medium) is significantly depressed when epinephrine (238, I 201, 830) but not when K^+ is the stimulating agent (830). The rapid (4 min) relaxation by anoxia of aortic strips partially contracted with epinephrine (1.0 to 3.0 $\times$ 10^{-9} w/v) and the recovery of the response to epinephrine after *prolonged* anoxia are interesting recent findings (238, 239). We cannot fully agree with the authors' conclusion that the rapid anoxic vasodilation is due to depletion of high-energy substrates. The large energy reserves and glycolytic potential (but *c.f.* 238) of vascular smooth muscle relative to the metabolic cost of maintaining contraction (Part I, sections VI B to D) are difficult to reconcile with the proposition that a few minutes of anoxic exposure can deplete ATP below the levels required for maintaining a considerably less than maximal contraction. The vasodilator effect of catecholamines observed after prolonged hypoxia, in glucose-containing media, is blocked by dichloroisoproterenol (446). It would be of interest to determine whether the immediate effect of anoxia on epinephrine-induced contractions is also influenced by *beta*-blockers. We have discussed previously (Part I, section IV C, p. 224) the longer persistence of the response to potassium and to histamine, than to epinephrine (I 370, I 373), during severe substrate-depletion (anoxic, glucose-free) of bovine mesenteric arteries.

The extent of glycolytic energy utilization during anaerobiosis may be influenced by the choice of buffers used. In cardiac muscle glucose supports metabolic needs (ATP levels, contractility, and membrane potential) more readily when bicarbonate, rather than phosphate, is used to buffer the medium (516).

Vasodilation of perfused skeletal muscle by modest increases (from 3 to 8 mM) of potassium (see also Part I, section VI A) is accentuated when hyperkalemia is combined with anoxia (842). As indicated earlier, it is also possible that in experiments with whole, perfused extremities, anoxic vasodilation itself is indirectly mediated.

Haugaard (404) recently reviewed the general problem of oxygen toxicity and its vascular effects. Most prominent among the latter is retinal artery constriction leading to retrolental fibroplasia (788) and the cerebral vasoconstrictor effect of hyperbaric oxygen (462).

Chronic hypoxia enhances the development of atherosclerosis in cholesterol-fed rabbits (510).

C. Ductus arteriosus: responses to oxygen and neurotransmitters

Selective vasoconstriction induced by the postnatal rise in P_{O_2} has been considered by a number of workers to be the physiologic mechanism of closure of the ductus arteriosus. Born *et al.* (131) described the constrictor effect of O_2 on the ductus of lambs *in situ*, and found that the sensitivity of the vessel to O_2 disappeared after a few hours' postnatal closure. The same authors also noted an asphyxial constriction of the ductus, and attributed it to circulating catecholamines, but others (846) considered it to be due to the hemodynamic effects of asphyxia.

Observations on the ductus arteriosus *in vitro* confirmed the constrictor effect of oxygen. Kovalčík (531) found that the ductus of lambs and guinea pigs was contracted by oxygen and relaxed by carbon dioxide. The responsiveness to O_2 persisted for about 5 hr, required calcium, and was not blocked by Dibenamine, atropine, or antihistamines. In glucose-free media O_2 did not produce vasoconstriction; dinitrophenol (reversibly) and iodoacetate (irreversibly) also abolished the response to oxygen. NaCN (1 to 20 mM) merely slowed but did not abolish O_2-stimulated ductal constriction, although it decreased O_2 consumption below measurable levels. Chlorpromazine (0.1 mM) blocked the effect of O_2 and Kovalčík (531) suggested that the constrictor effect involved a flavoprotein enzyme that was not inhibited by cyanide.

Species-specific variations in the sensitivity of the ductus and adjacent vessels to O_2 have been reported by Gillman and Burton (347). Piglets were more sensitive to O_2 than kittens and rabbits. A surprising finding of this study was the absence of the vasoconstrictor effect of O_2 on the ductus of dogs. Although ductal smooth muscle in certain mammals is constricted by catecholamines and acetylcholine (131, 347, 531, 846), the ductus of chickens is insensitive to these agents (395). If O_2 is the major agent responsible for closure of the ductus in most mammals including man (655) and in birds, then the insensitivity of canine ductus (347), if verified *in situ*, would represent a drastic evolutionary departure. The sensitivity of the preductal region of the aorta to O_2-induced vasoconstriction also varies among different species and has been suggested to play a role in preductal coarctation of the aorta (347).

D. Pulmonary vascular effects of changes in pH and P_{O_2}

The extraordinary interest of physiologists in the responses of the pulmonary circulation to hypoxia and acidosis is attested to by a voluminous literature of the subject. Comprehensive reviews of the earlier literature have been presented by Aviado (50) and Fishman (298). The present review will be concerned with local effects of pH and P_{O_2} on pulmonary blood vessels, and relies primarily on studies of isolated lungs and vascular strips. It is recognized that, in the intact animal, anoxia may also produce reflex pulmonary vasoconstriction *via* chemoreceptor stimulation (50, 207a). The neurogenic component of the asphyxial response of lambs increases with maturation (162). In considering the mechanism

of hypoxic pulmonary vasoconstriction the reader should also bear in mind that the responsiveness of pulmonary vessels to hypoxia is species-dependent and varies with experimental conditions (see below). Although attempts to find a unitary mechanism of hypoxic pulmonary vasoconstriction are laudable, a multifactorial mechanism (59) appears more likely.

Recognition of certain experimental variables that influence the sensitivity of isolated lung lobes to hypoxia explains some of the difficulties encountered by earlier workers in obtaining reproducible results. Lloyd (365, 571, 573) found that the response of isolated canine lung lobes to hypoxia (5.8% O_2) initially increased with time, but disappeared after about 1 hr of perfusion, although drugs at this time still continued to elicit pulmonary vasoconstriction. Daly *et al.* (208) found that high temperatures (38 to 39°C) accentuated the pulmonary pressor response to hypoxia. Cooling to 26°C eliminates the hypoxic response of canine lungs, but interestingly, storage at low temperatures (25 to 30°C) prolongs the postexcision interval during which the preparation remains sensitive to hypoxic vasoconstriction (573). The reactivity of perfused rat lungs is similarly influenced by perfusion time and temperature (405).

Acidosis markedly potentiates, and alkalosis inhibits or abolishes the pulmonary pressor response to hypoxia (365, 397, 572, 782, 836, 926). The potentiation of hypoxia by acidosis can be produced either by intra-arterial lactic and hydrochloric acid or by hypercapnic respiration (397, 572, 782, 836). The effectiveness of intra-arterial acidosis suggests that vascular smooth muscle, rather than perivascular tissue, is the site of hydrogen ion interaction with hypoxia.

Acidosis can elicit pulmonary vasoconstriction even in the presence of normal (20%) or elevated concentrations of O_2 in the ventilating mixture (58, 90, 449, 926). A formula predicting the interaction between pH and P_{O_2} on pulmonary artery pressure has been derived by Gomez (cited in 397). The initial response of isolated pulmonary artery strips to CO_2 is a slight relaxation (I 555, 575). Since this preparation has minimal resting tone, the possibility cannot be excluded that CO_2 would have a more pronounced dilator effect on preconstricted strips. Prolonged exposure to 100% CO_2 and the attendant marked ($pH < 6.0$) acidosis (I 555) leads to constriction of pulmonary artery strips (I 555) and perfused intrapulmonary blood vessels (787).

The major site of hypoxic vasoconstriction appears to be the arterial (precapillary) section of the pulmonary circulation (90, 490, 571, 653, I 513, but *cf.* 96).

The local mechanism of hypoxic pulmonary hypertension has been subject to considerable debate (for reviews see 50, 298, 405). The two major possibilities considered have been: first, an indirect action mediated through hypoxic release of a local vasoconstrictor metabolite, and second, a direct vasoconstrictor action of hypoxia on pulmonary vascular smooth muscle.

The greater pulmonary vasoconstrictor activity of alveolar, as contrasted with arterial, hypoxia ($P_{O_2} < 60$ mM Hg) (90, 571) and the inability to elicit hypoxic contraction in pulmonary vascular strips free of lung parenchyma (575) are the major findings favoring an indirect mechanism of hypoxic pulmonary

vasoconstriction. Catecholamines and, more recently, histamine have been suggested as possible mediators of indirect vasoconstriction. These suggestions generally derive their support from studies with blocking and amine-depleting agents.

Alpha-adrenergic blocking agents in low concentrations generally do not abolish, although they may blunt, hypoxic pulmonary vasoconstriction in dogs (208, 571, 573, 892), cats (59, 260), rats (405), or calves (835). In higher concentrations *alpha*-adrenergic blocking agents can inhibit hypoxic vasoconstriction in cats (59) and fetal lambs (174). The blocking effect may be due to a nonspecific depressant action of Dibenamine (163; section XIV) or to an opposing, *beta*-adrenergic vasodilator action of circulating catecholamines unmasked by the *alpha*-adrenergic blocking agent in recirculated preparations (573). The latter possibility is also supported by the potentiation of hypoxic vasoconstriction by propranolol (59, 892). Other arguments raised by Lloyd (573) against adrenergic mediation of the local vasoconstrictor action of hypoxia were the dissociation of neurogenic from hypoxic vasoconstriction by nerve block, alkalosis, and profound hypoxia. Acute asphyxia also elicits pulmonary vasoconstriction in chickens (159) although only the large (855) but not the small (853) pulmonary arteries of this species are constricted by norepinephrine.

Antihistamines inhibit and histaminase inhibitors potentiate the hypoxic pulmonary pressor response of rats, and this response can also be eliminated *in vitro*, but not *in vivo*, by the histamine-depleting agent 48/80 (405). According to a preliminary note by Duke (261), the hypoxic pressor response of feline lungs is not affected by an antihistamine or a histaminase inhibitor. It should also be noted that the nonspecific activity of antihistamines (section VIII), the relatively low sensitivity of rat pulmonary vasculature to histamines, and the lack of effect of 48/80 administered *in vivo* (405) preclude a definitive conclusion of histaminergic mediation of hypoxic pulmonary vasoconstriction in the rat.

Favoring the indirect mechanism of hypoxic vasoconstriction is the recent observation (576) that when the periarterial tissue is not removed from rabbit pulmonary artery strips the combined parenchymal-arterial preparation is contracted by hypoxia. These observations were made in the presence of procaine, an agent that potentiates the hypoxic pressor response of perfused canine lungs (574). It would be of interest to determine whether parenchymal-pulmonary artery strips of other species that are more sensitive to the pulmonary pressor effects of hypoxia behave like those of rabbits, a species considered (405) rather insensitive to this stimulus. The pulmonary circulation of calves is particularly sensitive to hypoxia (539, 836).

A direct mechanism of action of hypoxia on the pulmonary circulation is supported primarily by a single study *in vitro* (91). In this work the gain in Na and loss of K^+ were followed in pulmonary and systemic vascular smooth muscle, skeletal muscle, and visceral muscle. The authors interpreted their findings to indicate selective Na gain and K^+ loss from pulmonary arterial preparations, but not from others, and calculated that the resultant fall in K^+ equilibrium potential (E_K) would produce sufficient depolarization to contract pulmonary vascular

smooth muscle. We have reservations about accepting the conclusions of this work for the following reasons. The arterial preparations were stripped of adventitia, a procedure known to affect vascular electrolyte content (Part I, section VI A). The extent of adventitial stripping would vary in different preparations and hence may account for the variations reported. The hypoxic experiments were conducted after 90 min of incubation in salt solution, a time interval during which the hypoxic pressor response of perfused lung lobes is lost (see above). No temporal correlation was established between K^+ loss, measured after half hour incubation in hypoxic media, and the rapid onset of hypoxic pulmonary vasoconstrictor response; furthermore, as indicated earlier, pulmonary arterial strips of the size used in this study do not contract when hypoxic. The selective effect of hypoxia on pulmonary, but not on systemic, vascular smooth muscle is not fully substantiated by the data presented (table I in 91) that indicate the trend, common to many aerobic tissues, of K^+ loss and Na gain in hypoxic systemic arteries. The calculation of E_K by these authors (fig. 6 in 91) appears to be based on total tissue potassium, rather than intracellular potassium, and so leads to erroneous values. The ability of high K^+ to increase the hypoxic pulmonary pressor response cannot be accepted as evidence of a direct action of hypoxia on pulmonary vascular smooth muscle. Hyperkalemia also potentiates the contractile response of vascular smooth muscle, including pulmonary vascular smooth muscle (416, 575), to a number of exogenous vasoconstrictors, and thus it could also be expected to potentiate an endogenous substance released by hypoxia. In summary, we conclude that a direct pulmonary vasoconstrictor effect of hypoxia, if it exists, remains to be demonstrated.

Chronic hypoxia produces pulmonary hypertension in mammals (659, 944, 960) and birds (159). *Alpha*-methyl dopa inhibits the pulmonary vascular hypertrophic response to hypoxia in mice (659). Very severe hypoxia (anoxia) leads to pulmonary vasodilation (571).

Hyperbaric (910) and isobaric (204) hyperoxygenation produce pulmonary vasoconstriction. Recirculation of blood through the body prevents the pulmonary pressor response of dogs to oxygen (204).

XVII. ELECTRICAL STIMULATION: DIRECT AND INDIRECT EFFECTS

It has been pointed out by Furchgott (I 200) that the response of vascular strips to electrical stimulation may consist of two components: one due to a direct effect on smooth muscle, the other to catecholamines released from vascular stores. We shall limit the following discussion mainly to experiments involving mass-stimulation of entire vascular segments, thus excluding several interesting studies of vascular nerve-muscle preparations and of perfused vascular beds stimulated *via* their innervation.

Indirect stimulation of vascular segments is particularly favored by relatively low voltage repetitive pulses of short duration (usually 0.5 to 2.0 msec) (228, 445, 631, 712, 875, 919, 921). The adrenergic mediation of this type of electrical stimulus is indicated by elimination of the vasoconstrictor response by *alpha*-adrenergic blocking agents (228, 445, 919), reserpinization (445, 919), guane-

thidine or bretylium (228, 445, 631, 712, 919), local anesthetics, or tetrodotoxin (445, 712). Veratrine potentiates the effects of indirect stimulation, presumably by inducing repetitive firing of the stimulated adrenergic nerves (445). Su and Bevan (875) found, during field-stimulation, an increased radioisotope efflux from rabbit main pulmonary arteries loaded with H^3-norepinephrine, and De La Lande *et al.* (228) demonstrated small amounts of a biologically active (gut-relaxant) compound released from stimulated rabbit ear arteries. The response to indirect stimulation with short pulses is frequency-dependent (445, 631, 712, 919, 921), resembling in this as in other respects the effects of stimulating the isolated adrenergic nerves (*e.g.*, 100, 564, 894, I 410). In spontaneously rhythmic vascular beds the excitability to indirect stimulation varies with the period of spontaneous rhythm (821). The Ca^{++}-dependence of indirect stimulation (920) may be due to both the Ca^{++}-requirements of adrenergic release mechanisms (section IX A) and those of vascular smooth muscle (Part I, section VI C).

A relaxation of rabbit portal veins by low frequency (15 to 30/min) transmural stimulation with pulses of 0.5 to 1 msec duration has been observed by Hughes and Vane (445). This effect appeared to be due to neurogenic inhibition by a nonadrenergic transmitter, since it was abolished by local anesthetics and by tetrodotoxin, but not by adrenergic-neurone blocking agents or *beta*-blockers. Veratrine potentiated the electrically evoked relaxation. Anticholinergic, antihistamine, or serotonin blocking agents did not inhibit the relaxant effect. The authors discussed the possibility of a relationship between their observation and the nonadrenergic intestinal inhibitory innervation reported by several groups (for references see 445), and suggested adenine nucleotides as the possible inhibitory transmitters.

Sinusoidal stimulation of innervated vascular strips at 60 Hz elicits a contraction with a considerable indirect component that can be eliminated by reserpinization or *alpha*-adrenergic blocking agents (979, I 200). A delayed contractile component, has also been noted (I 551) in electrically-stimulated nerve-free human umbilical vessels. The mechanisms responsible for the late component of electrically-stimulated contractions are clearly different in the rabbit aorta and in the human umbilical vessels.

The effectiveness of sinusoidal field stimulation varies with the frequency and the strength of stimulation (852, I 551, I 557). The relative proportion of the indirect, neurally-mediated component varies with frequency and is rather large with the commonly employed 60 Hz stimuli (fig. 2 in 852). Stimulation with short pulses, discussed earlier, is also particularly effective at frequencies above 1/sec and readily blocked by phentolamine, whereas lower frequency stimuli seem less readily inhibited by *alpha*-blockade (fig. 5 in 919). The frequency-dependence of vascular smooth muscle response to electrical stimulation is not limited to the neurally-mediated effects, but is also observed with nerve-free umbilical vessels (I 557). The fall-off in contractile response at high (1000 Hz) frequencies (I 551, I 557) is probably due to capacitative shunting of transmembrane current and consequently smaller changes in membrane potential, in the manner directly demonstrated by Abe and Tomita (5) in taenia coli. The relatively high

frequency (100 to 500 Hz) required for optimal stimulation of umbilical vessels remains to be explained.

Direct current (d.c.) stimulation of vascular smooth muscle elicits contractions that increase gradually with stimulus strength (I 557). The maintained contraction elicited in rabbit main pulmonary arteries by strong d.c. stimuli (I 556, I 557) resembling the catch mechanism of molluscs (I 250, I 252, 783) has been discussed previously (Part I, sections IV A and VI H) We have also indicated that, for a given current strength, pulses of duration sufficient to stimulate spike-generating smooth muscle may be shorter than for gradedly-responsive vascular smooth muscle (Part I, section VI F).

Intracellular stimulation of rabbit main pulmonary arteries, with depolarizing currents delivered through the recording microelectrodes, did not elicit action potentials from these fibers (859). Although these findings tend to support the view that this type of vascular smooth muscle usually does not generate action potentials, intracellular depolarization is a notoriously unsatisfactory method to evoke action potentials even from fibers known to generate spikes when stimulated extracellularly (*e.g.*, 77). We have on one occasion unsuccessfully stimulated, with intracellular current, a rabbit coronary vein, only to record subsequently a burst of spontaneous spike activity from the same fiber. On the other hand, intracellular hyperpolarizing currents injected during spontaneous spike electrogenesis (guinea pig mesenteric vein) characteristically increase the action potential amplitude and rate of depolarization (859).

XIX. TEMPERATURE AND LIGHT

Changes in temperature can directly affect the contractile state of vascular smooth muscle and can also modify its responsiveness to vasoactive agents. The reflex effects of distal, as opposed to local, warming are outside the scope of this review.

Acute reduction of the temperature from 37°C generally results in vasoconstriction (301, 354, 381, 499, 766, 941) followed in intact animals and man by a cold vasodilation (301). Cold vasoconstriction *in situ* can be diminished by phentolamine (381, 499) and by acute sympathectomy (381, 941). In contrast to the contractile effect of cold on resting vascular smooth muscle, arterial strips contracted by epinephrine at 37°C are slightly relaxed after sudden cooling to 6.5°C (494). Spontaneously active bovine mesenteric veins are relaxed and the respective arteries contracted when cooled from 36°C to 25°C (765).

The vasoconstrictor response to drugs varies with ambient temperature. Among different types of blood vessels there are considerable variations of the temperature at which the contractile response is maximal, and of the lower limit of cooling below which vascular smooth muscle no longer responds to drugs. Superficial vessels normally exposed to environmental cooling continue to respond to drugs at lower temperatures than the deep-running arteries. The vasoconstrictor response of rabbit femoral arteries to norepinephrine decreases linearly below 37°C, whereas that of the rabbit ear artery passes through a temperature optimum at 24°C and persists until about 7°C is reached (354). The flipper

arteries of the seal are constricted by epinephrine at temperatures down to 1°C, whereas the internal arteries do not respond below 15°C (470). The rabbit aorta is most sensitive to epinephrine between 25°C and 30°C (99) and fails to respond to (submaximal) norepinephrine at 15°C (146). The bovine ulnar artery loses its responsiveness to epinephrine at about 12.5°C (494), whereas the rat tail artery maintains a reduced response to drugs even at 2°C (320). Reduction of the responses to norepinephrine by cooling has also been observed in man and intact animals (301, 336). The response of canine mesenteric arteries (766) and lateral saphenous veins to nerve stimulation and to exogenous norepinephrine is, however, greater at, respectively, 27°C and 17°C than at higher temperatures (922, 941). It should be noted that the optimal frequency of adrenergic nerve stimulation is also temperature-dependent (164) and this may confound results obtained with fixed frequency stimulation at different temperatures. Inhibition of catecholamine uptake by cocaine does not abolish the potentiating effect of cooling (940). The diminished rate of relaxation observed after cooling (301, 320, 941) would tend to oppose somewhat the effects of diminished vasoconstrictor response. The hypoxic pressor response of the pulmonary circulation is also temperature-dependent (section XVII D). The relaxant effect of glyceryl trinitrate on aortic strips is also reduced at lower temperatures (581).

The major question regarding the loss of the vasoconstrictor response to drugs at low temperatures is whether "cold-inhibition" is due to an inhibitory effect on the membrane or on the contractile proteins. The finding of Bohr *et al.* (fig. 1 C in I 66) that hog carotid artery actomyosin ATPase retains considerable activity at 0°C (pH 7.4), if applicable to other vascular smooth muscles, suggests that cold-inhibition of vasoconstrictor effects is not due to direct depression of the contractile protein. This assumption is further supported by Keatinge's observation (fig. 6 in 494) that the tension of already contracted vascular smooth muscle is maintained for a prolonged interval (12 min) after it has been cooled to a temperature at which it would not respond to added drugs. It is most likely, in our opinion, that the primary rate-limiting factor during cooling is the decreased response of the membrane to excitatory agents. This mechanism is also suggested by the absence of the depolarizing, as well as the contractile, effect of drugs on sheep carotid arteries at low temperatures (I 323). This failure of the depolarizing effect of drugs is not due to cold-induced depolarization (I 323), since (Part I, VI H), vascular smooth muscle is contracted by drugs even when completely depolarized. Cooling uncouples the depolarizing effect of potassium, which persists, from the normally ensuing contraction, which is abolished (I 323). In terms of the model adopted in this review (section XXII), the most probable mechanism responsible for cold-inhibition is an inability of excitatory agents at low temperatures to increase the permeability of the membrane to calcium. It would be futile to carry speculation further by questioning whether the affinity or the intrinsic activity of drugs is primarily affected by cooling, or whether the Ca^{++}-permeability of "cold membranes" is inherently so low that it cannot be sufficiently increased by excitation. It has also been suggested that at low pH levels the effects of temperature on actomyosin may become more pronounced

and contribute to thermal effects on vascular smooth muscle contraction (I 323). Complete recovery of the contractile response after cooling requires about 2 hr at 37°C (320, 494). Of course, the immediate and the delayed phases of recovery need not be due to the same process.

The contractile response of the rabbit aorta to potassium is decreased after prolonged (7 days) cold storage (829, 923). Recovery of the rabbit ear's vascular response to norepinephrine, after freezing to −10°C, has been reported (746). Cold storage appears to influence the membrane electrical properties of the normally electrically silent aorta in making it generate action potentials after storage (720). The effects of cold storage on adrenergic nerves are discussed elsewhere (section IX B).

In sucrose-gap studies of rabbit mesenteric veins and pulmonary arteries we found (I 557) a net depolarization of over 7 mV when the strips were warmed from 25°C to 35–37°C. The depolarization was sometimes preceeded by a slight hyperpolarizing phase. Sheep carotid arteries are only hyperpolarized when warmed from 5°C to 35°C (I 323). Thermal oscillations, in our experiments, were accompanied by similar oscillations of tension and of membrane potential.

Changes in temperature may affect, in addition to the constant field potential (196), both an electrogenic ion pump (216, 498, 850) and the permeability coefficient of the smooth muscle membrane (485). It would be premature to speculate about the relative contribution of these factors to temperature-induced changes in vascular smooth muscle membrane potentials. It is clear, however, that depolarization upon warming cannot be due to the temperature-dependence of the Nernst potential, which would predict an opposite, hyperpolarizing effect. Friedman *et al.* (320a) found that, during warming of the rat tail artery, the extrusion of sodium and the related uptake of potassium (Part I section VI A) was greater in unstretched than in longitudinally stretched preparations.

The greater thermostability of vascular than of skeletal myosin has been mentioned (Part I, section IV A). According to Hamoir and Gaspar-Godfroid (I 245), thermal inactivation of vascular actomyosin ATPase activity, if ATP is present during heating, begins at 40°C and is complete at 60°C. In view of this observation it would seem difficult to separate the effects of high temperature on receptors from those exerted on the contractile proteins. The effect of high temperatures (53.5°C) on the passive elastic properties of blood vessels is markedly influenced by thermal effects on collagen and elastin (504) but the contribution of smooth muscle is difficult to evaluate from this study of longitudinal strips of frog vessels.

In spontaneously active bat veins the frequency of spontaneous contractions increases with warming, and the Q_{10} (3.1 to 4.7) of this process is high (958). The frequency of action potentials triggering the contractions would also be expected to increase under these conditions, and this has been verified in spontaneously active rabbit mesenteric vein (I 557) and turtle vascular strip (763) preparations.

Cutaneous vascularization in growing piglets is more extensive in littermates raised at high ambient temperatures than in those raised in a cool environment (456).

Light-activated relaxation of vascular smooth muscle has been studied by Furchgott *et al.* (329) and these studies were extended to visceral smooth muscle (267, 327). Relaxation of rabbit aortic strips is maximal at a wavelength of 450 mμ and below; it is facilitated by anaerobiosis and is more pronounced at 25°C than at 37°C (329). Interestingly, drug-induced contractions are more readily relaxed by light than K^+-contractures (329). A detailed discussion of photorelaxation will be found in a recent paper by Furchgott (327). Ultraviolet-induced contractures can also be induced in vascular strips but only after photosensitization with acridine orange (I 557, 858).

XX. OSMOTIC EFFECTS

The peripheral vasodilator action of hypertonic solutions (199, 743, 861) and the possible role of plasma hyperosmolarity in exercise hyperemia (635) have been reviewed recently (I 410). The systemic vasodilator effect persists after denervation (635, 861), ganglionic blockade, or antihistamine treatment (743). An interesting observation of possible physiologic significance, in terms of renal effect of osmotic loads, is the inhibition of the renal vasoconstrictor responses to angiotensin by hypertonic mannitol (532).

The pulmonary vascular pressure, unlike the systemic, rises in response to hypertonic solutions. The pulmonary pressor response is not blocked by phentolamine or atropine (268) and is thought to be due to constriction of both pulmonary arteries and pulmonary veins (269). Other workers, however, suggested red cell agglutination as the mechanism of hypertonic pulmonary vasoconstriction (743, 822).

The cellular effects of hyperosmolarity have been studied by Johansson *et al.* (470a, 471, 635) and include, in spike-generating vascular smooth muscle, inhibition of spike electrogenesis and impaired intercellular conduction (I 312). The inhibition of spike activity can probably be accounted for by the hyperpolarization due to cell shrinkage that increases intracellular K^+ and hence E_K (138, 471). The impairment of conduction by hypertonic solutions is thought to be due to interruption of intercellular nexuses (I 42, I 312) but hyperpolarization could also contribute to this effect. The distribution of various solutes, and their effects on tissue water, are consistent with the suggestion that the near perfect osmotic response of rat portal veins to hypertonic solutions leads to changes in cell volume that result in electromechanical inhibition (42). Hypo-osmolarity stimulates the electrical and mechanical activity of rat portal veins, but this effect is markedly reduced if the sodium concentration of the medium is low (474a, 474b).

Canine aortic strips, in contrast to rat portal veins, are contracted by twice normal NaCl concentrations and, to a lesser extent, by hypertonic glucose (976). It is uncertain whether these and our similar observations on rabbit and canine pulmonary arteries (858) can be fully accounted for by osmotic shrinkage rather than active contraction. Rat aortic strips are not contracted by similarly hyperosmotic NaCl (976). The responses of the rat portal vein to osmotic changes may not represent the entire repertory of osmometric properties in other types of vascular smooth muscle.

XXI. REACTIONS OF BLOOD VESSELS OF HYPERTENSIVE ANIMALS

Morphological changes including hypertrophy of vascular smooth muscle in hypertensive animals have been described (Part I, section III D), but they probably represent secondary changes evoked by the rise in blood pressure. Similarly, changes in vascular electrolyte content observed in experimental hypertension (210, 253, 286, 314, 319, 424, 474, 520, 659a, 895, 897, 961) may be secondary to, rather than the cause of the rise in blood pressure. The increase in Na, Cl, and water content of the aorta in the hypertensive proximal, but not in the hypotensive distal, segment of an experimental coarctation indicates that a high distending pressure can elicit the changes associated with other types of experimental hypertension (424). Conversely, little change in electrolytes was found in the aortas of genetically hypertensive rats (632, 725a). The observed increases in vascular electrolyte content may also reflect alterations in the ion-binding properties of the extracellular matrix rather than intracellular concentrations (I 106, 319, 424). Much of the earlier work in this field was based on an assumption, not substantiated by recent studies (Part I, section VI A) that monovalent cations are major determinants of vascular smooth muscle contractility. The concentration of the ion more intimately involved with regulation of contraction, calcium, is reported to be unchanged (71, 253) or slightly increased (895) in fresh blood vessels of hypertensive animals. The significance of small increases (897) is uncertain. In future studies it may be desirable to determine plasma phosphate (Part I, section VI C) and calcium in conjunction with studies on blood vessels, particularly when dealing with renal hypertension, which may be associated with hyperphosphatemia. The fairly marked increase in calcium content of perfused hypertensive arteries (421) will be discussed subsequently.

The major question regarding the functional properties of hypertensive blood vessels is whether they are hyper-reactive (55, 66, 67, 166, 207, 219, 233, 256, 335, 364, 383a, 420, 421, 430, 431, 550, 607, 632, 636, 690, 725, 839, 862, 887, 902) or not (333, 598, 744, 819, 965) to excitatory stimuli. Critical evaluation of some of these studies, particularly those limited to blood pressure measurements, is difficult. Furthermore, experimental hypertension induced by a variety of methods and in different stages of chronicity is not a single entity nor a particularly suitable model of human essential hypertension. Subject to these reservations, the majority of studies is consistent with a relatively nonspecific hyper-reactivity of hypertensive blood vessels. The secondary question regarding this abnormal vascular function is whether it is a mechanical consequence of the structural changes in hypertensive vessels or whether it, indeed, represents an increased sensitivity to excitatory agents (or decreased activity of relaxing system) in vascular smooth muscle.

Increased wall-thickness and decreased lumen may lead to an "apparent" increase, due to mechanical factors, in the responsiveness of blood vessels to fixed concentrations of vasoconstrictors (55, 302, 335, 744, 839), although somewhat similar structural changes when due to Raynaud's disease do not produce vascular hyper-responsiveness (636). The contribution of structural changes

caused by well established (839) hypertension to the hyper-responsiveness of blood vessels studied *in situ*, does not account for hyper-reactivity of aortic strips (364). Furthermore, certain strains of rat that are sensitive to the experimental induction of hypertension exhibit exaggerated responses to pressor agents even when maintained normotensive on a low salt diet (207). Delayed relaxation of perfused arteries of hypertensive animals (420) is also not readily explained on the basis of structural changes alone. Our impression of the literature surveyed (see also 256, 550) is that genetic (human essential and rat) hypertension is associated with a true vascular hyper-reactivity. It may be worth while to consider the possibility that certain forms of hypertension are in fact due to a primary disease of vascular smooth muscle, rather than to excessive vasoconstrictor stimuli.

In terms of the model of major excitation-contraction coupling mechanism in vascular smooth muscle advocated by us (section XXII, and Part I, section VI), an abnormal increase in Ca^{++}-permeability or a decreased activity of the relaxing system of vascular smooth muscle would account for hypertensive hyper-reactivity. It would be of interest to compare the duration of K^{+}-contractures and the sensitivity to added Ca^{++} (850, 859) in strips of small arteries from genetic hypertensives and normotensives. The arteries of nephrectomized, salt and steroid-loaded rats have an enlarged labile calcium pool after perfusion with Krebs' solution containing a relatively high (2.1 mM) concentration of calcium (421). In the absence of calcium determinations on fresh, nonperfused vessels, it is uncertain whether this pool represents uptake, and if so, into what tissue compartment. In the same study, Hinke (421) also found that the dose-response curve of calcium-depleted vessels to added Ca^{++} was shifted to the left in hypertensive animals and considered an enlarged labile Ca^{++} pool or changes in contractile proteins as possible mechanisms of hyper-reactivity. Our interpretation of his data differs and we would regard his observations as possible evidence of increased membrane permeability to calcium or decreased activity of the relaxing system of vascular smooth muscle in the hypertensive animals. The earlier implication of altered contractile proteins in hypertension (982) was based on the assumption that two contractile protein systems, tonic and phasic, operate in vascular smooth muscle, but this assumption has been largely disproved by recent studies (Part I, section IV A).

The decreased sensitivity to the pressor effects of angiotensin associated with increased circulating renin concentrations in certain patients with renovascular hypertension and its possible diagnostic applications (649, 688, 819, 898) have been discussed earlier (section I B). It should be noted, however, that in experimental renal hypertension an increased sensitivity of perfused limbs to angiotensin, as well as to other vasoconstrictors, has been reported (66, 233, 607, 902).

XXII. GENERAL MECHANISMS OF DRUG ACTION ON CONTRACTILITY AND MEMBRANE PERMEABILITY

In this section on general drug mechanisms we shall attempt to consider the physiology and the pharmacology of smooth muscle within a consistent frame-

work, identifying the cellular events that may be acted upon by drugs producing vasoconstriction and vasodilation. We have adopted a particular model of excitation-contraction coupling based on permeability changes of the plasma membrane (see also Part I, section VI H and I 150, I 295, I 470, I 520) that, although not proved in its details, is supported by considerable evidence and, more important, can be readily tested by further direct experiments.

The major assumptions inherent in the model are that: a) excitatory drugs act primarily by a common mechanism of increasing the ion-permeability of the vascular smooth muscle plasma membrane; b) the quantitatively most important, though perhaps not the only, source of activator calcium mediating drug-induced contractures is a site external to the plasma membrane; and c) the primary determinant of contraction (or relaxation) is the rise (or fall) of intracellular free calcium ion concentration (see also Part I, section VI). This last assumption does not exclude the possibility of secondary regulatory mechanisms that may alter the actomyosin-ATP interaction at constant Ca^{++} levels (see below).

Possible pathways of excitation-contraction and inhibition-relaxation coupling are outlined in figure 1. The possibility that ionized calcium may not be the sole modulator of contractile activity is indicated. This is merely an informal restatement of the well-known biochemical observation that actomyosin ATPase activity, at a given Ca^{++}-concentration, can vary as the function of other variables (for example pH, temperature, Mg, phosphates). Whether drugs can produce vasoconstriction or vasodilation through these variables and without affecting intracellular Ca^{++}-ion concentration is completely unknown, but the possibility must be admitted on theoretical grounds. This somewhat unorthodox possibility, reminiscent of earlier ideas about soluble relaxing factors of striated muscles, is mentioned in view of some recent studies that failed to demonstrate the expected effect of certain smooth muscle relaxants on transmembrane calcium exchange (see below and section XIII A).

The strongest argument for a mechanism of excitatory drug action based on membrane permeability is that the effects of drugs on the plasma membrane have been unequivocally demonstrated. That excitatory drugs increase the ion

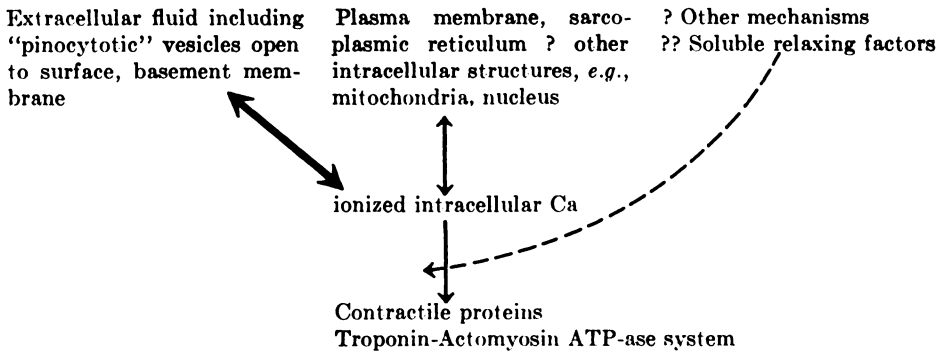

FIG. 1

TABLE 1

Evidence for pharmacomechanical coupling in polarized smooth muscle

1. The same blocking and potentiating agents are effective in polarized and in depolarized smooth muscle (I 166, I 560, I 611).
2. Depolarization by drugs may be less but the maximal contraction greater than the respective effects of high potassium solutions (I 557, 859).
3. The differences in the maximal contractile effects of different agonists are maintained after depolarization (I 557, 852).
4. Drug-induced contractions may be sustained in smooth muscles whose response to depolarization by high potassium is a transient, phasic contracture (852).
5. Relaxing agents can relax *polarized* smooth muscles without evidence of hyperpolarization (242).
6. Dissociation of the electrical and the contractile effects of drugs is readily seen in polarized smooth muscle (I 124, I 557, 851).

permeability of the smooth muscle membrane to ions is indicated by measurements of both radioisotope fluxes and membrane potentials (section VI and Part I, sections VI A, C, and E). Recent evidence also indicates that there is at least a semiquantitative correlation between the maximal contraction and the maximal permeability change produced by a given drug. For example the maximal serotonin-induced contractions of rabbit portal-mesenteric vein strips are only 30 to 40% of those produced by norepinephrine, and the maximal depolarization produced by serotonin is also less than that produced by norepinephrine (859). Similarly, both the depolarizing and the contractile effects of angiotensin on the rabbit aorta and the canine pulmonary and renal arteries are less than those of norepinephrine (851). Unequal contraction and depolarization of rabbit pulmonary arteries by serotonin and by norepinephrine has also been demonstrated in a Na-free medium containing calcium (851). These observations are very recent and too limited to permit conclusive formulation of a general mechanism. They are consistent with the view that an increased permeability to Ca^{++} is produced by several, and perhaps all, excitatory drugs and that this effect is the major mechanism of near-maximal and maximal contractions. To this extent there is support gained for the suggestion of Part I of this review that the unequal maximal contractile effects of different drugs are an expression of the unequal maximal increase in Ca^{++}-permeability produced by them.

Pharmacomechanical coupling (the action of compounds on the contractile system independent of the membrane potential and action potential) has been discussed in Part I of this review (section VI H) and we summarize here (table 1) the evidence supporting its existence under physiological conditions. The ease of electromechanical dissociation in vascular smooth muscle is shown by the observation that the same depolarization associated with a 75% maximal contraction when due to norepinephrine is not accompanied by any contraction when produced by isoproterenol in a slightly high K^+ (10.0 mM) medium (851). The sum of evidence, in our opinion, suggests that the mechanisms of drug action originally demonstrated in depolarized smooth muscle by Schild *et al.* (I 166, I 529) also contribute to excitatory and inhibitory drug effects on polarized

smooth muscle. Those who are still unprepared to accept the existence of pharmacomechanical coupling should support their objections by finding a biological switch that can turn off, in polarized muscle, excitatory and inhibitory mechanisms that are clearly present in depolarized muscle.

Recognition of the existence of pharmacomechanical coupling does not imply the exclusion of electromechanical mechanisms (regulation of the contractile system by changes in membrane potential, action potential frequency or both; Part I, section VI G). It is indeed probable, in view of the well demonstrated spike-generating properties of vascular smooth muscle in small arteries, that moment-to-moment regulation of the resistance vessels (hence physiological regulation of blood flow and pressure) is regulated by the tetanic mechanism (852) of variable frequency spike electrogenesis.

The assumption that excitatory drugs act through increasing the permeability of the plasma membrane to calcium implies that the major source of activator Ca^{++} is extracellular: the basement membrane, the ground substance, or the extracellular fluid. The proposed mechanism also admits to the possibility that drugs may increase the permeability of the membrane by displacing stabilizing Ca^{++} that itself also contributes to contractile activation (Part I, section VI H and I 557). Calculations designed to estimate the fixed Ca^{++} "available" on the smooth muscle plasma membrane (I 557) are based on several unknown variables and for the time being must be regarded as interesting speculations. It would be of very great interest to determine whether excitatory drugs can displace calcium from smooth muscle membrane preparations and, if so, whether the maximal amount of Ca^{++} displaced varies with the intrinsic activity of a given drug.

The question of "stable" calcium storage sites that may be affected by some, but not all, agonists has been the subject of some speculation (Part I, sections VI C and H; 357, I 273, I 290). In phasic striated muscles the existence of a stable calcium site is conclusively documented and anatomically localized to the sarcoplasmic reticulum. It is functionally demonstrated by the large caffeine contractures that can be elicited in severely Ca^{++}-depleted striated muscle in the presence of high concentrations of EDTA (107, I 520). The paucity of sarcoplasmic reticulum in smooth muscle has been pointed out by Peachy and Porter (I 470), but in certain types of vascular smooth muscle large numbers of vesicles have been observed (Part I, sections VI C and G; I 140, I 557, fig. 56 in 240). Without serial sections conventional electronmicrographs do not permit differentiation of plasmalemmal invaginations communicating with the extracellular space (pinocytotic vesicles, 240a) from a system of subplasmalemmal closed vesicles that are not in direct communication with the exterior (sarcoplasmic reticulum). The lanthanum-stained arteriolar smooth muscle sections illustrated by Devine (fig. 67–69 in 240, 240b) clearly show infiltration of this extracellular tracer into vesicles that, because of the plane of sectioning, would otherwise appear to be subplasmalemmal. More recent studies (240b) with lanthanum indicate that, in addition to those round vesicles communicating with the extracellular space, there is also a closed vesiculotubular system at least in the three types of spike-generating vascular smooth muscles examined. Some

of these closed tubules and vesicles appear to make contact with the open pinocytotic vesicles and may function analogously to the striated muscle triads. The ultrastructural findings at least permit the possiblity that electromechanical coupling of action potentials is due to the intracellular translocation of calcium, a mechanism suggested in mammalian (Part I section VI G and I 557) and more recently (137) implied in amphibian vascular smooth muscle.

In contrast to the caffeine contracture in Ca^{++}-depleted striated muscle, mammalian vascular smooth muscle cannot respond to any drug after equally severe Ca^{++}-depletion. Caffeine does have an effect on vascular smooth muscle bathed in *normal* Ca^{++}-containing media: it potentiates the epinephrine-induced contractions of rabbit aortic strips (121) and also has a slight contractile effect on canine renal arteries and human umbilical veins (I 557). Neither of these experiments was conducted in Ca^{++}-free medium, and therefore the earlier inference that caffeine displaced Ca^{++} from an internal site (I 557) remains open to question. Since caffeine, in addition to translocating Ca^{++} from the sarcoplasmic reticulum also increases the permeability of the striated muscle surface membrane to calcium (107), its effects on vascular smooth muscle could also be mediated by the latter mechanism.

The selective persistence of a contractile response to certain agonists after moderate Ca^{++}-depletion has been discussed in Part I section VI C (849) of this review. It should be noted that in the presence of magnesium (733) low concentrations of EDTA may not be sufficient to chelate all the contaminant calcium present in nominally Ca^{++}-free solutions. Hence the results of such experiments may not be representative of the responses of vascular smooth muscle in a completely Ca^{++}-free environment. The fact that certain types of vascular smooth muscle, when depolarized in Ca^{++}-free media, respond to 6.5×10^{-5} M added Ca^{++} with a half-maximal contracture (859), increases the probability that the residual response to an agonist producing a large increase in the permeability of the membrane can be mediated by incompletely chelated contaminant calcium. Furthermore, even in an initially Ca^{++}-free ($< 10^{-6}$ M) bath the Ca^{++}-concentration may increase with time because of equilibration of the bathing medium with extracellular Ca^{++}-binding sites. Low-resolution X-ray emission microanalysis of human aortas suggests that most of the calcium content is extracellular, associated with sulfate-groups (391), and hence would be expected to be in equilibrium with the extracellular fluid. The extent of the sarcoplasmic reticulum (240b), which may also vary among functionally different vascular smooth muscles, has not been quantified in mammalian vascular smooth muscle. The possibility that these sites contribute some calcium for the contractile effect of drugs must be considered, but the existence of major stable *intracellular* Ca^{++}-sites that are acted upon by drugs in excitation-contraction coupling has yet to be demonstrated in mammalian vascular smooth muscle. In turtle aorta, however, Bozler (137) was able to elicit contractions even after extreme Ca^{++}-depletion with 4.0 mM EGTA and we have confirmed this finding (854). Bozler (137) suggested that in the Ca^{++}-free medium the contractile effect of acetylcholine is due to an action of the drug on the sarcoplasmic reticulum. We believe that the pri-

mary action of the drug may still be on the permeability of the plasma membrane and the change in the latter could trigger the release of calcium from the reticulum. The contribution of intracellular calcium sites to the contractile process may be greater in the turtle aorta than in the mammalian blood vessels examined. Preliminary estimates of the sarcoplasmic reticulum in mammalian vascular smooth muscle [less than 1% in guinea pig small mesenteric arteries (240c)] suggest that it is insufficient to store enough calcium for the activation of a sizeable contraction. Smooth muscle of the turtle, unlike any of the mammalian smooth muscles, contains an extensive system of vesicles (240c) and this ultrastructural feature may account for its residual contractile response in Ca^{++}-free solutions. The mitochondria and the nucleus are indicated in figure 1 merely as theoretically possible cation stores and inference regarding their actual function would be premature.

The above arguments brought to bear for a common mechanism of excitatory drug action, based on ion-permeability of the plasma membrane, are in close agreement with those advanced by Douglas (254) in defining the role of Ca^{++}-influx in stimulus-secretion coupling. The equivalent of relaxation has not been examined in secretory epithelium but its study may be a profitable venture for those finding parallels between contraction and secretion (p. 469 in 254). The question of the mechanisms of relaxation, to be discussed next, is of course a major problem of vascular pharmacology.

If the excitatory drugs can produce contractions by increasing the permeability of the plasma membrane to calcium, then inhibitory drugs should be able to relax smooth muscle by decreasing its permeability to calcium. Certain relaxing agents do indeed decrease transmembrane Ca^{++}-fluxes in smooth muscle. Myometrial Ca^{++}-fluxes are inhibited by tetracaine (287) and Ca^{45}-uptake into the depolarized rat aorta is reduced by tetracaine and cinchocaine (685). Papaverine inhibits the lipid-facilitated transport of calcium between two solvents (167) although the relationship of this effect to drug action *in vivo* remains to be established. Cocaine depresses the K^+-permeability of the guinea pig ileum and relaxes contractures elicited by Ca^{++} and depolarizing concentrations of K^+ in this preparation (448).

Other smooth muscle relaxants, however, do not produce readily demonstrable changes in the ion-permeability of smooth muscle. Epinephrine and caffeine relax the depolarized myometrium without depressing Ca^{45}-exchange in the manner of tetracaine (287). Indomethacin and desipramine relax the depolarized rat aorta without reducing its Ca^{45}-uptake as tetracaine and cinchocaine do (685). The possibility that these agents stimulate Ca^{++}-extrusion (Part I, section VI H) is diminished by their lack of effect on Ca^{45}-efflux. Nevertheless, as Keatinge's studies on the sodium fluxes of carotid arteries have shown (I 327), a considerable proportion of a slowly-exchanging ion flux may be extracellular and indistinguishable from true cellular efflux by simple compartmental analysis. Thus, an effect of vasodilators on true cellular efflux may be difficult to detect if the latter constituted only a small proportion of the total Ca^{45}-efflux. Subject to these reservations, however, it will be necessary to examine seriously the possibility that certain smooth muscle relaxants act by stimulating intracellular

uptake of calcium to some unspecified site (I 529) or by increasing the concentration of an intracellular soluble relaxing factor that interferes with the calcium-troponin-actomyosin interaction.

The following empirical classification of the mechanisms of smooth muscle relaxation may be found useful for future experiments. We suggest that three types of relaxing mechanism be distinguished. 1) One would decrease the Ca^{++}-influx into depolarized smooth muscle. Examples of this class of agents are local anaesthetics (section XIII) and haloalkylamines in high concentrations (section XIV). Some agents acting on passive membrane properties might not decrease the resting ion-permeability of smooth muscle but inhibit drug-stimulated ion fluxes. Examples of this type of agent are ethanol (448) and low concentrations of haloalkylamines (154), each of which inhibits the cholinergically stimulated transmembrane K^+-fluxes in intestinal smooth muscle. Similar studies on the effects of vasodilators on drug-stimulated, as opposed to resting, Ca^{++}-fluxes in smooth muscle are not available, and it would be of interest to determine whether drugs such as desipramine and indomethacin (see above) may have such an effect. 2) A second mechanism would be mediated by the stimulation of active pumping of cytoplasmic Ca^{++} into the extracellular compartment or into an intracellular storage site. 3) A third mechanism would be implied by the finding of relaxing agents that do not decrease stimulated Ca^{++}-influx into smooth muscle and have a relaxant effect that cannot be accounted for by extracellular Ca^{++} pumping. Conclusive demonstration of this third mechanism would in fact necessitate a search for a soluble relaxing factor, since it is likely that, as had been suggested in the case of K^+-contractures (685), the uptake capacity of an intracellular Ca^{++}-store would be exhausted during maintained Ca^{++}-influx, and a smooth muscle relaxant that was still active under these conditions would have to act in the presence of maintained cytoplasmic calcium concentration. It should be kept in mind, of course, that a given relaxing agent may act through more than one mechanism.

The foregoing classification is concerned primarily with agents that can relax depolarized and polarized smooth muscle by pharmacomechanical mechanisms, as seems to be the case for the majority of smooth muscle relaxants (vasodilators) including *beta*-adrenergic amines (section IX I), phosphodiesterase inhibitors (section IX I), local anesthetics (section XIII), haloalkylamines (section XIV), acetylcholine (section VI B), and histamine (section VIII). It would be of interest to determine whether the hypotensive polypeptides can relax only polarized smooth muscle or whether these agents are also capable of pharmacomechanical inhibition. It is evident that solely electromechanical inhibition through hyperpolarization and inhibition of spike electrogenesis (Part I, sections VI F and H) could be produced by vasodilators having little effect on resting or drug-stimulated transmembrane Ca^{++}-fluxes. It is a general observation however, that some drugs that are capable of pharmacomechanical inhibition also inhibit, when present, spontaneous electrogenesis. Examples of such "dual" acting vasodilators are methylxanthines, isoproterenol, and acetylcholine (Part I, section VI F). Local anesthetics, papaverine, and nitroglycerin also reduce the frequency and

rising velocity of the spontaneous action potentials of the myometrium (241). As indicated above, definite evidence of an inhibitory agent that relaxes vascular smooth muscle by solely electrical mechanisms has yet to be obtained.

The contractile system of vascular smooth muscle, in relation to actomyosin ATPase activity, has been discussed in Part I of this review (sections I B and IV A). Since that time additional studies have demonstrated thick filaments in guinea pig taenia coli (495a, 684), chicken gizzard (495a), and in unfixed rat jejunum, thoracic aorta, splenic and glomerular arteries (718a). Thick filaments (200 to 280 Å) were also present in fixed preparations of rabbit main pulmonary arteries and portal-anterior mesenteric veins (240c). These findings support the impression that the contractile process of smooth muscle is based on a sliding filament mechanism.

Drug-receptor mechanisms have been extensively dealt with by others (39, 325, 716, 865, 884, 939), and therefore we have avoided a detailed discussion of this topic. It has been tacitly assumed in other parts of this review that, as the unequal maximal contractions produced by unrelated drugs, so also the different intrinsic activities or efficacies of members of a homologous series are proportional to their ability to increase the permeability of the membrane to calcium and other ions. Assuming the premise that the pharmacomechanical excitatory effect of drugs is due to an action on membrane permeability, the above conclusion regarding unequal maximal contractions is, in a mathematical sense, trivial and can be readily tested with available isotope flux and potentiometric techniques.

We have at times implied (sections I A and II A) that the selective pharmacological responsiveness of a given vascular bed may be influenced by variations in the metabolism of different agonists as well as by the distribution of receptors. Consideration of the metabolism of vasoactive hormones, recently reviewed by Vane (916), suggests that this may be a significant determinant of the actions of vasoactive peptides on regional circulations *in vivo*. Although of possible therapeutic significance, a more detailed discussion of the relationships between drug metabolism and the development of selective vasoconstrictors and vasodilators is outside the scope of this review.

It has been noted in several sections (II to IV and VI to X) of this review that many vasoactive drugs have dual, inhibitory and excitatory, actions with the dominant effect depending upon the concentration of the drug, the vascular bed tested, and other experimental variables. There is suggestive evidence that in certain instances the same type of receptor may mediate inhibitory and excitatory effects and different secondary messengers or specific ion-equilibrium potentials determine whether the drug will produce contraction or relaxation (sections II E and VI B). In other instances excitatory and inhibitory receptors may differ, as appears to be the case for adrenergic *alpha-* and *beta*-receptors. A given electromechanical event may also be mediated by two concurrent mechanisms, as occurs with combined *alpha-* and *beta*-adrenergic inhibition of intestinal smooth muscle (sections IX F and I). As indicated earlier, vasoconstrictor effects of drugs on polarized vascular smooth muscle can be mediated simultaneously by depolarization, increased frequency spike electrogenesis, and pharmacomechanical

coupling. The relative contribution of each of these mechanisms to the total contraction will vary in a manner that has to be determined experimentally in individual instances.

Spike-generating phasic smooth muscles and tonic vascular smooth muscles that are electrically silent when not stimulated and, when stimulated, usually respond with graded depolarization were discussed in Part I of this review, and the rare occurrence of very fast action potentials in the generally gradedly-responsive rabbit pulmonary artery has been described in detail elsewhere (851, 859). It might be noted here that a phasic response to a drug, rather than to depolarization with potassium, is in effect the "fade" required by Paton's rate theory (716, 939) and is undistinguishable, except semantically, from tachyphylaxis. It is interesting that a pronounced phasic "fade" (tachyphylaxis) at least to angiotensin is readily observed in portal-mesenteric veins and small blood vessels (section I B), in other word, in those types of vascular smooth muscle that exhibit phasic components in their K^+-contractures (850). Whether this implies that the development of tachyphylaxis to certain agonists and the time-dependent Ca^{++}-permeability of depolarized smooth muscle are related properties remains to be determined.

CONCLUSION

Regional and species differences in the responsiveness of vascular smooth muscle to drugs have been conclusively established during the period covered by this review. Differences among the membrane properties of different vascular smooth muscles have also been recognized, although in this area our knowledge is still limited. Several forms of spike electrogenesis, probably analogous to those produced by other excitable membranes, have been observed in certain types of vascular smooth muscle. The contractile mechanism of smooth muscle appears to be based on the sliding of two types of filaments in a manner fundamentally similar to that of striated muscles. Graded membrane-potential changes elicited by drugs and the increasing evidence of contractile regulation by mechanisms other than the membrane potential, however, clearly indicate that smooth muscles cannot be considered as reduced scale models of the frog sartorius fiber.

What may we anticipate to occur in this field within the next 15 years? The structural identification of receptors would be assigned high priority by most pharmacologists. The variable distribution of receptors in smooth muscle could be used, as was done with transport-negative and transport-positive mutants (708), for the specific labelling of receptors in a drug-sensitive population of cells. The nature of the physicochemical changes of the membrane that bring about an increase in ion-permeability and active transport is equally important and probably related to receptor-identification. It is our impression that the investigation of slow, graded potential changes common to smooth muscles, certain synaptic membranes, and epithelial cells will elucidate new aspects of membrane physiology. Because of their slow time course, these graded potential changes would be expected to reveal more readily the underlying physicochemical transients, that might also be qualitatively different from the rapid, regenerative

permeability change that characterizes the action potential. It is commonly assumed that conformational changes of specific polar groups determine the permeability of the membrane, but a plausible hypothesis of synaptic electrogenesis based on the hydrolysis of membrane phospholipids has also been proposed (263) and may be relevant to the generation of graded potential changes in smooth muscle.

It is well within the reach of available technology to accurately determine what fraction of total vascular calcium is external to the plasma membrane and how much is available at internal sites for excitation-contraction coupling. It will be equally suitable to determine whether the relative ion permeability changes produced by peptide and amine agonists are only quantitatively different or whether these different drugs have selective effects on different ion channels. The classification of vasodilators according to their effects on resting and on stimulated transmembrane calcium-fluxes will be essential to the understanding of their mechanism of action as well as a necessary first step in rigorously testing the possibility of the existence of auxiliary mechanisms that can regulate smooth muscle actomyosin ATPase without inhibiting Ca^{++}-influx.

The atherogenic role of vascular smooth muscle (Part I, section III B) and the possibility of hypertension as a vascular myopathy (section XXI) will probably undergo close scrutiny as interest in these diseases persists. Perhaps biochemical studies can reveal whether the increased AMPase activity of hypertensive vascular smooth muscle (Part I, section III D) is wholly nonspecific, or whether abnormal (low) cyclic AMP and other nucleotide levels are involved in the pathogenesis of hypertension.

The above list is admittedly speculative and perhaps presumes too much in anticipating scientific trends. We have intentionally emphasized those areas of research that are largely peculiar to smooth muscle and to vascular smooth muscle in particular, rather than the exploration of the similarities to phasic striated muscles, without denying the usefulness and further need for the latter. Our choice of emphasis was strongly influenced by the role of vascular smooth muscle in the development of cardiovascular diseases and also by the belief that a specific field of research serves the general cause of science better by asking it an occasional original question.

Acknowledgments. We again thank our colleagues and friends mentioned in Part I of this review for their advice and encouragement, and Dr. G. Haeusler for critical reading and helpful comments about this manuscript. Dr. George Acheson's editorial contributions to both Part I and Part II of this review have been invaluable to the authors and readers. We also wish to thank Drs. George M. Laws and R. P. Custer for their continued support. The enthusiastic assistance of Miss Louise Dicke has been essential in seeing this manuscript to its completion. We thank Mrs. M. F. Keating, Librarian, for her continued cooperation, Drs. M. Goldberg and B. Staum for Brattleboro rats and Dr. J. H. Trapold for oxytocin.

REFERENCES

1. Abboud, F. M.: Vascular responses to norepinephrine, angiotensin, vasopressin and serotonin. Fed. Proc. 27: 1391–1395, 1968.
2. Abboud, F. M. and Eckstein, J. W.: Vasodilator action of guanethidine. Circ. Res. 11: 788–796, 1962.
3. Abboud, F. M. and Eckstein, J. W.: Vascular responses after alpha adrenergic receptor blockade. II. Responses of venous and arterial segments to adrenergic stimulation in the forelimb of dog. J. Clin. Invest. 47: 10–19, 1968.

4. ABBOUD, F. M., ECKSTEIN, J. W. AND ZIMMERMAN, B. G.: Venous and arterial responses to stimulation of beta adrenergic receptors. Amer. J. Physiol. 209: 383–389, 1965.
5. ABE, Y. AND TOMITA, T.: Cable properties of smooth muscle. J. Physiol. (London) 196: 87–100, 1968.
6. ABIKO, Y., ITO, G., HIGUCHI, I., KANEKO, Y., ISHIKAWA, H. AND ITO, M.: The inhibitory effect of procaine on the initial pressor response to acetylcholine in atropinized dogs. Arch. Int. Pharmacodyn. Ther. 170: 445–452, 1967.
7. ABRAMS, H. L.: Altered drug response of tumour vessels in man. Nature (London) 201: 167–170, 1964.
8. ACHER, R.: Neurophysin and neurohypophysial hormones. Proc. Roy. Soc. 170: 7–16, 1968.
9. ACHER, R., CHAUVET, J., CHAUVET, M. T. AND CREPY, D.: Les hormones neurohypophysaires des amphibiens: isolement et caractérisation de la mésotocine et de la vasotocine chez le crapaud (Bufo bufo). Gen. Comp. Endocrinol. 8: 337–343, 1967.
10. ACHESON, G. H. (ed.): Second Symposium on Catecholamines. Pharmacol. Rev. 18: 1–804, 1966.
11. AFONSO, S. AND O'BRIEN, G. S.: Enhancement of coronary vasodilator action of adenosine triphosphate by dipyridamole. Circ. Res. 20: 403–408, 1967.
12. AFONSO, S., O'BRIEN, G. S. AND CRUMPTON, C. W.: Enhancement of coronary vasodilating action of ATP and adenosine by lidoflazine. Circ. Res. 22: 43–48, 1968.
13. AHLQUIST, R. P.: Agents which block adrenergic β-receptors. Annu. Rev. Pharmacol. 8: 259–272, 1968.
14. AHLQUIST, R. P. AND LEVY, B.: Adrenergic receptive mechanism of canine ileum. J. Pharmacol. Exp. Ther. 127: 146–149, 1959.
15. ALTURA, B. M.: Contactile responses of microvascular smooth muscle to antihistamines. Amer. J. Physiol. 218: 1082–1091, 1970.
16. ALTURA, B. M.: Differential actions of polypeptides and other drugs on coronary inflow vessels. Amer. Heart J. 72: 709–711, 1966.
17. ALTURA, B. M.: Role of glucocorticoids in local regulation of blood flow. Amer. J. Physiol. 211: 1393–1397, 1966.
18. ALTURA, B. M.: Antihistamine constriction in mouse skin microcirculation. J. Pharm. Pharmacol. 20: 71–72, 1968.
19. ALTURA, B. M. AND HERSHEY, S. G.: Pharmacology of neurohypophyseal hormones and their synthetic analogues in the terminal vascular bed. Angiology 18: 428–439, 1967.
20. ALTURA, B. M. AND HERSHEY, S. G.: Structure-activity relationships of neurohypophyseal polypeptides in the microcirculation. A molecular basis for shock therapy. *In* Intermedes Proceedings 1968: Combined Injuries and Shock, ed. by B. Schildt and L. Thoren, pp. 247–259, Försvarets Forskningstalt, Stockholm, 1968.
21. ALTURA, B. M. AND ZWEIFACH, B. W.: Antihistamines and vascular reactivity. Amer. J. Physiol. 209: 545–549, 1965.
22. ALTURA, B. M. AND ZWEIFACH, B. W.: Pharmacologic properties of antihistamines in relation to vascular reactivity. Amer. J. Physiol. 209: 550–556, 1965.
23. ALTURA, B. M. AND ZWEIFACH, B. W.: Influence of reserpine and guanethidine on vascular reactivity and antihistamine constrictor action in the microcirculation. Angiology 17: 493–502, 1966.
24. ALTURA, B. M. AND ZWEIFACH, B. W.: Endogenous histamine formation and vascular reactivity. Amer. J. Physiol. 212: 559–564, 1967.
25. AMORIM, D. S., MANÇO, J. C., FERREIRA, S. H., TANAKA, A. AND CARDOSO, S. S.: Hemodynamic effects of bradykinin potentiated by a factor contained in the "Bothrops Jararaca" venom. Comparative results with eledoisin. Acta Physiol. Latinoamer. 17: 258–266, 1967.
26. ANASTASI, A., BERTACCINI, G. AND ERSPAMER, V.: Pharmacological data on phyllokinin (bradykinyl-isoleucyl-tyrosine o-sulphate) and bradykinyl-isoleucyl-tyrosine. Brit. J. Pharmacol. Chemother. 27: 479–485, 1966.
27. ANDERSON, B., JR. AND MCINTOSH, H. D.: Retinal circulation. Annu. Rev. Med. 18: 15–26, 1967.
28. ANDERSSON, C. J.: Adrenergic block by reserpine on isolated vessel preparation. Acta Pharmacol. Toxicol. 13: 225–227, 1957.
29. ANDERSSON, R., LUNDHOLM, L. AND MOHME-LUNDHOLM, E.: Relationship between mechanical and metabolic events in vascular smooth muscle. *In* Vascular Neuroeffector Systems, ed. by J. A. Bevan, R. F. Furchgott, R. A. Maxwell and A. P. Somlyo, S. Karger, Basel, in press.
30. ANDREATTA, T. AND HOFMANN, K.: Studies on polypeptides. XLI. The synthesis of (5-valine, 6-beta (pyrazolyl-3)-alanine)-angiotensin II, a potent hypertensive peptide. J. Amer. Chem. Soc. 90: 7334–7338, 1968.
31. ANGELAKOS, E. T. AND GLASSMAN, P. M.: Hypotensive and cardiac effects of adenosine and its phosphorylated derivatives. Arch. Int. Pharmacodyn. Ther. 154: 82–88, 1965.
32. ÄNGAÅRD, E. AND BERGSTRÖM, S.: Biological effects of an unsaturated trihydroxy acid ($PGF_{2\alpha}$) from normal swine lung. Acta Physiol. Scand. 58: 1–12, 1963.
33. ANTONCECCHI, E. AND CHIEPPA, E.: Azione dell'eledoisina su arterie coronarie isolate di cane e di bue. Arch. Sci. Biol. 49: 212–216, 1965.
34. ANTONCECCHI, E., CHIEPPA, D. AND CORTESE, I.: Azione di amine simpaticomimetiche sulle coronarie. Arch. Sci. Biol. 48: 361–365, 1964.
35. ANTONIO, A. AND ROCHA E SILVA, M.: Coronary vasodilation produced by bradykinin on isolated mammalian heart. Circ. Res. 11: 910–915, 1962.
36. ARAKAWA, K. AND NAKAMURA, M.: Studies on human angiotensin. Circ. Res. 20 and 21 (suppl. II): 101–107, 1967.
37. ARAKAWA, K., NAKATANI, M. AND NAKAMURA, M.: Species specificity in reaction between renin and angiotensinogen. Nature (London) 207: 636, 1965.
38. ARCIDIACONO, F. G., REININGER, E. J. AND SAPIRSTEIN, L. A.: Effect of bradykinin on total peripheral resistance and regional vascular resistance in the rat. *In* 4th European Conference on Microcirculation, ed. by H. Harders, pp. 29–32, S. Karger, Basel, New York, 1966.
39. ARIENS, E. J. AND SIMONIS, A. M.: A molecular basis for drug action. J. Pharm. Pharmacol. 16: 137–157, 1964.

40. ARMIN, J. AND GRANT, R. T.: Vasoconstrictor activity in the rabbit's blood and plasma. J. Physiol. (London) 128: 511–540, 1955.
41. ARMIN, J. AND GRANT, R. T.: Further observations on vasoconstrictor substances in blood of rabbit and man. J. Physiol. (London) 138: 401–416, 1957.
42. ARVILL, A., JOHANSSON, B. AND JONSSON, O.: Effects of hyperosmolarity on the volume of vascular smooth muscle cells and the relation between cell volume and muscle activity. Acta Physiol. Scand. 75: 484–495, 1969.
43. ÅSTRÖM, A.: Influence of some local anesthetics upon the adrenaline contraction of isolated strips of rabbit aorta. Acta Physiol. Scand. 60: 30–38, 1964.
44. ÅSTRÖM, A., CRAFOORD, J. AND SAMELIUS-BROBERG, U.: Vasoconstrictor action of acetylcholine on kidney blood vessels. Acta Physiol. Scand. 61: 159–164, 1964.
45. ÅSTRÖM, A. AND SAMELIUS, U.: The action of 5-hydroxytryptamine and some of its antagonists on the umbilical vessels of the human placenta. Brit. J. Pharmacol. Chemother. 12: 410–414, 1957.
46. AUERSWALD, W. AND DOLESCHEL, W.: On the potentiation of kinins by sulfhydrylic compounds. Arch. Int. Pharmacodyn. Ther. 168: 188–198, 1967.
47. AUGUSTYNIAK, M. AND LITWIN, J.: Blocking of hypotensive effects of histamine by the drugs blocking beta-adrenergic receptors. Bull. Acad. Pol. Sci. 15: 55–58, 1967.
48. AUKLAND, K.: Vasopressin and intrarenal blood flow distribution. Acta Physiol. Scand. 74: 173–182, 1968.
49. AVAKIAN, O. V. AND GILLESPIE, J. S.: Uptake of noradrenaline by adrenergic nerves, smooth muscle and connective tissue in isolated perfused arteries and its correlation with the vasoconstrictor response. Brit. J. Pharmacol. Chemother. 32: 168–184, 1968.
50. AVIADO, D. M.: The lung circulation. Physiology and Pharmacology, vol. 1, Pergamon Press, Oxford, London Edinburgh, New York, Paris, Frankfurt, 1965.
51. AXELSSON, J. AND HOLMBERG, B.: The effects of extracellulary applied ATP and related compounds on electrical and mechanical activity of the smooth muscle taenia coli from the guinea-pig. Acta Physiol. Scand. 75: 149–156, 1969.
52. BÄCHTOLD, H. P. AND PLETSCHER, A.: Abschwächung der Noradrenalin-Wirkung auf die isolierte Aorta bei Hemmung der Monoaminoxydase. Experientia (Basel) 15: 265–267, 1959.
53. BAEZ, S.: Anesthetics and the microcirculation. *In* Effects of Anesthetics on the Circulation, ed. by H. L Price and P. J. Cohen, pp. 182–198, Charles C Thomas, Springfield, Ill., 1964.
54. BAEZ, S., KAPMAN, A. F. AND ORKIN, L. R.: Microvascular hypersensitivity subsequent to chemical denervation. Circ. Res. 20: 328–337, 1967.
54a. BAKHLE, Y. S., REYNARD, A. M. AND VANE, J. R.: Metabolism of the angiotensins in isolated perfused tissues. Nature (London) 222: 956–959, 1969.
55. BÁRÁNY, F. R.: Reactivity of the skin vessels to noradrenalin and angiotensin in arterial hypertension. Scand. J. Clin. Lab. Invest. 15: 317–322, 1963.
56. BARER, G. R.: A comparison of the circulatory effects of angiotensin, vasopressin and adrenaline in the anaesthetized cat. J. Physiol. (London) 156: 49–66, 1961.
57. BARER, G. R.: The action of vasopressin, a vasopressin analogue (PLV_2), oxytocin, angiotensin, bradykinin and theophylline ethylene diamine on renal blood flow in the anaesthetized cat. J. Physiol. (London) 169: 62–72, 1963.
58. BARER, G. R., HOWARD, P. AND MCCURRIE, J. R.: The effect of carbon dioxide and changes in blood pH on pulmonary vascular resistance in cats. Clin. Sci. 32: 361–376, 1967.
59. BARER, G. R. AND MCCURRIE, J. R.: Pulmonary vasomotor responses in the cat; the effects and interrelationships of drugs, hypoxia and hypercapnia. Quart. J. Exp. Physiol. Cog. Med. Sci. 54: 156–172, 1969.
60. BARTELSTONE, H. J. AND NASMYTH, P. A.: Vasopressin potentiation of catecholamine actions in dog, rat, cat, and rat aortic strip. Amer. J. Physiol. 208: 754–762, 1965.
61. BARTELSTONE, H. J., NASMYTH, P. A. AND TELFORD, J. M.: The significance of adenosine cyclic 3′,5′-monophosphate for the contraction of smooth muscle. J. Physiol. (London) 188: 159–176, 1967.
62. BARTH, T., PLIŠKA, V. AND RYCHLÍK, I.: Chymotryptic and tryptic cleavage of oxytocin and vasopressin. Collect. Czech. Chem. Commun. Engl. Edition 32: 1058–1063, 1967.
63. BASSENGE, E., WALTER, P. AND DOUTHEIL, U.: Wirkungsumkehr der adrenergischen Coronargefässreaktion in Abhängigkeit vom Coronargefässtonus. Pflügers Arch. Gesamte Physiol. Menschen Tiere 297: 146–155, 1967.
64. BAUM, T.: Vascular reactivity of reserpine-pretreated dogs. J. Pharmacol. Exp. Ther. 141: 30–35, 1963.
65. BAUM, T. AND GLUCKMAN, M. I.: *In vitro* interactions of the new anorexic agent WY-5244 with cardiac and vascular tissue and with adrenergic mechanisms. J. Pharmacol. Exp. Ther. 158: 510–518, 1967.
66. BAUM, T. AND SHROPSHIRE, A. T.: Vasoconstriction induced by sympathetic stimulation during development of hypertension. Amer. J. Physiol. 212: 1020–1024, 1967.
67. BAUM, T. AND SHROPSHIRE, A. T.: Sympathetic and humoral vasoconstrictor responses in deoxycorticosterone hypertension. Amer. J. Physiol. 213: 499–503, 1967.
68. BAYLEY, T., CLEMENTS, J. A. AND OSBAHR, A. J.: Pulmonary and circulatory effects of fibrinopeptides. Circ. Res. 21: 469–485, 1967.
69. BEDDOE, F. AND SMITH, H. J.: Irreversible inhibition of acetylcholinesterase by dibenamine. Nature (London) 216: 706–707, 1967.
70. BEILENSON, S., SCHACHTER, M. AND SMAJE, L. H.: Secretion of kallikrein and its role in vasodilatation in the submaxillary gland. J. Physiol. (London) 199: 303–317, 1968.
71. BEILIN, L. J., GARCIA, R. AND BLACKWELL, E.: Vascular ionic composition and blood pressure changes in experimental renal hypertension. Clin. Sci. 36: 387–399, 1969.

72. Belej, M. A., Papacostas, C. A., Sevy, R. W. and Jackson, A. F.: The mechanism of "nicotine reversal" in phenoxybenzamine-treated dogs. J. Pharmacol. Exp. Ther. 164: 342–347, 1968.
73. Bell, C.: Differential effects of tetrodotoxin on sympathomimetic actions of nicotine and tyramine. Brit. J. Pharmacol. Chemother. 32: 96–103, 1968.
74. Bell, C.: Dual vasoconstrictor and vasodilator innervation of the uterine arterial supply in the guinea pig. Circ. Res. 23: 279–289, 1968.
75. Bell, C.: Fine structural localization of acetylcholinesterase at a cholinergic vasodilator nerve-arterial smooth muscle synapse. Circ. Res. 24: 61–70, 1969.
76. Bell, C.: Transmission from vasoconstrictor and vasodilator nerves to single smooth muscle cells of the guinea-pig uterine artery. J. Physiol. (London), 205: 695–708, 1969.
77. Bennett, M. R.: The effect of intracellular current pulses in smooth muscle cells of the guinea pig vas deferens at rest and during transmission. J. Gen. Physiol. 50: 2459–2475, 1967.
78. Bentley, G. A.: The effect of local anaesthetic and anti-adrenaline drugs on the response of sympathetically innervated smooth muscle preparations to electrical stimulation at different frequencies. Brit. J. Pharmacol. Chemother. 27: 64–80, 1966.
79. Bentley, P. J.: The potentiating action of magnesium and manganese on the oxytocic effect of some oxytocin analogues. J. Endocrinol. 32: 215–222, 1965.
80. Bentley, P. J.: Mechanism of action of neurohypophysial hormones: actions of manganese and zinc on the permeability of the toad bladder. J. Endocrinol. 39: 493–506, 1967.
81. Bentley, P. J.: Natriferic and hydro-osmotic effects on the toad bladder of vasopressin analogues with selective antidiuretic activity. J. Endocrinol. 39: 299–304, 1967.
82. Berankova-Ksandrova, Z., Bisset, G. W., Joet, K., Krejci, I., Pliska, V., Rudinger, J., Rychlik, I. and Sorm, F.: Synthetic analogues of oxytocin acting as hormonogens. Brit. J. Pharmacol. Chemother. 26: 615–632, 1966.
83. Berde, B. and Boissonnas, R. A.: Synthetic analogues and homologues of the posterior pituitary hormones. *In* The Pituitary Gland, ed. by G. W. Harris and B. T. Donovan, vol. 3, pp. 624–661, University of California Press Berkeley, 1966.
84. Berde, B., Boissonnas, R. A., Huguenin, R. L. and Stürmer, E.: Vasopressin analogues with selective pressor activity. Experientia (Basel) 20: 42–43, 1964.
85. Berde, B., Doepfner, W. and Konzett, H.: Some pharmacological actions of four synthetic analogues of oxytocin. Brit. J. Pharmacol. 12: 209–214, 1957.
86. Berde, B., Weidmann, H. and Cerletti, A.: Über Phenylalanin-Lysin-Vasopressin. Helv. Physiol. Pharmacol. Acta 19: 285–302, 1961.
87. Beretta, C., Aguggini, G. and Rubbiani, M.: Pressor and oxitocic-like effects of angiotensin affected by aldosterone pretreatment in guinea-pigs. Experientia (Basel) 23: 545–548, 1967.
88. Bergamaschi, M. and Glässer, A. H.: Peripheral vasodilator action of eledoisin, bradykinin, and nitroglycerin in anesthetized dogs. Circ. Res. 15: 371–379, 1964.
89. Bergamaschi, M., Glässer, A. H. and Silvestri, R.: Vasodilating action of eledoisin on the intact and denervated skeletal muscle preparation of the dog. Arzneimittel-Forschung 16: 1668–1671, 1966.
90. Bergofsky, E. H., Haas, F. and Procelli, R.: Determination of the sensitive vascular sites from which hypoxia and hypercapnia elicit rises in pulmonary arterial pressure. Fed. Proc. 27: 1420–1425, 1968.
91. Bergofsky, E. H. and Holtzman, S.: A study of the mechanisms involved in the pulmonary arterial pressor response to hypoxia. Circ. Res. 20: 506–519, 1967.
92. Bergström, S., Carlson, L. A. and Weeks, J. R.: The prostaglandins: a family of biologically active lipids. Pharmacol. Rev. 20: 1–48, 1968.
93. Berman, H. J. and Siggins, G. R.: Neurogenic factors in the microvascular system. Fed. Proc. 27: 1384–1390, 1968.
94. Bernard, P. J., Rowe, H. M. and Gardier, R. W.: Influence of vasopressin on postganglionic nerve stimulation in the isolated cat spleen. Arch. Int. Pharmacodyn. Ther. 171: 217–220, 1968.
95. Berne, R. M.: Regulation of coronary blood flow. Physiol. Rev. 44: 1–29, 1964.
96. Berry, W. B., McLaughlin, J. S., Clark, W. D. and Morrow, A. G.: The effects of acute hypoxia on pressure, flow, and resistance in the pulmonary vascular bed. Surgery 58: 404–411, 1965.
97. Bertaccini, G., Caro, G. De, Endean, R., Erspamer, V. and Impicciatore, M.: The action of caerulein on the systemic arterial blood pressure of some experimental animals. Brit. J. Pharmacol. Chemother. 33: 59–71, 1968.
98. Besse, J. C. and Bass, A. D.: Potentiation by hydrocortisone of responses to catecholamines in vascular smooth muscle. J. Pharmacol. Exp. Ther. 154: 224–238, 1966.
99. Bevan, J. A.: The use of the rabbit aorta strip in the analysis of the mode of action of *l*-epinephrine on vascular smooth muscle. J. Pharmacol. Exp. Ther. 129: 417–427, 1960.
100. Bevan, J. A.: Some characteristics of the isolated sympathetic nerve-pulmonary artery preparation of the rabbit J. Pharmacol. Exp. Ther. 137: 213–218, 1962.
100a. Bevan, J. A.: Personal communication.
101. Bevan, J. A., Furchgott, R. F., Maxwell, R. A. and Somlyo, A. P.: Vascular Neuroeffector Systems, S. Karger, Basel, London, New York, in press.
102. Bevan, J. A. and Osher, J. V.: Relative sensitivity of some large blood vessels of the rabbit to sympathomimetic amines. J. Pharmacol. Exp. Ther. 150: 370–374, 1965.
103. Bevan, J. A., Osher, J. V. and Bevan, R. D.: Distribution of bound norepinephrine in the arterial wall. European J. Pharmacol. 5: 299–301, 1969.

104. BEVAN, J. A., OSHER, J. V. AND SU, C.: Response of vascular smooth muscle to potassium and its antagonism by phenoxybenzamine. J. Pharmacol. Exp. Ther. 139: 216–221, 1963.
105. BEVAN, J. A. AND SU, C.: The sympathetic mechanism in the isolated pulmonary artery of the rabbit. Brit. J. Pharmacol. 22: 176–182, 1964.
106. BEVAN, J. A. AND VERITY, M. A.: Sympathetic nerve-free vascular muscle. J. Pharmacol. Exp. Ther. 157: 117–124, 1967.
106a. BIAMINO, G. AND KRUCKENBERG, P.: Synchronization and conduction of excitation in the rat aorta. Amer. J. Physiol. 217: 376–382, 1969.
107. BIANCHI, C. P.: The effect of caffeine on radiocalcium movement in frog sartorius. J. Gen. Physiol. 44: 845–858, 1961.
108. BIANCHI, C. P. AND BOLTON, T. C.: Action of local anesthetics on coupling systems in muscle. J. Pharmacol. Exp. Ther. 157: 388–405, 1967.
109. BISHOP, J. G., RICHARDSON, A. W. AND MUHLER, J. C.: The effect of different fluorides on vascular tone and alteration in the rate of blood flow. J. Dent. Res. 34: 478–488, 1955.
110. BISSET, G. W.: The milk-ejection reflex and the actions of oxytocin, vasopressin and synthetic analogues on the mammary gland. *In* Handbook of Experimental Pharmakologie, vol. 23, pp. 475–544, ed. by B. Berde, Springer-Verlag, New York, 1968.
111. BISSET, G. W. AND CLARK, B. J.: Synthetic 1-N-carbamylhemicystine-2-O-methyltyrosine-oxytocin (N-carbamyl-O-methyl-oxytocin): a specific antagonist to the actions of oxytocin and vasopressin on the uterus and mammary gland. Nature (London) 218: 197–199, 1968.
112. BISSET, G. W. AND LEWIS, G. P.: A spectrum of pharmacological activity in some biologically active peptides. Brit. J. Pharmacol. 19: 168–182, 1962.
113. BLACK, G. W. AND MCARDLE, L.: The effects of halothane on the peripheral circulation in man. Brit. J. Anaesth. 34: 2–10, 1962.
114. BLACK, J. W. AND STEPHENSON, J. S.: Pharmacology of a new adrenergic beta-receptor-blocking compound (Nethalide). Lancet 2: 311–314, 1962.
115. BLAIR-WEST, J. R., HARDING, R. AND MCKENZIE, J. S.: Effect of sodium concentration on the vasoconstrictor action of angiotensin in the rabbit ear. European J. Pharmacol. 4: 77–82, 1968.
116. BLOMQUIST, A. T., RICH, D. H., HRUBY, V. J., NANGERONI, L. L., GLOSE, P. AND DU VIGNEAUD, V.: Deuterated oxytocins: the synthesis and biological properties of three crystalline analogs of deamino-oxytocin deuterated in the 1-beta-mercaptopropionic acid position. Proc. Nat. Acad. Sci. U.S.A. 61: 688–692, 1968.
117. BOBBIN, R. P. AND GUTH, P. S.: Venoconstrictive action of bradykinin. J. Pharmacol. Exp. Ther. 160: 11–21, 1968.
118. BODAMMER, G.: Untersuchungen über den Mechanismus der Blutdruckwirkung des Anaphylatoxins bei Katzen und Meerschweinchen. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 262: 197–207, 1969.
119. BOGDANSKI, D. F. AND BRODIE, B. B.: The effects of inorganic ions on the storage and uptake of H^3-norepinephrine by rat heart slices. J. Pharmacol. Exp. Ther. 165: 181–189, 1969.
120. BOHR, D. F.: Contraction of vascular smooth muscle. Can. Med. Ass. J. 90: 174–179, 1964.
121. BOHR, D. F.: Individualities among vascular smooth muscles. *In* Electrolytes and Cardiovascular Diseases, ed. by E. Bajusz, pp. 342–355, S. Karger, Basel, New York, 1965.
122. BOHR, D. F., GOULET, P. L. AND TAQUINI, A. C., JR.: Direct tension recording from smooth muscle of resistance vessels from various organs. Angiology 12: 478–485, 1961.
123. BOHR, D. F. AND JOHANSSON, B.: Contraction of vascular smooth muscle in response to plasma. Comparison with response to know vasoactive agents. Circ. Res. 19: 593–601, 1966.
123a. BOHR, D. F., SEIDEL, C. AND SOBIESKI, J.: Possible role of sodium-calcium pumps in tension development of vascular smooth muscle. Microvasc. Res. 1: 335–343, 1969.
124. BOHR, D. F. AND SOBIESKI, J.: A vasoactive factor in plasma. Fed. Proc. 27: 1396–1398, 1968.
125. BOHR, D. F. AND UCHIDA, E.: Individualities of vascular smooth muscles in response to angiotensin. Circ. Res. 20 and 21 (suppl. II): 135–145, 1967.
126. BOISSONNAS, R. A. AND GUTTMANN, S.: Chemistry of the neurohypophysial hormones. *In* Handbook of Experimental Pharmakologie, vol. 23, pp. 40–66, ed. by B. Berde, Springer-Verlag, New York, 1968.
127. BOLME, P., NGAI, S. H. AND ROSELL, S.: Influence of vasoconstrictor nerve activity on the cholinergic vasodilator response in skeletal muscle in the dog. Acta Physiol. Scand. 71: 323–333, 1967.
128. BOLTON, T. B.: Spontaneous and evoked release of neurotransmitter substances in the longitudinal muscle of the anterior mesenteric artery of the domestic fowl. Brit. J. Pharmacol. 35: 112–120, 1969.
129. BOOZ, K. H.: Die Bedeutung Eines Serumfaktors Für Die Tätigkeit Der Aktiv Pulsierenden V. Portae Der Negetiere. Anat. Anz. 113: 81–86, 1963.
130. BORN, G. V. R. AND BÜLBRING, E.: The movement of potassium between smooth muscle and the surrounding fluid. J. Physiol. (London) 131: 690–703, 1956.
131. BORN, G. V. R., DAWES, G. S., MOTT, J. C. AND RENNICK, B. R.: The constriction of the ductus arteriosus caused by oxygen and by asphyxia in newborn lambs. J. Physiol. (London) 132: 304–342, 1956.
132. BORN, G. V. R., HASLAM, R. J. AND GOLDMAN, M.: Comparative effectiveness of adenosine analogues as inhibitors of blood-platelet aggregation and as vasodilators in man. Nature (London) 205: 678–680, 1965.
133. BOULLIN, D. J.: Effect of divalent ions on release of ^{3}H-noradrenalin by sympathetic nerve stimulation. J. Physiol. (London) 183: 76–77, 1965.
134. BOURA, A. L. A. AND GREEN, A. F.: Adrenergic neurone blocking agents. Annu. Rev. Pharmacol. 5: 183–212, 1965.

135. Bowman, W. C. and Stafford, A.: Effects of dipyridamole on contractions of the cat's nictitating membrane. European J. Pharmacol. 3: 131–138, 1968.
136. Boyd, I. A. and Forrester, T.: The release of adenosine triphosphate from frog skeletal muscle *in vitro*. J. Physiol. (London) 199: 115–135, 1968.
137. Bozler, E.: Role of calcium in initiation of activity of smooth muscle. Amer. J. Physiol. 216: 671–674, 1969.
138. Brading, A. F. and Setekleiv, J.: The effect of hypo- and hypertonic solutions on volume and ion distribution of smooth muscle of guinea-pig taenia coli. J. Physiol. (London) 195: 107–118, 1968.
139. Branda, L. A., Drabarek, S. and du Vigneaud, V.: The synthesis and pharmacological properties of deamino-4-decarboxamido-oxytocin (1-β-mercaptopropionic acid-4-α-aminobutyric acid-oxytocin). J. Biol. Chem. 241: 2572–2575, 1966.
140. Branda, L. A. and du Vigneaud, V.: Deoxy-4-decarboxamido-oxytocin and deamino-deoxy-4-decarboxamido-oxytocin. J. Biol. Chem. 241: 4051–4054, 1966.
141. Branda, L. A. and du Vigneaud, V.: Synthesis and pharmacological properties of 9-decarboxamido-oxytocin. J. Med. Chem. 9: 169–172, 1966.
142. Branda, L. A., Ferrier, B. M., Archimaut, G., Marchelli, E. A. and Rucanski, B.: Deamino-oxytocin: inactivation by plasma of women in labor. Science 160: 81–82, 1968.
143. Branda, L. A., Hruby, V. J. and du Vigneaud, V.: 2-Isoleucine-oxytocin and deamino-2-isoleucine-oxytocin: their synthesis and some of their pharmacologic activities. Mol. Pharmacol. 3: 248–253, 1967.
143a. Brecht, K., Konold, P. and Gebert, G.: The effect of potassium, catecholamines and other vasoactive agents on isolated arterial segments of the muscular type. Physiol. Bohemoslov. 18: 15–22, 1969.
144. Brick, I., Hutchinson, K. J. and Roddie, I. C.: The vasodilator properties of noradrenaline in the human forearm. Brit. J. Pharmacol. Chemother. 30: 561–567, 1967.
145. Briggs, A. H. and Shibata, S.: Ca and ouabain interaction on vascular smooth muscle. Proc. Soc. Exp. Biol. Med. 121: 274–278, 1966.
146. Brodie, D. C., Bohr, D. F. and Smit, J.: Dual contractile response of the aorta strip. Amer. J. Physiol. 197: 241–246, 1959.
147. Brody, M. J.: Neurohumoral mediation of active reflex vasodilatation. Fed. Proc. 25: 1583–1592, 1966.
148. Brody, M. J. and Dixon, R. L.: Vascular reactivity in experimental diabetes mellitus. Circ. Res. 14: 494–501, 1964.
149. Brotánesk, V. and Kazda, S.: Differences in the vasodepressor reaction to oxytocin in men and nonpregnant and pregnant women. Amer. J. Obstet. Gynecol. 93: 547–552, 1965.
150. Brunner, H., Hedwall, P. R. and Meier, M.: Influence of adrenergic beta-receptor blockade on the acute cardiovascular effects of hydralazine. Brit. J. Pharmacol. Chemother. 30: 123–133, 1967.
151. Brutsaert, D.: The effects of reserpine and of adrenolytic agents on the pulmonary arterial pressor response to serotonin. Exp. Med. Surg. 23: 13–27, 1965.
152. Bülbring, E. and Tomita, T.: Suppression of spontaneous spike generation by catecholamines in the smooth muscle of the guinea-pig taenia coli. Proc. Roy. Soc. 172: 103–119, 1969.
153. Bumpus, F. M.: Biochemical aspects of the renin-angiotensin system. Trans. N. Y. Acad. Sci. 27: 445–449, 1965.
154. Burgen, A. S. V. and Spero, L.: The action of acetylcholine and other drugs on the efflux of potassium and rubidium from smooth muscle of the guinea-pig intestine. Brit. J. Pharmacol. 34: 99–115, 1968.
155. Burks, T. F. and Long, J. P.: Catecholamine-induced release of 5-hydroxytryptamine (5-HT) from perfused vasculature of isolated dog intestine. J. Pharm. Sci. 55: 1383–1386, 1966.
155a. Burn, J. H. and Epstein, H. G.: Hypotension due to halothane. Brit. J. Anaesth. 31: 199–204, 1959.
156. Burn, J. H. and Hobbs, R.: Mechanism of arterial spasm following intra-arterial injection of thiopentone. Lancet 1: 1112–1115, 1959.
157. Burn, J. H. and Rand, M. J.: The action of sympathomimetic amines in animals treated with reserpine. J. Physiol. (London) 144: 314–336, 1958.
158. Burnstock, G. and Kirby, S.: Absence of inhibitory effects of catecholamines on lower vertebrate arterial strip perparations. J. Pharm. Pharmacol. 20: 404–406, 1968.
159. Burton, R. R., Besch, E. L. and Smith, A. H.: Effect of chronic hypoxia on the pulmonary arterial blood pressure of the chicken. Amer. J. Physiol. 214: 1438–1442, 1968.
160. Bygdeman, S.: Vascular reactivity in cats during induced changes in the acid-base balance of the blood. Acta Physiol. Scand. 61: 5–66, 1963.
161. Bygdeman, S.: Effect of respiratory acidosis on vasoconstrictor effects of directly and indirectly acting sympathomimetic amines in cats. Acta Physiol. Scand. 66: 444–447, 1966.
162. Campbell, A. G. M., Cockburn, F., Dawes, G. S. and Milligan, J. E.: Pulmonary vasoconstriction in asphyxia during cross-circulation between twin foetal lambs. J. Physiol. (London) 192: 111–121, 1967.
163. Campbell, A. G. M., Dawes, G. S., Fishman, A. P. and Hyman, A. I.: Pulmonary vasoconstriction and changes in heart rate during asphyxia in immature foetal lambs. J. Physiol. (London) 192: 93–110, 1967.
164. Campbell, G., Burnstock, G. and Wood, M.: A method for distinguishing between adrenergic and cholinergic excitatory innervation of smooth muscle. Quart. J. Exp. Physiol. Cog. Med. Sci. 49: 268–276, 1964.
165. Campbell, I. K. and Farmer, J. B.: The response of an isolated artery to sympathomimetic amines. J. Pharm. Pharmacol. 20: 19–25, 1968.
166. Capon, A.: Etude photoélectrique de la réactivité vasculaire de l'oreille du lapin en hypertension rénale. Arch. Int. Physiol. Biochim. 66: 105–108, 1958.
167. Carpenedo, F., Ferrari, M. and Furlanut, M.: Effects of some spasmolytic agents on the lipid-facilitated transport of calcium ions. J. Pharm. Pharmacol. 20: 733–734, 1968.

168. CARRIER, O., JR., COWSERT, M. HANCOCK, J. AND GUYTON, A. C.: Effect of hydrogen ion changes on vascular resistance in isolated artery segments. Amer. J. Physiol. 207: 169–172, 1964.
169. CARRIER, O., JR. AND HOLLAND, W. C.: Supersensitivity in perfused isolated arteries after reserpine. J. Pharmacol. Exp. Ther. 149: 212–218, 1965.
170. CARRIER, O., JR. AND SHIBATA, S.: A possible role for tissue calcium in reserpine supersensitivity. J. Pharmacol. Exp. Ther. 155: 42–49, 1967.
171. CARRIER, O., JR., WALKER, J. R. AND GUYTON, A. C.: Role of oxygen in autoregulation of blood flow in isolated vessels. Amer. J. Physiol. 206: 951–954, 1964.
172. CARTER, A. M., LEWIS, P. J. AND BENGTSSON, L. P.: Effects of vasopressin on uterine blood flow in the rabbit. Acta Pharmacol. Toxicol. 24: 435–442, 1966.
173. CASH, W. D. AND SMITH, B. L.: Synthesis and biological properties of 1-acetyl-8-lysine-vasopressin. J. Biol. Chem. 278: 994–997, 1963.
174. CASSIN, S., DAWES, G. S. AND ROSS, B. B.: Pulmonary blood flow and vascular resistance in immature foetal lambs. J. Physiol. (London) 171: 80–89, 1964.
175. CASTELS, R.: The action of ouabain on the smooth muscle cells of the guinea-pig's taenia coli. J. Physiol. (London) 184: 131–142, 1966.
176. CASTELLI, M. AND BAGGIO, G.: Antagonismo sulle strisce di aorta di coniglio tra alcuni β-bloccanti e noradrenalina ed istamina. Boll. Soc. Ital. Biol. Sper. 44: 958–961, 1968.
177. CEMBRANO, J., LILLO, M., VAL, J. AND MARDONES, J.: Influence of sex difference and hormones on elastine and collagen in the aorta of chickens. Circ. Res. 8: 527–529, 1960.
178. CERLETTI, A., WEBER, H. AND WEIDMANN, H.: Zur Wirkung von Phenylalanin^2-Lysin-Vasopressin (Octapressin) auf den arteriellen und venösen Anteil eines peripheren Gefassgebietes. Helv. Physiol. Pharmacol. Acta 21: 394–401, 1963.
179. CHALMERS, J. P. AND KORNER, P. I.: Effects of arterial hypoxia on the cutaneous circulation of the rabbit. J. Physiol. (London) 184: 685–697, 1966.
180. CHAN, W. Y., FEAR, R. AND DU VIGNEAUD, V.: Some pharmacologic studies on 1-L-penicillamine-oxytocin and 1-deaminopenillamine-oxytocin: two potent oxytocin inhibitors. Endocrinology 81: 1267–1277, 1967.
181. CHAN, W. Y. AND KELLEY, N.: A pharmacologic analysis on the significance of the chemical functional groups of oxytocin to its oxytocic activity and on the effect of magnesium on the *in vitro* and *in vivo* oxytocic activity of neurohypophysial hormones. J. Pharmacol. Exp. Ther. 156: 150–158, 1967.
182. CHAN, W. Y. AND WAHRENBURG, M.: Inactivation of oxytocin and deaminooxytocin by nonpregnant and pregnant rat uterine homogenates. Endocrinology 82: 475–479, 1968.
183. CHARBON, G. A.: Parathormone—a selective vasodilator. Excerpta Med. Int. Congr. Ser. No. 159: 475–484, 1967.
184. CHARBON, G. A.: A rapid and selective vasodilator effect of parathyroid hormone. European J. Pharmacol. 3: 275–278, 1968.
185. CHAUDHURY, R. R. AND TARAK, T. K.: Action of neurohypophysial hormones on the vascular system of the male monkey and the rooster. J. Pharm. Pharmacol. 17: 316–317, 1965.
186. CHENG, K. K. AND LI, K. M.: The hypotensive action of puffer fish toxin. J. Pathol. Bacteriol. 92: 471–476, 1966.
187. CHESLEY, L. C., TALLEDO, E., BOHLER, C. S. AND ZUSPAN, F. P.: Vascular reactivity to angiotensin II and norepinephrine in pregnant and nonpregnant women. Amer. J. Obstet. Gynecol. 91: 837–842, 1965.
188. CHESLEY, L. C. AND TEPPER, I. H.: Effects of progesterone and estrogen on the sensitivity to angiotensin II. J. Clin. Endocrinol. Metab. 27: 576–581, 1967.
189. CHOU, C. C., FROHLICH, E. D. AND TEXTER, E. C., JR.: A comparative study of the effects of bradykinin, kallidin II and eledoisin on segmental superior mesenteric resistance. J. Physiol. (London) 176: 1–11, 1965.
190. CHOU, C.-C. AND TEXTER, E. C., JR.: Comparison of effects of Fe^{++}, Fe^{+++}, and ferritin on intestinal circulation. Amer. J. Physiol. 210: 1447–1450, 1966.
191. CHRISTIANSEN, G. E., STEWART, G. M. AND BACON, R. L.: Direct observations on the response of blood vessels of fetal mice to norepinephrine. Angiology 14: 110–115, 1963.
192. CIUCHTA, H. P. AND GAUTIERI, R. F.: Effect of certain drugs on perfused human placentas. II. Vasodilators. J. Pharm. Sci. 52: 974–978, 1963.
193. CIUCHTA, H. P. AND GAUTIERI, R. F.: Effect of certain drugs on perfused human placenta. III. Sympathomimetics, acetylcholine, and histamine. J. Pharm. Sci. 53: 184–188, 1964.
194. CLEMENT, D., VANHOUTTE, P. AND LEUSEN, I.: Capacitance reactions of isolated veins to monoamines and acetylcholine. Arch. Int. Physiol. Biochim. 77: 73–87, 1969.
195. COHN, J. N., TRISTANI, F. E. AND KHATRI, I. M.: Systemic vasoconstrictor and renal vasodilator effects of PLV-2 (octapressin) in man. Circulation 38: 151–157, 1968.
196. COLE, K. S.: Membranes Ions and Impulses, University of California Press, Berkeley and Los Angeles, 1968.
197. COLEMAN, R. W., OSBAHR, A. J. AND MORRIS, R. E., JR.: New vasoconstrictor, bovine peptide B, released during blood coagulation. Nature (London) 215: 292–293, 1967.
198. CONCHA, J. AND NORRIS, B.: Studies on renal vasomotion. Brit. J. Pharmacol. 34: 277–290, 1968.
199. CONSTANTIN, B., TIEFFENBACH, L. AND ARDISSON, J. L.: Action du glucose hypertonique sur la vaso-motricité du territoire musculo-cutané chez le chien normal. Ann. Anesthésiol. Fr. 8: 3–18, 1967.
200. CORBIT, J. D., JR.: Effect of oxytocin on oxygen exchange between maternal and fetal circulation at the time of cesarean section. Amer. J. Obstet. Gynecol. 84: 1313–1315, 1962.
201. CREMA, A. AND CORONA, G. L.: Azione della idroclorotiazide sulla aorta isolata di coniglio. Boll. Soc. Ital. Biol. Sper. 37: 211–214, 1961.
202. CRISTOFORO, M. F. AND BRODY, M. J.: Non-adrenergic vasoconstriction produced by halothane and cyclopropane anesthesia. Anesthesiology 29: 44–56, 1968.

203. Cristoforo, M. F. and Brody, M. J.: The effects of halothane and cyclopropane on skeletal muscle vessels and baroreceptor reflexes. Anesthesiology 29: 36–43, 1968.
204. Cropp, G. J. A.: Effect of high intra-alveolar O_2 tension on pulmonary circulation in perfused lungs of dogs. Amer. J. Physiol. 208: 130–138, 1965.
205. Cutchin, J. H., McGaughey, H. S., Jr., Scoggin, W. A., Harbert, G. M., Jr. and Thornton, W. N., Jr.: Contractility of the isolated human uterine artery. Amer. J. Obstet. Gynecol. 90: 143–146, 1964.
206. D'Agostino, S. A. and Segura, E. T.: Effect of aldosterone and corticosterone upon vasomotor reactivity in adrenalectomized rats. Acta Physiol. Latinoamer. 14: 352–357, 1964.
207. Dahl, L. K., Heine, M. and Tassinari, L.: Effects of chronic excess salt ingestion. Vascular reactivity in two strains of rats with opposite genetic susceptibility to experimental hypertension. Circulation 29 and 30 (suppl. II): 11–22, 1964.
207a. Daly, I. de B. and Daly, M. de B.: The effects of stimulation of the carotid body chemoreceptors on the pulmonary vascular bed in the dog: the "vasosensory controlled perfused living animal" preparation. J. Physiol. (London) 148: 201–219, 1959.
208. Daly, I. de B., Michel, C. C., Ramsay, D. J. and Waaler, B. A.: Conditions governing the pulmonary vascular response to ventilation hypoxia and hypoxaemia in the dog. J. Physiol. (London) 196: 351–379, 1968.
209. Danforth, D. N., Manalo-Estrella, P. and Buckingham, J. C.: The effect of pregnancy and of enovid on the rabbit vasculature. Amer. J. Obstet. Gynecol. 88: 952–962, 1964.
210. Daniel, E. E. and Dawkins, O.: Aorta and smooth muscle electrolytes during early and late hypertension. Amer. J. Physiol. 190: 71–76, 1957.
211. Daniel, E. E., Dodd, A. and Hunt, J.: Effects of pitressin and isoproterenol on aorta electrolytes. Arch. Int. Pharmacodyn. Ther. 119: 43–55, 1959.
212. Daniel, E. E. and Irwin, J.: On the mechanism whereby certain nucleotides produced contractions of smooth muscle. Can. J. Physiol. Pharmacol. 43: 89–109, 1965.
213. Daniel, E. E. and Marks, G. S.: Pressor response to acetylcholine and the effects of N-diethylaminoethyl-N-isopentyl-N′N′-di-isopropylurea. Brit. J. Pharmacol. Chemother. 24: 449–454, 1965.
214. Daniel, E. E. and Nash, C. W.: The effects of diuretic and nondiuretic benzothiadiazine and of structurally related diuretic drugs on active ion transport and contractility in smooth muscles. Arch. Int. Pharmacodyn. Ther. 158: 139–154, 1965.
215. Daniel, E. E., Paton, D. M., Taylor, G. S. and Hodgson, B. J.: Adrenergic receptors for catecholamine effects on tissue electrolytes. Fed. Proc., in press.
216. Daniel, E. E., Robinson, K., Kidwai, A. M., Wolowyk, M. W., Taylor, G. S. and Paton, D. M.: The sodium pump in smooth muscle. *In* Vascular Neuroeffector Systems, ed. by J. A. Bevan, R. F. Furchgott, R. A. Maxwell and A. P. Somlyo, S. Karger, Basel, New York, in press.
217. Daniels, A. E. and Buckley, J. P.: Relation of the centrally evoked pressor effect of angiotensin II to the calcium ion. European J. Pharmacol. 4: 152–164, 1968.
218. Daugherty, R. M., Jr., Scott, J. B., Dabney, J. M. and Haddy, F. J.: Local effects of O_2 and CO_2 on limb, renal, and coronary vascular resistances. Amer. J. Physiol. 213: 1102–1110, 1967.
218a. Davies, B. N. and Withrington, P. G.: The effects of prostaglandins E_1 and E_2 on the smooth muscle of the dog spleen and on its responses to catecholamines, angiotensin and nerve stimulation. Brit. J. Pharmacol. Chemother. 32: 136–144, 1967.
219. Davis, E. and Landau, J.: The influence of adrenaline on the small blood vessels in normotension and hypertension. Bibl. Anat. 9: 1–6, 1966.
220. Dawes, G. S., Lewis, B. V., Milligan, J. E., Roach, M. R. and Talner, N. S.: Vasomotor responses in the hind limbs of foetal and newborn lambs to asphyxia and aortic chemoreceptor stimulation. J. Physiol. (London) 195: 55–81, 1968.
221. Day, M. D., McCubbin, J. W. and Page, I. H.: Limited hypertensive effect of infusion of angiotensin. Amer. J. Physiol. 209: 264–268, 1965.
222. Day, M. D. and Owen, D. A. A.: The interaction between angiotensin and sympathetic vasoconstriction in the isolated artery of the rabbit ear. Brit. J. Pharmacol. 34: 499–507, 1968.
223. Day, M. D., Owen, D. A. A. and Warren, P. R.: An adrenergic neuron blocking action of propranolol in isolated tissues. J. Pharm. Pharmacol. 20: 130S–134S, 1968.
224. De Freitas, F. M., Faraco, D. Z., De Azevdo, D. F. and Lewin, I.: Action of bradykinin on human pulmonary circulation. Observations in patients with mitral valvular disease. Circulation 34: 385–390, 1966.
225. De La Lande, I. S., Cannell, V. A. and Waterson, J. G.: The interaction of serotonin and noradrenaline on the perfused artery. Brit. J. Pharmacol. Chemother. 28: 255–272, 1966.
226. De La Lande, I. S., Frewin, D. and Waterson, J. G.: The influence of sympathetic innervation on vascular sensitivity to noradrenalin. Brit. J. Pharmacol. Chemother. 31: 82–93, 1967.
227. De La Lande, I. S., Frewin, D., Waterson, J. and Canell, V.: Factors influencing supersensitivity to noradrenalin in the isolated perfused artery; comparative effects of cocaine, denervation, and serotonin. Circ. Res. 20 and 21 (suppl. III): 177–181, 1967.
228. De La Lande, I. S., Paton, W. D. M. and Waud, B.: Output of sympathetic transmitter in the isolated rabbit ear. Aust. J. Exp. Biol. Med. Sci. 46: 727–738, 1968.
229. De La Lande, I. S. and Rand, M. J.: A simple isolated nerve-blood vessel preparation. Aust. J. Exp. Biol. Med. Sci. 43: 639–656, 1965.
230. De La Lande, I. S. and Waterson, J. G.: A comparison of the pharmacology of the isolated rabbit ear and its central artery. Aust. J. Exp. Biol. Med. Sci. 46: 739–745, 1968.

231. De La Lande, I. S. and Waterson, J. G.: The action of tyramine on the rabbit ear artery. Brit. J. Pharmacol. 34: 8–18, 1968.
232. Delaney, J. P., Goodale, R. L., Jr., Cheng, J. and Wangensteen, O. H.: The influence of vasopressin on upper gastrointestinal blood flow. Surgery 59: 397–400, 1966.
233. Demura, H., Fukuchi, S., Takahashi, H. and Goto, K.: The vascular reactivity to vasoactive substances and the electrolyte contents on arterial walls. Tohoku J. Exp. Med. 86: 366–379, 1965.
234. Dengler, H.: Über einen reninartigen Wirkstoff in Arterienextrakten. Arch. Exp. Pathol. Pharmakol. (Naunyn-Schmiedebergs) 227: 481–487, 1956.
235. DePasquale, N. P. and Burch, G. E.: Effect of angiotensin II on the intact forearm veins of man. Circ. Res. 13: 239–245, 1963.
236. DePasquale, N. P. and Burch, G. E.: Digital vascular responses to intraarterial injections of bradykinin, kallidin, and eledoisin in man. Circulation 34: 211–217, 1966.
237. DePasquale, N. P. and Burch, G. E.: Influence of bradykinin on isolated canine venous strips. Amer. Heart J. 75: 630–633, 1968.
238. Detar, R. and Bohr, D. F.: Adaptation to hypoxia in vascular smooth muscle. Fed. Proc. 27: 1416–1419, 1968.
239. Detar, R. and Bohr, D. F.: Oxygen and vascular smooth muscle contraction. Amer. J. Physiol. 214: 241–244 1968.
240. Devine, C. E.: The innervation of smooth muscle with particular reference to blood vessels. Thesis, Universisy of Otago, Dunedin, New Zealand, 1968.
240a. Devine, C. E., Simpson, F. O. and Bertaud, W. S.: Surface vesicles in vascular smooth muscle cells: a freeze-etch study. Proc. Univ. Otago Med. Sch. 47: 44–46, 1969.
240b. Devine, C. E. and Somlyo, A. P.: Ultrastructure of vascular smooth muscle (VSM) studied with lanthanum. Fed. Proc., 29: 455 Abs, 1970.
240c. Devine, C. E. and Somlyo, A. P.: Unpublished observations.
241. Diamond, J. and Marshall, J. M.: A comparison of the effects of various smooth muscle relaxants on the electrical and mechanical activity of rat uterus. J. Pharmacol. Exp. Ther. 168: 21–30, 1969.
242. Diamond, J. and Marshall, J. M.: Smooth muscle relaxants: dissociation between resting membrane potential and resting tension in rat myometrium. J. Pharmacol. Exp. Ther. 168: 13–20, 1969.
243. Diana, J. N. and Masden, R. R.: Effect of vasopressin infusion and sciatic nerve stimulation in isolated dog hindlimb. Amer. J. Physiol. 209: 390–396, 1965.
244. Diana, J. N., Schwinghamer, J. and Young, S.: Direct effect of histamine on arterial and venous resistance in isolated dog hindlimb. Amer. J. Physiol. 214: 494–505, 1968.
245. Dickinson, C. J. and Yu, R.: Mechanisms involved in the progressive pressor response to very small amounts of angiotensin in conscious rabbits. Circ. Res. 20 and 21 (suppl. II): 157–165, 1967.
246. Dikstein, S. and Sulman, F. G.: Interaction of dibenamine with the phospholipids of the aorta. Biochem. Pharmacol. 14: 881–885, 1965.
247. Distler, A., Liebau, H. and Wolf, H. P.: Action of angiotensin on sympathetic nerve endings in isolated blood vessels. Nature (London) 207: 764–765, 1965.
248. Dodd, J. M., Perks, A. M. M. and Dodd, M. H.: Physiological functions of neurohypophysial hormones in sub-mammalian vertebrates. *In* The Pituitary Gland, ed. by G. W. Harris and B. T. Donovan, vol. 3, pp. 578–623, University of California Press, Berkeley, 1966.
249. Dorevitch, N., Nayler, W. G. and Lowe, T. E.: The action on isolated smooth muscle of kinekard, a cardioactive fraction isolated from human plasma. J. Pharmacol. Exp. Ther. 155: 367–375, 1967.
250. Dorigotti, L. and Glässer, A. H.: Comparative effects of caerulein, pancreozymin and secretin on pancreatic blood flow. Experientia 24: 806–807, 1968.
251. Dörner, J. and Kuschke, H.-J.: Die Beeinflussung der neurogenen Adrenalin und Arterenoldilatation der Skeletmuskelgefässe durch Novocain, Atropin und Physostigmin, zugleich ein Beitra8 zur Frage der Existenz Vasodilatatorischer. Arch. Exp. Pathol. Pharmakol. 224: 368–377, 1955.
252. Dorr, L. D. and Brody, M. J.: Functional separation of adrenergic and cholinergic fibers to skeletal muscle vessels. Amer. J. Physiol. 208: 417–424, 1965.
253. Douglas, B. H., Carrier, O., Jr. and Garret, L.: Electrolyte changes in aortas of hypertensive pregnant and nonpregnant animals. Amer. J. Obstet. Gynecol. 97: 1092–1095, 1967.
254. Douglas, W. W.: Stimulus-secretion coupling: the concept and clues from chromaffin and other cells. Brit. J. Pharmacol. 34: 451–474, 1968.
255. Doutheil, U., Ten Bruggencate, H. G. and Kramer, K.: Coronar-vasomotorik unter L-Noradrenalin and Isopropylnoradrenalin nach Blockierung der adrenergischen β-Receptoren durch Nethalide. Pflügers Arch. Gesamte Physiol. Menschen Tiere 81: 181–190, 1964.
256. Doyle, A. E.: Vascular reactivity in human hypertension. N. Z. Med. J. 67: 295–303, 1968.
257. Dřímal, J.: Effects of angiotensin II on coronary smooth muscle. European J. Pharmacol. 5: 56–62, 1968.
258. Ducharme, D. W., Weeks, J. R. and Montgomery, R. G.: Studies on the mechanism of the hypertensive effect of prostaglandin $F_{2\alpha}$. J. Pharmacol. Exp. Ther. 160: 1–10, 1968.
259. Ducrot, H. and Astoin, M.: L'angiotensine peut-elle avoir une action vaso-dilatatrice? Pathol. Biol. 16: 525–528, 1968.
260. Duke, H. N.: The effect of adrenergic α-blocking agents on the pulmonary vasoconstrictor response to hypoxia in isolated cats' lungs. J. Physiol. (London) 196: 59–61, 1968.
261. Duke, H. N.: The pulmonary pressor response to hypoxia in isolated perfused lungs of cats; the influence of mepyramine maleate and semicarbazide. J. Physiol. (London) 200: 133–135, 1968.

261a. DULING, B. R. AND BERNE, R. M.: Propagated vasodilation in the microcirculation of the hamster cheek pouch. Circ. Res. 26: 163–170, 1970.

261b. DULING, B. R., BERNE, R. M. AND BORN, G. V. R.: Microiontophoretic application of vasoactive agents to the microcirculation of the hamster cheek pouch. Microvasc. Res. 1: 158–173, 1968.

262. DURBIN, R. P. AND JENKINSON, D. H.: The effect of carbachol on the permeability of depolarized smooth muscle to inorganic ions. J. Physiol. (London) 157: 74–89, 1961.

263. DURELL, J., GRALAND, J. T. AND FRIEDEL, R. O.: Acetylcholine action: biochemical aspects. Two major approaches to understanding the mechanism of action of acetylcholine are examined. Science 165: 862–866, 1969.

264. DU VIGNEAUD, V., DENNING, G. S., JR., DRABAREK, S. AND CHAN, W. Y.: The synthesis and pharmacological study of 4-decarboxamido-oxytocin (4-alpha-aminobutyric acid-oxytocin) and 5-decarboxamido-oxytocin (5-alanine-oxytocin). J. Biol. Chem. 239: 472–478, 1964.

265. DU VIGNEAUD, V., FLOURET, G. AND WALTER, R.: Synthesis and some biological properties of 4-valine-oxytocin and 1-deamino-4-valine-oxytocin. J. Biol. Chem. 241: 2093–2096, 1966.

266. EHRENPREIS, S., BIGO-GULLINO, M. AND AVERY, M. A.: The effect of cholinesterase inhibitors and lipid soluble quaternary ammonium compounds on contractions of rabbit aortic strip. Arch Int. Pharmacodyn. Ther. 156: 1–21, 1965.

267. EHRREICH, S. J. AND FURCHGOTT, R. F.: Relaxation of mammalian smooth muscles by visible and ultraviolet radiation. Nature (London) 218: 682–684, 1968.

268. ELIAKIM, M., ROSENBERG, S. Z. AND BRAUM, K.: Effect of hypertonic saline on the pulmonary and systemic pressures. Circ. Res. 6: 357–362, 1958.

269. ELIAKIM, M., STERN, S. AND NATHAN, H.: Site of action of hypertonic saline in the pulmonary circulation. Circ. Res. 9: 327–332, 1961.

270. ELTHERINGTON, L. G., STOFF, J., HUGHES, T. AND MELMON, K. L.: Constriction of human umbilical arteries. Interaction between oxygen and bradykinin. Circ. Res. 22: 747–752, 1968.

271. EMERSON, T. E., JR.: Changes of venous return and other hemodynamic parameters during bradykinin infusion. Amer. J. Physiol. 212: 1455–1460, 1967.

272. EMERSON, T. E., JR., HINSHAW, L. B. AND BRAKE, C. M.: Vascular effects of angiotensin and norepinephrine in the dog, cat, and monkey. Amer. J. Physiol. 208: 260–264, 1965.

273. EMERSON, T. E., JR. AND MASSION, W. H.: Direct and indirect vascular effects of cyclopropane and halothane in the dog forelimb. J. Appl. Physiol. 22: 217–222, 1967.

274. ERDÖS, E. G.: Hypotensive peptides: bradykinin, kallidin, and eledoisin. *In* Advances in Pharmacology, ed. by S. Garattini and P. A. Shore, vol. 4, pp. 1–90, Academic Press, New York, London, 1966.

275. ERDÖS, E. G., CANO, G. AND YANG, H. Y. T.: Hypotensive effect of LYS9-bradykinin in the guinea pig. Biochem. Pharmacol. 16: 1035–1041, 1967.

276. ERDÖS, E. G., MIWA, I. AND GRAHAM, W. J.: Studies on the evolution of plasma kinins: reptilian and avian blood. Life Sci. 6: 2433–2439, 1967.

277. ERSPAMER, V., ANASTASI, A., BERTACCINI, G. AND CEI, J. M.: Structure and pharmacological actions of physalaemin, the main active polypeptide of the skin of *Physalaemus fuscumulatus*. Experientia (Basal) 20: 489–492, 1964.

278. ERSPAMER, V. AND GLAESSER, A.: The action of eledoisin on the systemic arterial blood pressure of some experimental animals. Brit. J. Pharmacol. 20: 516–527, 1963.

279. EULER, U. S. V. AND LISHAJKO, F.: Catechol amines in the vascular wall. Acta Physiol. Scand. 42: 333–341, 1958.

280. EULER, U S. V. AND LISHAJKO, F.: Inhibitory action of adrenergic blocking agents on catecholamine release and uptake in isolated nerve granules. Acta Physiol. Scand. 68: 257–262, 1966.

281. EVERETT, S. D. AND MANN, S. P.: Catecholamine release by histamine from the isolated intestine of the chick. European J. Pharmacol. 1: 310–320, 1967.

282. FARMER, J. B.: The biphasic response of an isolated artery to tyramine. Brit. J. Pharmacol. Chemother. 28: 340–347, 1966.

283. FARMER, J. B. AND CAMPBELL, I. K.: Calcium and magnesium ions: influence on the response of an isolated artery to sympathetic nerve stimulation, noradrenalin and tyramine. Brit. J. Pharmacol. Chemother. 29: 319–328, 1967.

284. FAZEKAS, J. F. AND ALMAN, R. W.: Cerebral hemodynamic response to combined vasoactive agents. Amer. J. Med. Sci. 250: 70/36–75/41, 1965.

285. FEIGL, E. O.: Sympathetic control of coronary circulation. Circ. Res. 20: 262–271, 1967.

286. FEIGL, E. O., PETERSON, L. H. AND JONES, A. W.: Mechanical and chemical properties of arteries in experimental hypertension. J. Clin. Invest. 42: 1640–1647, 1963.

287. FEINSTEIN, M. B.: Inhibition of contraction and calcium exchangeability in rat uterus by local anesthetics. J. Pharmacol. Exp. Ther. 152: 516–524, 1966.

288. FEINSTEIN, M. B. AND PAIMRE, M.: Mechanism of cardiovascular action of tetrodotoxin in the cat. Block of conductance in peripheral sympathetic fibers. Circ. Res. 23: 553–565, 1968.

289. FEINSTEIN, M. B., PAIMRE, M. AND LEE, M.: Effect of local anesthetics on excitation-coupling mechanisms. Trans. N. Y. Acad. Sci. 30: 1073–1081, 1968.

290. FELDBERG, W. AND LEWIS, G. P.: Further studies on the effects of peptides on the suprarenal medulla of cats. J. Physiol. (London) 178: 239–251, 1965.

291. FERRARO, J. J. AND DU VIGNEAUD, V.: 7-D-Proline-oxytocin and its deamino analog. Diastereoisomers of oxytocin and deamino-oxytocin. J. Amer. Chem. Soc. 88: 3847–3850, 1966.

292. FERRIER, B. M. AND DU VIGNEAUD, V.: 9-Deamidooxytocin, an analog of the hormone containing a glycine residue in place of the glycinamide residue. J. Med. Chem. 9: 55–57, 1966.

293. FERRY, C. B.: Cholinergic link hypothesis in adrenergic neuroeffector transmission. Physiol. Rev. 46: 420–456, 1966.
294. FERUGLIO, F. S., GRECO, F., CESANO, L., INDOVINA, D., SARDI, G. AND CHIANDUSSI, L.: Effect of drug infusion on the systemic and splanchnic circulation. I. Bradykinin infusion in normal subjects. Clin. Sci. (London) 26: 487–491, 1964.
295. FERUGLIO, F. S., GRECO, F., CESANO, L., INDOVINA, D., SARDI, G. AND CHIANDUSSI, L.: Effect of drug infusion on the systemic and splanchnic circulation. II. Octapressin infusion in normal and cirrhotic subjects. Clin. Sci. (London) 26: 493–498, 1964.
296. FEWINGS, J. D., HANNA, M. J. D., WALSH, J. A. AND WHELAN, R. F.: The effects of ethyl alcohol on the blood vessels of the hand and forearm in man. Brit. J. Pharmacol. Chemother. 27: 93–106, 1966.
297. FEWINGS, J. D., RAND, M. J., SCROOP, G. C. AND WHELAN, R. F.: The action of nicotine on the blood vessels of the hand and forearm in man. Brit. J. Pharmacol. Chemother. 26: 567–579, 1966.
298. FISHMAN, A. P.: Respiratory gases in the regulation of the pulmonary circulation. Physiol. Rev. 41: 214–280, 1961.
299. FLEISHMAN, M., SCOTT, J. AND HADDY, F. J.: Effect of pH change upon systemic large and small vessel resistance. Circ. Res. 5: 602–606, 1957.
300. FLÜCKIGER, E. AND BALTHASAR, H. U.: Dihydroergocristin: unterschiedliche Wirkungen und venösem and arteriellem Gewebe. Arzneimittel-Forschung 17: 6–9, 1967.
301. FOLKOW, B., FOX, R. H., KROG, J., ODELRAM, H. AND THORÉN, O.: Studies on the reactions of the cutaneous vessels to cold exposure. Acta Physiol. Scand. 58: 342–354, 1963.
302. FOLKOW, B. AND SIVERTSSON, R.: Adaptive changes in "reactivity" and wall/lumen ratio in cat blood vessels exposed to prolonged transmural pressure difference. Life Sci. 7: 1283–1289, 1968.
303. FOLLE, L. E. AND AVIADO, D. M.: Cardiovascular effects of anoxia and the influence of a new *beta* adrenergic receptor blocking drug. J. Pharmacol. Exp. Ther. 149: 79–90, 1965.
304. FOLLETT, B. K. AND HELLER, H.: The neurohypophysial hormones of bony fishes and cyclostomes. J. Physiol. (London) 172: 74–91, 1964.
305. FONG, C. T. O., SILVER, L. AND LOUIE, D. D.: Necessity of the disulfide bond of vasopressin for antidiuretic activity. Biochem. Biophys. Res. Commun. 14: 302–306, 1964.
306. FOO, J. W., JOWETT, A. AND STAFFORD, A.: The effects of some β-adrenoreceptor blocking drugs on the uptake and release of noradrenaline by the heart. Brit. J. Pharmacol. 34: 141–147, 1968.
307. FORSTER, R. E.: Oxygenation of the tissue cell. Ann. N.Y. Acad. Sci. 117: 730–735, 1965.
308. FORTNER, C. L., MANLEY, E. S., JR. AND WOODBURY, R. A.: Effects of synthetic oxytocin with and without preservatives upon coronary blood flow in the dog. J. Pharmacol. Exp. Ther. 165: 258–266, 1969.
309. FOURMAN, J., KENNEDY, G. C. AND MOFFAT, D. B.: The blood vessels of the renal medulla. J. Physiol. (London) 191: 51–52p, 1967.
310. FOWLER, N. O. AND CHOU, N. H.: Potentiation of smooth muscle contraction by adrenal steroids. Circ. Res. 9: 153–156, 1961.
311. FOWLER, N. O. AND HOLMES, J. C.: Pulmonary pressor action of *l*-norepinephrine and angiotensin. Amer. Heart J. 70: 66–78, 1965.
312. FOZARD, J. R. AND LEACH, G. D. H.: The hypotensive action of 5-hydroxytryptamine (5-ht) in anaesthetised and pithed rats. European J. Pharmacol. 2: 239–249, 1968.
313. FRAY, R., JR. AND LEADERS, F. E.: Demonstration of separate adrenergic and cholinergic fibres to the vessels of the rear quarters of the rat by hemicholinium and a proposed role in peripheral vascular regulation. Brit. J. Pharmacol. Chemother. 30: 265–273, 1967.
314. FREED, S. C., GEORGE, S. S. AND ROSENMAN, R. H.: Arterial wall potassium in renal hypertensive rats. Circ. Res. 7: 219–223, 1959.
315. FREGNAN, G. B. AND GLÄSSER, A. H.: Vasodilating activity of the natural polypeptide physalaemin on hind limb and on coronary vascular beds of dog. Comparison with eledoisin and nitroglycerin. Arch. Int. Pharmacodyn. Ther. 171: 435–448, 1968.
316. FREGNAN, G. B., GLÄSSER, A. H. AND BERETTA, C.: Further studies of the action of smooth muscle of eledoisin-fragments and eledoisin-like hepta- and hexapeptides. European J. Pharmacol. 4: 421–426, 1968.
317. FREWIN, D. B. AND WHELAN, R. F.: The action of ephedrine on forearm blood vessels in man. Aust. J. Exp. Biol. Med. Sci. 46: 425–434, 1968.
318. FREY, H. M. M.: Peripheral circulatory and metabolic consequences of thyrotoxicosis. III. Vascular reactivity to catecholamines and the effect of sympathetic receptor blockade on blood flow and oxygen consumption of skeletal muscle in experimental thyrotoxicosis in the dog. Scand. J. Clin. Lab. Invest. 19: 132–142, 1967.
319. FRIEDMAN, S. M. AND FRIEDMAN, C. L.: The ionic matrix of vasoconstriction. Circ. Res. 20 and 21(suppl. II): 147–155, 1967.
320. FRIEDMAN, S. M., NAKASHIMA, M. AND FRIEDMAN, C. L.: Effects of cooling and rewarming on Na, K, and tension changes in rat tail artery. Can. J. Physiol. Pharmacol. 46: 25–34, 1968.
320a. FRIEDMAN, S. M., NAKASHIMA, M. AND PALATY, V.: Glass electrode measurement of ion transfers during rewarming of the single rat tail artery. Can. J. Physiol. Pharmacol. 47: 863–869, 1969.
321. FRIEDMANN, N. AND PARK, C. R.: Early effects of 3′,5′-adenosine monophosphate on the fluxes of calcium and potassium in the perfused liver of normal and adrenalectomized rats. Proc. Nat. Acad. Sci. 61: 504–508, 1968.
322. FROHLICH, E. D.: Local effect of adenosine mono-, di-, triphosphate vessel resistance. Amer. J. Physiol. 204: 28–30, 1963.
323. FROHLICH, E. D.: Vascular effects of the Krebs intermediate metabolites. Amer. J. Physiol. 208: 149–153, 1965.
324. FULLERTON, A. AND MORRISON, J. F. B.: A comparison of certain responses of the vascular system of rats after the administration of progesterone and oestrogen. J. Endocrinol. 33: 75–81, 1965.

325. FURCHGOTT, R. F.: Receptor mechanisms. Annu. Rev. Pharmacol. 4: 21-50, 1964.
326. FURCHGOTT, R. F.: The pharmacological differentiation of adrenergic receptors. Ann. N.Y. Acad. Sci. 139: 553-570, 1967.
327. FURCHGOTT, R. F.: Effects of various agents on photorelaxation of rabbit aortic strips. *In* Vascular Neuroeffector Systems, ed. by J. A. Bevan, R. F. Furchgott, R. A. Maxwell and A. P. Somlyo, S. Karger, Basel, in press.
328. FURCHGOTT, R. F. AND BURSZTYN, P.: Comparison of dissociation constants and of relative efficacies of selected agonists acting on parasympathetic receptors. Ann. N. Y. Acad. Sci. 144: 882-899, 1967.
329. FURCHGOTT, R. F., EHRREICH, S. J. AND GREENBLATT, E.: The photoactivated relaxation of smooth muscle of rabbit aorta. J. Gen. Physiol. 44: 499-519, 1961.
330. FURCHGOTT, R. F. AND GARCIA, P. S.: Effects of inhibition of monoamine oxidase on the actions and interactions of norepinephrine, tyramine and other drugs on guinea-pig left atrium. J. Pharmacol. Exp. Ther. 163: 98-122, 1968.
331. FURCHGOTT, R. F., KIRPEKAR, S. M., RIEKAR, M. AND SCHWAB, A.: Actions and interactions of norepinephrine, tyramine and cocaine on aortic strips of rabbit and left atria of guinea pig and cat. J. Pharmacol. Exp. Ther. 142: 39-58, 1963.
332. GARATTINI, S. AND VALZELLI, L.: Serotonin, Elsevier Publ. Co., Amsterdam, London, New York, 1965.
333. GARDNER, D. L. AND HONORÉ, L. H.: Vascular response to catecholamines and to acetylcholine in adrenal-regeneration hypertension. Arch. Int. Pharmacodyn. Ther. 150: 504-515, 1964.
334. GARRETT, J. AND SOUSA, C.: Effects of guanethidine on smooth muscles. Arzneimittel-Forschung 13: 125-130, 1963.
335. GASKELL, P.: Digital vascular response to angiotensin II in normotensive and hypertensive subjects. Evidence for a qualitatively abnormal response to angiotensin in essential hypertension. Circ. Res. 20: 174-184, 1967.
336. GASKELL, P. AND HOEPPNER, D. L.: The effect of local temperature on the reactivity to noradrenalin of digital vessels. Can. J. Physiol. Pharmacol. 45: 93-102, 1967.
337. GATTI, A., CAVAGNA, G. AND GIUSTINA, G.: Variazioni del contenuto di acqua e degli ioni Na e K delle arterie di coniglio *in vivo* e *in vitro* per effetto dell' idroclorotiazide. Clin. Ter. 22: 245-249, 1962.
338. GEBERT, G., KONOLD, P. AND SEBOLDT, H.: Eigenschaften und Beeinflussbarkeif der mechanischen Spontanaktivität isolierter Arterien. Pflügers Arch. Gesamte Physiol. Menschen Tiere 299: 285-294, 1968.
339. GELLER, R. G. AND KENDRICK, J. E.: Flow responses to angiotensin in innervated and denervated kidneys. Proc. Soc. Exp. Biol. Med. 129: 727-730, 1968.
340. GENEST, J., SIMARD, S., ROSENTHAL, J. AND BOUCHER, R.: Norepinephrine and renin content in arterial tissue from different vascular beds. Can. J. Physiol. Pharmacol. 47: 87-91, 1969.
341. GEROVÁ, M. AND GERO, J.: The effect of prolonged sympathetic stimulation on conduit vessel diameter. Experientia (Basel) 24: 1134-1135, 1968.
342. GEUMEI, A., ISSA, I. AND MAHFOUZ, M.: Intra-hepatic vascular response to sodium nitrite. Brit. J. Pharmacol. 35: 456-459, 1969.
343. GHOURI, M. S. K. AND HALEY, T. J.: Structure-activity relationships in the adrenergic-blocking agents. J. Pharm. Sci. 58: 511-538, 1969.
344. GILBERT, R. P., HINSHAW, L. B., KUIDA, H. AND VISSCHER, M. B.: Effects of histamine, 5 hydroxytryptamine and epinephrine on pulmonary hemodynamics with particular reference to arterial and venous segment resistances. Amer. J. Physiol. 194: 165-170, 1968.
345. GILLESSEN, D. AND DU VIGNEAUD, V.: The synthesis and pharmacological properties of 4-decarboxamido-8-lysine-vasopressin, 5-decarboxamide-8-lysine-vasopressin, and their 1-deamino analogues. J. Biol. Chem. 242: 4806-4812, 1967.
346. GILLIS, C. N. AND PATON, D. M.: Cation dependence of sympathetic transmitter retention by slices of rat ventricle. Brit. J. Pharmacol. Chemother. 29: 309-318, 1967.
347. GILLMAN, R. G. AND BURTON, A. C.: Constriction of the neonatal aorta by raised oxygen tension. Circ. Res. 19: 755-765, 1966.
348. GINSBURG, J. AND DUFF, R. S.: Influence of intra-arterial hydrocortisone on adrenergic responses in the hand. Brit. Med. J. No. 5093: 424-427, 1958.
349. GINSBURG, M.: Production, release, transportation and elimination of the neurohypophysial hormones. *In* Handbook of Experimental Pharmakologie, vol. 23, pp. 286-371, ed. by B. Berde, Springer-Verlag, New York, 1968.
350. GIRARD, M. H.: Action de la noradrénaline et de l'adrénaline sur la circulation embryonnaire du poulet. C. R. Hebd. Séances Acad. Sci. Paris 265: 2023-2026, 1967.
351. GLADNER, J. A., MURTAUGH, P. A., FOLK, J. E. AND LAKI, K.: Nature of peptides released by thrombin. Ann. N.Y. Acad. Sci. 104: 47-52, 1963.
352. GLOVER, W. E., HANNA, M. J. D. AND SPEDEN, R. N.: Actions of cardiac glycosides on the vessels of the forearm and hand. Cardiovasc. Res. Center Bull. (Baylor Univ. Houston) 1: 341-348, 1967.
353. GLOVER, W. E. AND HUTCHISON, K. J.: The effect of a beta-receptor antagonist (propranolol) on the cardiovascular response to intravenous infusions of noradrenalin in man. J. Physiol. (London) 177: 59-60, 1965.
354. GLOVER, W. E., STRANGEWAYS, D. H. AND WALLACE, W. F. M.: Responses of isolated ear and femoral arteries of the rabbit to cooling and to some vasoactive drugs. J. Physiol. (London) 194: 78-79, 1967.
355. GLYNN, I. M.: Membrane adenosine triphosphatase and cation transport. Brit. Med. Bull. 24: 165-169, 1968.
356. GODFRAIND, T.: Pharmacology of angiotensin antagonists. *In* Pharmacology of Hormonal Polypeptides and Proteins, pp. 497-506, Plenum Press, New York, 1968.
357. GODFRAIND, T. AND KABA, A.: Actions phasique et tonique de l'adrénaline sur un muscle lisse vasculaire et leur inhibition par des agents pharmacologiques. Arch. Int. Pharmacodyn. Ther. 178: 488-491, 1969.

358. GODFRAIND, T. AND KABA, A.: Blockade or reversal of the contraction induced by calcium and adrenaline in depolarized arterial smooth muscle. Brit. J. Pharmacol., 36: 549–560, 1969.
359. GODFRAIND, T. AND POLSTER, P.: Etude comparative de médicaments inhibant la réponse contractile de vaisseaux isolés d'origine humaine ou animale. Therapie, 23: 120–122, 1968.
360. GOKHALE, S. D., GULATI, O., KELKAR, L. V. AND KELKAR, V. V.: Effect of some drugs on human umbilical artery in vitro. Brit. J. Pharmacol. Chemother. 27: 332–346, 1966.
361. GOLDMAN, H.: Oxytocin modulation of blood flow in the unanesthetized male rat. Amer. J. Physiol. 214: 860–862, 1968.
362. GOLENHOFEN, K. AND PETRÁNYI, P.: Spikes of smooth muscle in calcium-free solution (isolated taenia coli of the guinea-pig). Experientia (Basel) 25: 271–273, 1969.
363. GOODRICH, S. M. AND WOOD, J. E.: Th effect of estradiol-17β on peripheral venous distensibility and velocity of venous blood flow. Amer. J. Obstet. Gynecol. 96: 407–412, 1966.
364. GORDON, D. B. AND NOGUEIRA, A.: Increased vascular reactivity in experimental hypertension. Circ. Res. 10: 269–273, 1962.
365. GORSKY, B. H. AND LLOYD, T. C., JR.: Effects of perfusate composition on hypoxic vasoconstriction in isolated lung lobes. J. Appl. Physiol. 23: 683–686, 1967.
366. GOSTIMIROVICH, D.: Estrogen effects on the aortic wall in young immature rabbits. Virchows Arch. Pathol. Anat. Physiol. Klin. Med. 343: 258–264, 1968.
367. GOULD, A. B., SKEGGS, L. T., JR. AND KAHN, J. R.: The presence of renin activity in blood vessel walls. J. Exp. Med. 119: 389–400, 1964.
368. GRAHAM, J. D. P. AND AL KATIB, H.: The effect of 2-halogenoalkylamines on the biological activity of some peptides. Brit. J. Pharmacol. Chemother. 27: 377–386, 1966.
369. GRANT, R. T.: The effects of denervation on skeletal muscle blood vessels (rat cremaster). J. Anat. 100: 305–316, 1966.
370. GREEN, H. D. AND DENISON, A. B., JR.: Absence of vasomotor responses to epinephrine and arterenol in an isolated intracranial circulation. Circ. Res. 4: 565–573, 1956.
371. GREEN, J. P.: Uptake and binding of histamine. Fed. Proc. 26: 211–218, 1967.
372. GREENBERG, R. A. AND SPARKS, H. V.: Prostaglandins and consecutive vascular segments of the canine hindlimb. Amer. J. Physiol. 216: 567–571, 1969.
373. GREISS, F. C., JR. AND WILKES, D. V.: Effects of sympathomimetic drugs and angiotensin on the uterine vascular bed. Obstet. Gynecol. 23: 925–930, 1964.
374. GRÉVISSE, J. AND GOFFART, M.: "Activation" de l'ion plomb par la cystéamine sur certains muscles lisses isolés du lapin. J. Physiol. (Paris) 51: 471–472, 1959.
375. GRIESEMER, E. C. AND CORET, I. A.: "Recovery" responses of hypoxic arterial smooth muscle. J. Pharmacol. Exp. Ther. 130: 294–302, 1960.
376. GULATI, O. D., GOKHALE, S. D., PARIKH, H. M. UDWADIA, B. P. AND KRISHNAMURTY, V. S. R.: Evidence for a sympathetic *alpha* receptor blocking action of *beta* receptor blocking agents. J. Pharmacol. Exp. Ther. 166: 35–43, 1969.
377. GUNN, S. A., GOULD, T. C. AND AND ANDERSON, W. A. D.: The selective injurious response of testicular and epididymal blood vessels to cadmium and its prevention by zinc. Amer. J. Pathol. 42: 685–702, 1963.
378. GUTH, P. S., BOBBIN, R., CANO, G. AND AMARO, J.: Venoconstriction induced by bradykinin in the rabbit ear. *In* Hypotensive Peptides, ed. by E. E. Erdos, N. Back and F. Sicuteri, Springer-Verlag, New York, 1966.
379. GUTTMANN, S. AND BOISSONNAS, R. A.: Synthèse de la sér^4-oxytocine, de l'ala^4-oxytocine, de la sér^5-oxytocine et de l'ala^5-oxytocine. Helv. Chim. Acta 46: 1626–1636, 1963.
380. GYERMEK, L.: 5-Hydroxytryptamine antagonists. Pharmacol. Rev. 13: 399–439, 1961.
381. HADDY, F. J., FLEISHMAN, M. AND SCOTT, J. B., JR.: Effect of change in air temperature upon systemic small and large vessel resistance. Circ. Res. 5: 58–63, 1957.
382. HADDY, F. J., GORDON, P. AND EMANUEL, D. A.: The influence of tone upon responses of small and large vessels to serotonin. Circ. Res. 7: 123–130, 1959.
383. HADDY, F. J. AND SCOTT, J. B.: Metabolically linked vasoactive chemicals in local regulation of blood flow. Physiol. Rev. 48: 688–707, 1968.
383*a*. HAEUSLER, G., HAEFELY, W. AND HUERLIMANN, A.: Effect of surgical and chemical adrenergic denervation on vascular responses. *In* Vascular Neuroeffector Systems, ed by J. A. Bevan, R. F. Furchgott, R. A. Maxwell and A. P. Somlyo, S. Karger, Basel, New York, in press.
384. HAUESLER, G., THOENEN, H., HAEFELEY, W. AND HUERLIMANN, A.: Electrical events in cardiac adrenergic nerves and noradrenaline release from the heart induced by acetylcholine and KCl. Nauyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 261: 389–411, 1968.
384*a*. HAEUSLER, G., THOENEN, H., HAEFELY, W. AND HUERLIMANN, A.: Elektrosekretorische Koppelung bei der Noradrenalinfreisetzung aus adrenergen Nervenfasern durch nicotinartig wirkende Substanzen. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 263: 217, 1969.
385. HÄGGENDAL, E.: Effects of some vasoactive drugs on the vessels of cerebral grey matter in the dog. Acta Physiol. Scand. 66: 55–79, 1965.
386. HÄGGENDAL, J. AND SVEDMYR, N.: Studies on the destruction of adrenaline in nutrient solution. Acta Pharmacol. Toxicol. 25: 364–386, 1967.
387. HAGIWARA, S., GRUENER, R., HAYASHI, H., SAKATA, H. AND GRINNELL, A. D.: Effect of external and internal pH changes on K and Cl conductances in the muscle fiber membrane of a giant barnacle. J. Gen. Physiol. 52: 773–792, 1968.

388. HAGIWARA, S. AND NAKAJIMA, S.: Differences in Na and Ca spikes as examined by application of tetrodotoxin, procaine, and manganese ions. J. Gen. Physiol. 49: 793–806, 1966.
389. HAIGH, A. L., KITCHIN, A. H. AND PICKFORD, M.: The effect of oxytocin on hand blood flow in man following the administration of an oestrogen and isoprenaline. J. Physiol. (London) 169: 161–166, 1963.
390. HAIGH, A. L., LLOYD, S. AND PICKFORD, M.: A relationship between adrenaline and the mode of action of oxytocin and oestrogen on vascular smooth muscle. J. Physiol. (London) 178: 563–576, 1965.
391. HALE, A. J., HALL, T. AND CURRAN, R. C.: Electron-microprobe analysis of calcium phosphorus and sulphur in human arteries. J. Pathol. Bacteriol. 93: 1–17, 1967.
392. HALPERN, B. N., BINAGHI, R., MAYER, M. AND BUGNARD, C.: The mechanism of the inhibition by carbonic acid of the smooth muscle contraction produced by histamine and oxytocin. Brit. J. Pharmacol. 14: 19–25, 1959.
393. HANDA, J., MEYER, J. S. AND YOSHIDA, K.: Regional pharmacologic responses of the vertebral and internal carotid arteries. J. Pharmacol. Exp. Ther. 152: 251–264, 1966.
394. HANNA, C.: Tachyphylaxis. V. Actions of optical isomers of sympathomimetic amines on rabbit aortic strips. Arch. Int. Pharmacodyn. Ther. 129: 191–200, 1960.
395. HARMS, D.: Über den Verschluss der Ductus arteriosi von *Gallus domesticus*. Z. Zellforsch. Mikroskop. Anat. 81: 433–444, 1967.
396. HARRISON, T. S.: Adrenal medullary and thyroid relationships. Physiol. Rev. 44: 161–185, 1964.
397. HARVEY, R. M.: The influence of hydrogen ion in the control of pulmonary artery pressures in patients with obstructive disease of the lungs. Med. Thorac. 22: 108–117, 1965.
398. HASHIMOTO, K., KUMAKURA, S. AND IGARASHI, S.: Pharmacological features of coronary vascular vessels. Jap. Circ. J. 27: 149–153, 1963.
399. HASHIMOTO, K., KUMAKURA, S. AND TANEMURA, I.: Mode of action of adenine, uridine and cytidine nucleotides and 2,6-bis (diethanolamino)-4,8-dipiperidino-pyrimidino (5,4-d) pyrimidine on the coronary, renal and femoral arteries. Arzneimittel-Forschung 14: 1252–1254, 1964.
400. HASHIMOTO, K. AND SANO, N.: Potentiation of the coronary vasodilator effect of norepinephrine by 2,6-bis (diethanolamino)-4,8-dipiperidino-pyrimido (5,4-d) pyrimidine (dipyridamole). Tohoku J. Exp. Med. 96: 207–208, 1968.
401. HATAKEYAMA, I. AND KATO, R.: Vasodilative and vasoconstrictive action of acetylcholine on the hindlimb perfusion preparation. Yokohama Med. Bull. 9: 391–408, 1958.
402. HATAKEYAMA, I. AND KATO, R.: A comparison of sensitivity of large blood vessels to adrenaline and acetylcholine. Yokohama Med. Bull. 10: 34–38, 1959.
403. HATTORI, K. AND SHIBATA, S.: Effect of tranylcypromine on the mechanical activity of rabbit aorta and esophagus and guinea pig taenia coli. European J. Pharmacol. 5: 291–295, 1969.
404. HAUGAARD, N.: Cellular mechanisms of oxygen toxicity. Physiol. Rev. 48: 311–373, 1968.
405. HAUGE, A.: Studies on the Effect of Acute Hypoxia on Pulmonary Vascular Resistance. Universitetsforlagets Trykningssentral, Oslo, 1968.
406. HAUGE, A., LUNDE, P. K. M. AND WAALER, B. A.: The effect of bradykinin, kallidin and eledoisin upon the pulmonary vascular bed of an isolated blood-perfused rabbit lung preparation. Acta Physiol. Scand. 66: 266–277, 1966.
407. HAUGE, A., LUNDE, P. K. M. AND WAALER, B. A.: Effects of prostaglandin E_1 and adrenaline on the pulmonary vascular resistance (PVR) in isolated rabbit lungs. Life Sci. 6: 673–680, 1967.
408. HÁVA, M. AND HELFERT, I.: Steroid blocking effect on smooth muscle contraction. Arch. Int. Pharmacodyn. Ther. 166: 79–86, 1967.
409. HEEG, E. AND MENG, K.: Die Wirkung des Bradykinins, Angiotensins und Vasopressins auf Vorhof, Papillarmuskel und isoliert durchströmte Herzpräparate des Meerschweinchens. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 250: 35–41, 1965.
410. HELMER, O. M.: Action of natural angiotensin II and synthetic analogues on strips of rabbit aorta. Amer. J. Physiol. 207: 368–370, 1964.
411. HENNING, M. AND JOHNSSON, G.: Interference of phenoxybenzamine and guanethidine with the vasoconstrictor responses of noradrenaline and angiotensin II in the hand. Acta Pharmacol. Toxicol. 25: 373–384, 1967.
412. HERTTING, G. AND SUKO, J.: Influence of angiotensin, vasopressin or changes in flow rate of vasoconstriction, changes in volume and (^{3}H)-noradrenaline release following postganglionic sympathetic nerve stimulation in the isolated cat spleen. Brit. J. Pharmacol. Chemother. 26: 686–696, 1966.
413. HETTIARATCHI, E. S. G.: Some vascular effects of angiotensin in the rat. J. Physiol. (London) 190: 28P, 1967.
414. HETTIARATCHI, E. S. G. AND PICKFORD, M.: The effect of oestrogen and progesterone on the pressor action of angiotensin in the rat. J. Physiol. (London) 196: 447–451, 1968.
415. HICKLER, R. B., LAULER, D. P., SARAVIS, C. A., VAGNUCCI, A. I., STEINER, G. AND THORN, G. W.: Vasodepressor lipid from the renal medulla. Can. Med. Ass. J. 90: 280–287, 1964.
416. HILDEBRAND, G. J. AND SEYS, Y.: Depolarizing action of endotoxin. Nature (London) 206: 406–407, 1965.
417. HILL, A. J. AND KOHLI, J. D.: Adrenoceptive receptors in the duodenum, aorta and atria of the rabbit. J. Pharm. Pharmacol. 19: 350–354, 1967.
418. HILTON, S. M.: Local mechanisms regulating peripheral blood flow. Physiol. Rev. 42 (suppl. 5): 265–275, 1962.
419. HILTON, S. M. AND JONES, M.: The role of plasma kinin in functional vasodilatation in the pancreas. J. Physiol. (London) 195: 521–533, 1968.
420. HINKE, J. A. M.: In vitro demonstration of vascular hyper-responsiveness in experimental hypertension. Circ. Res. 17: 359–371, 1965.
421. HINKE, J. A. M.: Effect of Ca^{++} upon contractility of small arteries from DCA-hypertensive rats. Circ. Res. 18 and 19(suppl. I): 23–34, 1966.

422. HINKE, J. A. M. AND WILSON, M. L.: Effects of electrolytes on contractility of artery segments in vitro. Amer. J. Physiol. 203: 1161-1166, 1962.
423. HODARI, A. A., SMEBY, R. AND BUMPUS, F. M.: A renin-like substance in the human placenta. Obstet. Gynecol. 29: 313-317, 1967.
424. HOLLANDER, W., KRAMSCH, D. M., FARMELANT, M. AND MADOFF, I. M.: Arterial wall metabolism in experimental hypertension of coarctation of the aorta of short duration. J. Clin. Invest. 47: 1221-1229, 1968.
425. HOLMES, S. W., HORTON, E. W. AND MAIN, I. H. M.: The effect of prostaglandin E_1 on responses of smooth muscle to catecholamines, angiotensin and vasopressin. Brit. J. Pharmacol. 21: 538-543, 1963.
426. HONDA, F. AND IMAMURA, H.: Inhibition of cyclic 3',5'-nucleotide phosphodiesterase by phenothiazine and reserpine derivatives. Biochim. Biophys. Acta 161: 267-269, 1968.
427. HONG, E. AND RODRÍGUEZ, R.: Influence of several catecholamine depleting compounds on the reactivity of aorta strips. Acta Physiol. Latinoamer. 15: 88-90, 1965.
428. HONIG, C. R.: Control of smooth muscle actomyosin by phosphate and 5'AMP: possible role in metabolic autoregulation. Microvasc. Res. 1: 133-146, 1968.
429. HONORÉ, L. H.: The vascular responses of male and female rats to vasopressin and oxytocin following a single dose of testosterone propionate. Quart. J. Exp. Physiol. Cog. Med. Sci. 49: 15-20, 1964.
430. HONORÉ, L. H. AND GARDNER, D. L.: Cardiovascular reactivity of rats during the development of salt hypertension. I. The response to polypeptides. Arch. Int. Pharmacodyn. Ther. 164: 173-182, 1966.
431. HONORÉ, L. H. AND GARDNER, D. L.: Cardiovascular reactivity of rats during the development of salt hypertension. II. The responses to adrenaline, noradrenaline and acetylcholine. Arch. Int. Pharmacodyn. Thér. 164: 183-191, 1966.
432. HONORÉ, L. H. AND LLOYD, S.: The effects of castration on the vascular responses of male rats to posterior pituitary hormones. J. Physiol. (London) 159: 183-190, 1961.
433. HOROWITS, J. D. AND MASHFORD, M. L.: Vasoactivity of human plasma and plasma protein fractions. Experientia (Basel) 24: 1126-1127, 1968.
434. HOROWITS, J. D. AND MASHFORD, M. L.: A perfused vein preparation sensitive to plasma kinins. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 263: 332-339, 1969.
435. HOROWITZ, J. D. AND MASHFORD, M. L.: The action of adrenal steroids on the pharmacological reactivity of the isolated vein of the rabbit ear. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 263: 324-331, 1969.
436. HOROWTIZ, J. D. AND MASHFORD, M. L.: Bradykinin antagonism by dimethothiazine. J. Pharm. Pharmacol 21: 51-53, 1969.
437. HORTON, E. W.: Action of prostaglandin E_1 on tissues which respond to bradykinin. Nature (London) 200: 892-893, 1963.
438. HORTON, E. W.: Hypotheses on physiological roles of prostaglandins. Physiol. Rev. 49: 122-161, 1969.
440. HRDINA, P., BONACCORSI, A. AND GARATTINI, S.: Pharmacological studies on isolated and perfused rat renal arteries. European J. Pharmacol. 1: 99-108, 1967.
441. HRDINA, P. AND GARATTINI, S.: Desipramine and potentiation of noradrenaline in the isolated perfused renal artery. J. Pharm. Pharmacol. 18: 259-260, 1966.
441a. HRUBY, V. J. AND DU VIGNEAUD, V.: Synthesis and some pharmacological activities of (2-L-valine)-oxytocin and (2-L-leucine)-oxytocin. J. Med. Chem. 12: 731-733, 1969.
442. HRUBY, V. J., FLOURET, G. AND DU VIGNEAUD, V.: The synthesis and some of the pharmacological properties of (4-L-isoleucine)-oxytocin and (4-L-leucine)-oxytocin. J. Biol. Chem. 244: 3890-3894, 1969.
443. HRUZA, Z. AND ZWEIFACH, B. W.: Effect of age on vascular reactivity to catecholamines in rats. J. Gerontol. 22: 469-473, 1967.
444. HUDGINS, P. M. AND FLEMING, W. W.: A relatively nonspecific supersensitivity in aortic strips resulting from pretreatment with reserpine. J. Pharmacol. Exp. Ther. 153: 70-80, 1966.
445. HUGHES, J. AND VANE, J. R.: An analysis of the responses of the isolated portal vein of the rabbit to electrical stimulation and to drugs. Brit. J. Pharmacol. Chemother. 30: 46-66, 1967.
446. HUGHES, M. J. AND CORET, I. A.: Evolution of epinephrine responses of hypoxic rabbit aortic muscle. Amer. J. Physiol. 216: 1423-1428, 1969.
447. HUIDOBRO, H. V. AND PALADINI, A. C.: Potentiation of angiotensin action on smooth muscle by alkaline pH. Experientia (Basel) 19: 572, 1963.
448. HURWITZ, L., BATTLE, F. AND WEISS, G. B.: Action of the calcium antagonists cocaine and ethanol on contraction and potassium efflux of smooth muscle. J. Gen. Physiol. 46: 315-332, 1962.
449. HYDE, R. W., LAWSON, W. H. AND FORSTER, R. E.: Influence of carbon dioxide on pulmonary vasculature. J. Appl. Physiol. 19: 734-744, 1964.
450. HYMAN, A. L.: The pulmonary veins. Annu. Rev. Med. 17: 431-446, 1966.
451. HYMAN, A. L.: The effects of bradykinin on the pulmonary veins. J. Pharmacol. Exp. Ther. 161: 78-87, 1968.
452. HYMAN, A. L.: The active responses of pulmonary veins in intact dogs to prostaglandins F_2 *Alpha* and E_1. J. Pharmacol. Exp. Ther. 165: 267-273, 1969.
453. HYMAN, C. AND PALDINO, R. L.: Influence of intravascular and topically administered bradykinin on microcirculation of several tissues. Bibl. Anat. 9: 38-45, 1966.
454. ICHIKAWA, S.: Muscle-stimulating fatty acid isolated from placenta. Amer. J. Physiol. 198: 1094-1098, 1960.
455. ICHIKAWA, S. AND YAMADA, J.: Biological actions of free and albumin-bound arachidonic acid. Amer. J. Physiol. 203: 681-684, 1962.
456. INGRAM, D. L. AND WEAVER, M. E.: A quantitative study of the blood vessels of the pig's skin and the influence of environmental temperature. Anat. Rec. 163: 517-524, 1969.
457. IRISAWA, H., SHIGETO, N. AND SEYAMA, I.: Dual effect of acetylcholine on bivalve heart. Physiologist 10: 210, 1967.

458. Isaac, L. and Goth, A.: The mechanism of the potentiation of norepinephrine by antihistaminics. J. Pharmacol. Exp. Ther. 156: 463–468, 1967.
459. Ishida, Y. and Hara, K.: Studies on inhibitory actions of synthetic peptides on the effects of oxytocin and vasopressin. Chem. Pharm. Bull. 12: 872–877, 1964.
460. Issekutz, B., Dobrovits, T. and Székely, M.: Über die Wirkung von Pharmaka auf die Venen. Acta Physiol. Acad. Sci. Hung. 12: 153–169, 1958.
461. Iversen, L. L.: The Uptake and Storage of Noradrenaline in Sympathetic Nerves, Cambridge University Press, Cambridge, 1967.
462. Jacobson, I., Harper, A. M. and McDowall, D. G.: Effects of oxygen at 1 and 2 atmospheres on blood flow and oxygen uptake of cerebral cortex. Surg. Gynecol. Obstet. Int. Abstr. Surg. 119: 737–742, 1964.
463. Jahn, W.: Kreislaufwirkungen 5'-substituierter Adenosinderivate. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 251: 95–104, 1965.
464. Janczewska, H. and Zieliński, A.: Influence of tetanization of the skeletal muscles of the hind leg of the dog on the vasoconstrictor effect of noradrenaline. Bull. Acad. Pol. Sci. 15: 697–701, 1967.
465. Jaques, R.: A substance from eel serum producing slow contractions. Nature (London) 175: 212, 1955.
466. Jarvis, D. and du Vigneaud, V.: The effect of decreasing the size of the ring present in deamino-oxytocin by one methylene group on its biological properties. The synthesis of 1-mercaptoacetic acid-oxytocin. J. Biol. Chem. 242: 1768–1771, 1967.
467. Jarvis, D., Manning, M. and du Vigneaud, V.: 1-Mercaptoacetic acid-4-β-alanine-oxytocin. Biochemistry 6: 1223–1225, 1967.
468. Jelliffe, R. W.: Dilator and constrictor effects of acetylcholine on isolated rabbit aortic chains. J. Pharmacol. Exp. Ther. 135: 349–353, 1962.
469. Jenkinson, D. H. and Morton, I. K. M.: The role of α- and β-adrenergic receptors in some actions of catecholamines on intestinal smooth muscle. J. Physiol. (London) 188: 387–402, 1967.
470. Johansen, K.: Adaptive responses to cold in arterial smooth muscle from heterothermic tissues of marine mammals. Nature (London) 223: 866–867, 1969.
470a. Johansson, B.: Permeability characteristics of vascular smooth muscle cells as revealed by their osmotic responses to non-electrolytes. Acta Physiol. Scand. 77: 282–297, 1969.
471. Johansson, B. and Jonsson, O.: Cell volume as a factor influencing electrical and mechanical activity of vascular smooth muscle. Acta Physiol. Scand. 72: 456–468, 1968.
472. Johnson, G. L. and Kahn, J. B., Jr.: Cocaine and antihistaminic compounds: comparison of effects of some cardiovascular actions of norepinephrine, tyramine and bretylium. J. Pharmacol. Exp. Ther. 152: 458–468, 1966.
473. Johnsson, G.: The effects of intra-arterially administered propranolol and H 56/28 on blood flow in the forearm—a comparative study of two β-adrenergic receptor antagonists. Acta Pharmacol. Toxicol. 25 (suppl. II): 63–74, 1967.
474. Jones, A. W., Feigl, E. O. and Peterson, L. H.: Water and electrolyte content of normal and hypertensive arteries in dogs. Circ. Res. 15: 386–392, 1964.
474a. Jonsson, O.: Changes in the activity of isolated vascular smooth muscle in response to reduced osmolarity. Acta Physiol. Scand. 77: 191–200, 1969.
474b. Jonsson, O.: Changes in the cell volume of isolated vascular smooth muscle in response to reduced osmolarity. Acta Physiol. Scand. 77: 201–211, 1969.
475. Jørgensen, L., Rowsell, H. C., Hovig, T., Glynn, M. F. and Mustard, J. F.: Adenosine diphosphate-induced platelet aggregation and myocardial infarction in swine. Lab. Invest. 17: 616–644, 1967.
475a. Jorgensen, E. C., Windbridge, G. C., Patton, W. and Lee, T. C.: Angiotensin II analogs. I. Synthesis and biological evaluation of (Gly^1, Gly^2, Ile^5)-angiotensin II, (Ac-Gly^1, Gly^2, Ile^5)-angiotensin II, and (Gly^1, Gly^2, Ile^5, His(Bzl)^6)-angiotension II. J. Med. Chem. 12: 733–737, 1969.
476. Jošt, K. and Rudinger, K.: Synthesis of two biologically active analogues of deamino-oxytocin not containing a disulphide bond. Collect. Czech. Chem. Commun. Engl. Edition 32: 1229–1241, 1967.
477. Joubert, L., Tétreault, L. and Biron, P.: Vasoconstrictor effect of angiotensin on the isolated rat-lung preparation. Rev. Can. Biol. 25: 293–294, 1966.
478. Kadar, D., Cooper, P. D. and Sunahara, F. A.: Extraction, isolation, and some pharmacological characteristics of rabbit renal medullary extracts. Can. J. Physiol. Pharmacol. 45: 1071–1080, 1967.
479. Kahn, P. C. and Wise, H. M., Jr.: The use of epinephrine in selective angiography of renal masses. J. Urol. 99: 133–138, 1968.
480. Kalsner, S.: Mechanism of hydrocortisone potentiation of responses to epinephrine and norepinephrine in rabbit aorta. Circ. Res. 24: 383–395, 1969.
481. Kalsner, S. and Nickerson, M.: A method for the study of mechanisms of drug disposition in smooth muscle. Can. J. Physiol. Pharmacol. 46: 719–730, 1968.
482. Kalsner, S. and Nickerson, M.: Disposition of phenylephrine in vascular tissue, determined by the oil-immersion technique. J. Pharmacol. Exp. Ther. 163: 1–10, 1968.
483. Kalsner, S. and Nickerson, M.: Mechanism of cocaine potentiation of responses to amines. Brit. J. Pharmacol. 35: 428–439, 1969.
484. Kalsner, S. and Nickerson, M.: Effects of reserpine on the disposition of sympathomimetic amines in vascular tissue. Brit. J. Pharmacol. 35: 394–405, 1969.
485. Kao, C. Y. and Nishiyama, A.: Ion concentrations and membrane potentials of myometrium during recovery from cold. Amer. J. Physiol. 217: 525–531, 1969.
486. Kao, C. Y., Suzuki, T., Kleinhaus, A. L. and Siegman, M. J.: Vasomotor and respiratory depressant actions of tetrodotoxin and saxitoxin. Arch. Int. Pharmacodyn. Thér. 165: 438–450, 1967.

487. KARIM, S. M. M.: The identification of prostaglandins in human umbilical cord. Brit. J. Pharmacol. Chemother. 29: 230-237, 1967.
488. KARLSBERG, P., ELLIOTT, H. W. AND ADAMS, J. E.: Effect of various pharmacologic agents on cerebral arteries. Neurology 13: 772-778, 1963.
489. KASUYA, Y. AND GOTO, R. K.: The mechanism of supersensitivity to norepinephrine induced by cocaine in rat isolated vas deferens. European J. Pharmacol. 4: 355-362, 1968.
490. KATO, M. AND STAUB, N. C.: Response of small pulmonary arteries to unilobar hypoxia and hypercapnia. Circ. Res. 19: 426-440, 1966.
491. KATZ, B.: Nerve, Muscle, and Synapse, ed. by G. Wald, McGraw-Hill, Inc., New York, 1966.
492. KATZ, R. L.: Antiarrhythmic and cardiovascular effects of synthetic oxytocin. Anesthesiology 25: 653-661, 1964.
493. KAYAALP, S. O. AND TÜRKER, R. K.: Release of catecholamines from the adrenal medulla by prostaglandin E_1. European J. Pharmacol. 2: 175-180, 1967.
494. KEATINGE, W. R.: The effect of low temperatures on the responses of arteries to constrictor drugs. J. Physiol. (London) 142: 395-405, 1958.
495. KELKAR, V. V. GULATI, O. D. AND GOKHALE, S. D.: Effect of ganglion blocking drugs on the responses of the rabbit aortic strip to adrenaline, noradrenaline and other vasoactive substances. Arch. Int. Pharmacodyn. Thér. 149: 209-222, 1964.
495a. KELLY, R. E. AND RICE, R. V.: Ultrastructural studies on the contractile mechanism of smooth muscle. J. Cell Biol. 42: 683-694, 1969.
496. KENDRICK, J. E.: Effect of vasoconstrictor tone on pressure responses to epinephrine and norepinephrine. Amer. J. Physiol. 208: 1000-1005, 1965.
497. KERKUT, G. A. AND MEECH, R. W.: Microelectrode determination of the intracellular chloride concentration in nerve cells. Life Sci. 5: 453-456, 1966.
498. KERNAN, R. P.: Membrane potential and chemical transmitter in active transport of ions by rat skeletal muscle. J. Gen. Physiol. 51: 204-210, 1968.
499. KETTEL, L. J., OVERBECK, H. W., DAUGHERTY, R. M., LILLEHEI, J. P., COBURN, R. F. AND HADDY, F. J.: Responses of the human upper extremity vascular bed to exercise, cold, levarterenol, angiotensin, hypertension, heart failure, and respiratory tract infection with fever. J. Clin. Invest. 43: 1561-1575, 1964.
500. KHAIRALLAH, P. A. AND PAGE, I. H.: A new vasopressor agent in blood extracts. Nature (London) 206: 835-836, 1965.
501. KHAIRALLAH, P. A., PAGE, I. H., BUMPUS, F. M. AND TÜRKER, R. K.: Angiotensin tachyphylaxis and its reversal. Circ. Res. 19: 247-254, 1966.
502. KHAIRALLAH, P. A., PAGE, I. H. AND TÜRKER, K. R.: Potentiation of vascular myotropic responses by metanephrine and other noncatecholamines. Circ. Res. 19: 538-543, 1966.
503. KHAIRALLAH, P. A., PAGE, I. H. AND TÜRKER, R. K.: Some properties of prostaglandin E_1 action on muscle. Arch. Int. Pharmacodyn. Thér. 169: 328-341, 1967.
504. KIMOTO, Y. AND GOTO, M.: The effects of temperature on tension, hysteresis loop and stress-relaxation of the blood vessels. Jap. J. Physiol. 16: 365-376, 1967.
505. KIMOTO, Y. AND GOTO, M.: Analyses of the pH dependence of resting and active tensions of some toad blood vessels. Jap. J. Physiol. 18: 256-265, 1968.
506. KIRPEKAR, S. M. AND FURCHGOTT, R. F.: The sympathomimetic action of bretylium on isolated atria and aortic smooth muscle. J. Pharmacol. Exp. Ther. 143: 64-76, 1964.
507. KIRPEKAR, S. M. AND LEWIS, J. J.: Antagonism to the actions of hydrallazine, reserpine, potassium cyanide, sodium azide and anoxia on arterial smooth muscle. J. Pharm. Pharmacol. 10: 307-314, 1958.
508. KIRPEKAR, S. M. AND LEWIS, J. J.: Effects of reserpine and hydrallazine on isolated strips of carotid arteries. J. Pharm. Pharmacol. 10: 255-259, 1958.
509. KIRPEKAR, S. M. AND WAKADE, A. R.: Release of noradrenaline from the cat spleen by potassium. J. Physiol. (London) 94: 595-608, 1968.
510. KJELDSEN, K., WANSTRUP, J. AND ASTRUP, P.: Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. J. Atheroscler. Res. 8: 835-845, 1968.
511. KJELLMER, I. AND ODELRAM, H.: The effect of some physiological vasodilators on the vascular bed of skeletal muscle. Acta Physiol. Scand. 63: 94-102, 1965.
512. KLAUS, D., HEIZMANN, A. AND UEHLEKE, H.: Beeinflussung der Blutdruckwirkung von Angiotensin durch Aminopeptidasen und Carboxypeptidase. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 251: 28-38, 1965.
513. KLIDE, A. M. AND AVIADO, D. M.: Mechanism for the reduction in pulmonary resistance induced by halothane. J. Pharmacol. Exp. Ther. 158: 28-35, 1967.
514. KLINGE, E., MATTILA, M. J., PENTTILÄ, O. AND JUKARAINEN, E.: Influence of drugs on vasoactive peptides and amines in perfused human placenta. Ann. Med. Exp. Fenn. 44: 369-375, 1966.
515. KLUPP, H. AND KONZETT, H.: Der Einfluss von Bradykinin und Kallidin auf den Druck in der Arteria pulmonalis. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 249: 479-485, 1965.
516. KO, K.-C., GIMENO, A. L. AND BERMAN, D. A.: Effects of buffers on developed tension, membrane potentials, and ATP levels of atria. Amer. J. Physiol. 216: 853-859, 1969.
517. KOEHN, M. A., SCHINDLER, W. J. AND STANTON, H. C.: Thyroid state and vascular reactivity in rats. Proc. Soc. Exp. Biol. Med. 126: 861-864, 1967.
518. KOHLI, J. D.: Receptors for sympathomimetic amines in the rabbit aorta: differentiation by specific antagonists. Brit. J. Pharmacol. Chemother. 32: 273-279, 1968.

519. KOHLI, J. D. AND LING, G. M.: α-Adrenergic blocking action of propranolol. J. Pharm. Pharmacol. 19: 629–631, 1967.
520. KOLETSKY, S. AND RIVERA-VELEZ, J. M.: Factors in the pathogenesis of salt hypertension. *In* Electrolytes and Cardiovascular Diseases, ed. by E. Bajusz, pp. 363–382, S. Karger, Basel, New York, 1965.
521. KONOLD, P., GEBERT, G. AND BRECHT, K.: The antagonism of potassium and catecholamines on the vascular tone of isolated arterial segments. Experientia (Basel) 24: 692, 1968.
522. KONTOS, H. A., GOLDIN, D., RICHARDSON, D. W. AND PATTERSON, J. L., JR.: Effect of dipyridamole on vasodilator responses to ischemia, hypoxia, ATP, and AMP. Amer. J. Physiol. 214: 107–114, 1968.
523. KONTOS, H. A., MAGEE, J. H., SHAPIRO, W. AND PATTERSON, J. L., JR.: General and regional effects of synthetic bradykinin in man. Circ. Res. 14: 351–356, 1964.
524. KONTOS, H. A., MAUCK, H. P., JR., RICHARDSON, D. W. AND PATTERSON, J. L., JR.: Circulatory responses to hypocapnia in the anesthetized dog. Amer. J. Physiol. 208: 139–143, 1965.
525. KONTOS, H. A., RICHARDSON, D. W. AND PATTERSON, J. L., JR.: Effects of hypercapnia on human forearm blood vessels. Amer. J. Physiol. 212: 1070–1080, 1967.
526. KONTOS, H. A., RICHARDSON, D. W. AND PATTERSON, J. L., JR.: Vasodilator effect of hypercapnic acidosis on human forearm blood vessels. Amer. J. Physiol. 215: 1403–1405, 1968.
527. KOPIN, I. J.: Storage and metabolism of catecholamines: the role of monoamine oxidase. Pharmacol. Rev. 16: 179–191, 1964.
528. KOPIN, I. J.: Acetylcholine, bretylium and release of norepinephrine from sympathetic nerve endings. Ann. N.Y. Acad. Sci. 144: 558–562, 1967.
529. KOPIN, I. J.: False adrenergic transmitters. Annu. Rev. Pharmacol. 8: 377–394, 1968.
530. KOVALČÍK, V.: Effect of bradykinin on isolated coronary arteries. Nature (London) 196: 174, 1962.
531. KOVALČÍK, V.: The response of the isolated ductus arteriosus to oxygen and anoxia. J. Physiol. (London) 169: 185–197, 1963.
532. KÖVÉR, G., HARZA, T., MÁLYUSZ, M. AND SZŐCS, É.: Protective effect of sucrose and mannitol against vasoconstriction induced by angiotensin II in the kidney. Acta Physiol. Acad. Sci. Hung. 33: 19–26, 1968.
533. KÖVÉR, G., MÁLYUSZ, M., ÉLLŐ, E. AND SZŐCS, É.: The effect of angiotensin on renal circulation. Acta Physiol. Acad. Sci. Hung. 28: 53–57, 1965.
534. KREJČÍ, I., KUPKOVÁ, B. AND VÁVRA, I.: The effect of some 2-O-alkyltyrosine analogues of oxytocin and lysine vasopressin on the blood pressure of the rat, rabbit, and cat. Brit. J. Pharmacol. Chemother. 30: 397–505, 1967.
535. KREJČÍ, I. AND POLÁČEK, I.: Effect of magnesium on the action of oxytocin and a group of analogues on the uterus *in vitro*. European J. Pharmacol. 2: 393–398, 1968.
536. KREJČÍ, I., POLÁČEK, I. AND RUDINGER, J.: The action of 2-O-methyl-tyrosine-oxytocin on the rat and rabbit uterus: effect of some experimental conditions on change from agonism to antagonism. Brit. J. Pharmacol. Chemother. 30: 506–517, 1967.
537. KRZANOWSHI, J. J., JR. AND WOODBURY, R. A.: Influence of tyramine on receptor interaction with dibenamine in aortic strips from reserpine-treated rabbits. J. Pharmacol. Exp. Ther. 154: 472–480, 1966.
538. KÜBLER, W. AND BRETSCHNEIDER, H. J.: Kompetitive Hemmung der katalysierten Adenosindiffusion als Mechanismus der coronarerweiternden Wirkung eines Pyrimido-pyrimidin-Derivates. Pflügers Arch. Gesamte Physiol. Menschen Tiere 280: 141–157, 1964.
539. KUIDA, H., BROWN, A. M., THORNE, J. L., LANGE, R. L. AND HECHT, H. H.: Pulmonary vascular response to acute hypoxia in normal, unanesthetized calves. Amer. J. Physiol. 203: 391–396, 1962.
540. KULBERTUS, H.: Etude des échanges d'ions H+ au cours de la contraction des parois carotidiennes soumises à différents agents vasomoteurs. Angiologica 1: 275–283, 1964.
541. KUMAR, D.: In vitro inhibitory effect of progesterone on extrauterine human smooth muscle. Amer. J. Obstet. Gynecol. 84: 1300–1304, 1962.
542. KURAMOTO, K., MURATA, K., FUJII, J., KURIHARA, H., KIMATA, S.-I., MATSUSHITA, S., KURAMOCHI, M., IKEDA, M. AND NAKAO, K.: Sympathetic coronary vasoconstriction after adrenergic beta blockade. Tohoku J. Exp. Med. 91: 95–101, 1967.
543. LANDS, A. M., ARNOLD, A., MCAULIFF, J. P., LUDUENA, F. P. AND BROWN, T. G., JR.: Differentiation of receptor systems activated by sympathomimetic amines. Nature (London) 214: 597–598, 1967.
544. LANG, W. J. AND PEARSON, L.: Studies on the pressor responses produced by bradykinin and kallidin. Brit. J. Pharmacol. Chemother. 32: 330–338, 1968.
545. LANGER, S. Z. AND TRENDELENBURG, U.: Decrease in effectiveness of phenoxybenzamine after chronic denervation and chronic decentralisation of the nictitating membrane of the pithed cat. J. Pharmacol. Exp. Ther. 163: 290–299, 1968.
546. LAPIDUS, J. B., TYE, A. AND PATIL, P. N.: Steric aspects of adrenergic drugs. VII. Certain pharmacological actions of D(—)-pseudoephedrine. J. Pharm. Sci. 56: 1125–1130, 1967.
547. LASZT, L.: Reinigung, Bestimmung und Charakterisierung eines neuen, in der Gefässwand vorkommenden vasoaktiven Polypeptides. Angiologica 4: 147–160, 1967.
548. LAUSON, H. D.: Metabolism of antidiuretic hormones. Amer. J. Med. 42: 713–744, 1967.
549. LAVERTY, R.: Relation in rat hind-limb blood vessels between nervous vasomotor tone and the response to vasoconstrictor drugs. Brit. J. Pharmacol. 18: 451–464, 1962.
550. LAVERTY, R., MCGREGOR, D. D. AND MCQUEEN, E. G.: Vascular reactivity in experimental hypertension. N. Z. Med. J. 67: 303–309, 1968.
551. LAW, H. D. AND DU VIGNEAUD, V.: Synthesis of 2-*p*-methoxyphenylalanine oxytocin (O-methyl-oxytocin) and some observations on its pharmacological behavior. J. Amer. Chem. Soc. 82: 4579–4581, 1960.

552. LECOMTE, J. AND TROQUET, J.: Actions vasculaires de certains polypeptides endogenes. Role physio-pathologique de ces derniers. Acta Cardiol. 17: 797–818, 1962.
553. LEE, J. B., CROWSHAW, K., TAKMAN, B. H. AND ATTEEP, K. A.: The identification of prostaglandins E_2, $F_{2\alpha}$, and A_2 from rabbit kidney medulla. Biochem. J. 105: 1251–1260, 1967.
554. LEFER, A. M., MANWARING, J. L. AND VERRIER, R. L.: Effect of corticosteroids on the cardiovascular responses to angiotensin and norepinephrine. J. Pharmacol. Exp. Ther. 154: 83–91, 1966.
555. LEONARD, E.: Alteration of contractile response of artery strips by a potassium-free solution, cardiac glycosides and changes in stimulation frequency. Amer. J. Physiol. 189: 185–190, 1957.
556. LEVIN, J. A. AND BECK, L.: Selective reduction in neurogenically induced constriction by phenoxybenzamine. J. Pharmacol. Exp. Ther. 155: 31–40, 1967.
557. LEVY, B. AND WILKENFELD, B. E.: An analysis of selective beta receptor blockade. European J. Pharmacol. 5: 227–234, 1969.
558. LEVY, J. V.: Myocardial and local anesthetic actions of β-adrenergic receptor blocking drugs: relationship to physicochemical properties. European J. Pharmacol. 1: 250–257, 1968.
559. LEWIS, G. P.: Pharmacological actions of bradykinin and its role in physiological and pathological reactions. Ann. N.Y. Acad. Sci. 104: 236–249, 1963.
560. LEWIS, J. E. AND MILLER, J. W.: The use of tritiated phenoxybenzamine for investigating receptors. J. Pharmacol. Exp. Ther. 154: 46–55, 1966.
561. LIKAR, I. N., LIKAR, L. J. AND ROBINSON, R. W.: Levels and patterns of acid mucopolysaccharides in bovine coronary arteries without gross lesions. Acta Endocrinol. 59: 668–681, 1968.
562. LIPSIUS, M. R., SIEGMAN, M. J. AND KAO, C. Y.: Direct relaxant actions of procaine and tetrodotoxin on vascular smooth muscle. J. Pharmacol. Exp. Ther. 164: 60–74, 1968.
563. LITWIN, J., DIL, A. H. AND AVIADO, D. M.: Effects of hypercapnia on the vascular resistance of the dog's hind limb. Pflügers Arch. Gesamte Physiol. Menschen Tiere 277: 387–396, 1963.
564. LJUNG, B.: Local transmitter concentrations in vascular smooth muscle during vasoconstrictor nerve activity. Acta Physiol. Scand. 77: 212–223, 1969.
565. LLOYD, S.: The vascular responses of the rat during the reproductive cycle. J. Physiol. (London) 148: 625–632, 1959.
566. LLOYD, S.: Vascular responses of the rat to bradykinin. Brit. J. Pharmacol. 19: 503–507, 1962.
567. LLOYD, S. AND PICKFORD, M.: The persistence of a depressor response to oxytocin in the fowl after denervation and blocking agents. Brit. J. Pharmacol. Chemother. 16: 129–136, 1961.
568. LLOYD, S. AND PICKFORD, M.: The effect of oestrogens and sympathetic denervation on the response to oxytocin of the blood vessels in the hind limb of the dog. J. Physiol. (London) 163: 362–371, 1962.
569. LLOYD, S. AND PICKFORD, M.: An examination of certain factors which might, or do, affect the vascular response to oxytocin. J. Physiol. (London) 193: 547–569, 1967.
570. LLOYD, S. AND PICKFORD, M.: The effect of oxytocin and adrenaline on blood flow in the hind limb of the dog following chronic lumbar sympathectomy. J. Physiol. (London) 192: 43–52, 1967.
571. LLOYD, T. C., JR.: Effect of alveolar hypoxia on pulmonary vascular resistance. J. Appl. Physiol. 19: 1086–1094, 1964.
572. LLOYD, T. C., JR.: Influence of blood pH on hypoxic pulmonary vasoconstriction. J. Appl. Physiol. 21: 358–364, 1966.
573. LLOYD, T. C., JR.: Role of nerve pathways in the hypoxic vasoconstriction of lung. J. Appl. Physiol. 21: 1351–1355, 1966.
574. LLOYD, T. C., JR.: pO_2-dependent pulmonary vasoconstriction caused by procaine. J. Appl. Physiol. 21: 1439–1442, 1966.
575. LLOYD, T. C., JR.: Influence of pO_2 and pH on resting and active tensions of pulmonary arterial strips. J. Appl. Physiol. 22: 1101–1109, 1967.
576. LLOYD, T. C., JR.: Hypoxic pulmonary vasoconstriction: role of perivascular tissue. J. Appl. Physiol. 25: 560–565, 1968.
577. LOCKETT, M. S. AND EAKINS, K. E.: The release of sympathetic amines by tyramine from the aortic walls of cats. J. Pharm. Pharmacol. 12: 720–725, 1960.
578. LONG, J. P. AND HIGHGENBOTEN, C. L.: Mechanism of nicotine induced vascular resistance in the superior mesenteric artery of the cat. Arch. Int. Pharmacodyn. Ther. 149: 385–392, 1964.
579. LORENZEN, I.: Corticosteroids and vascular connective tissue. Acta Endocrinol. 60: 586–594, 1969.
580. LORENZEN, I. AND HANSEN, L. K.: Effect of glucocorticoids on human vascular connective tissue. Vasc. Dis. 4: 335–341, 1967.
581. LORENZETTI, O. J., TYE, A. AND NELSON, J. W.: Effects of glyceryl trinitrate on the aortic strip of rabbits. J. Pharm. Pharmacol. 19: 634–636, 1967.
582. LOUIS, W. J. AND JERUMS, G.: Tachyphylaxis to alpha- and beta-angiotensin in dogs perfused with Ringer's solution or blood. Circ. Res. 22: 75–82, 1968.
583. LÜBKE, K., ZÖLLNER, G. AND SCHRÖDER, E.: The influence of substitution or omission of an amino group on the hypotensive activity of the C-terminal sequences of eledoisin. *In* Hypotensive Peptides, ed. by E. G. Erdös, N. Back and F. Sicuteri, pp. 45–54, Springer-Verlag, New York, 1966.
584. LUDUENA, F. P.: Effect of reserpine on the vasoconstrictor action of tyramine on the rabbit ear, with a discussion of the mechanisms of action of reserpine and tyramine. Acta Physiol. Latinoamer. 13: 221–241, 1963.
585. LUM, B. K. B. AND RASHLEIGH, P. L.: Potentiation of vasoactive drugs by ganglionic blocking agents. J. Pharmacol. Exp. Ther. 132: 13–18, 1961.
586. LUNDBORG, P.: Studies on the uptake and subcellular distribution of catecholamines and their α-methylated analogues. Acta Physiol. Scand. 302 (Suppl. I): 3–34, 1967.

587. LUNDE, P. K. M., WAALER, B. A. AND WALLØE, L.: The inhibitory effect of various phenols upon ATP-induced vasoconstriction in isolated perfused rabbit lungs. Acta Physiol. Scand. 72: 331–337, 1968.
588. MACMILLAN, W. H. AND RAND, M. J.: The effects in rabbits of thyroidectomy and treatment with triiodothyronine on the sensitivity to noradrenaline and the content of noradrenaline in aorta and spleen. J. Pharm. Pharmacol. 14: 257–267, 1962.
589. MACMILLAN, W. H., SMITH, D. J. AND JACOBSON, J. H.: Response of normal, denervated, and reserpine-treated arteries to sympathomimetic amines and nicotine in dogs. Brit. J. Pharmacol. 18: 39–48, 1962.
590. MACRI, F. J. AND BROWN, J. G.: The constrictive action of acetazolamide on the iris arteries of the cat. Arch. Ophthalmol. 66: 570–577, 1961.
591. MAENGWYN-DAVIES, G. D.: Effect of phenylephrine on responses of the rabbit aortic strip to isoproterenol. Proc. Soc. Exp. Biol. Med. 110: 470–473, 1962.
592. MAENGWYN-DAVIES, G. D.: The dual mode of action of histamine in the cat isolated tracheal chain. J. Pharm. Pharmacol. 20: 572–573, 1968.
593. MAENGWYN-DAVIES, G. D., COWAN, F. F. AND KOPPANYI, T.: Tachyphylaxis. VI. Amphetamine in the isolated rabbit aortic strip. Arch. Int. Pharmacodyn. Ther. 160: 454–472, 1966.
594. MAENGWYN-DAVIES, G. D., COWAN, F. F., KOPPANYI, T. AND LEI, B. W.: Tachyphylaxis, V. Tyramine in isolated organs. Arch. Int. Pharmacodyn. Thér. 160: 438–453, 1966.
595. MAENGWYN-DAVIES, G. D., CRISP, T. M., DANIEL, E. E. AND THOA, N. B.: Comparison of contracting agents on the isolated guinea pig aortic strip. Arch. Int. Pharmacodyn. Thér. 178: 344–350, 1969.
596. MAENGWYN-DAVIES, G. D. AND KOPPANYI, T.: Cocaine tachyphylaxis and effects on indirectly-acting sympathomimetic drugs in the rabbit aortic strip and in splenic tissue. J. Pharmacol. Exp. Ther. 154: 481–492, 1966.
596a. MARTZ, J. AND RANKIN, J. C.: Quelques aspects du role biologique des hormones neurohypophysaires chez les poissons. Coll. Int. Centre Nat. Recherche Sci. No. 177: 45–55, Paris, 1969.
597. MAJNO, G., GILMORE, V. AND LEVENTHAL, M.: On the mechanism of vascular leakage caused by histamine-type mediators. A microscopic study in vivo. Circ. Res. 21: 833–847, 1967.
597a. MAJNO, G., SHEA, S. M. AND LEVENTHAL, M.: Endothelial contraction induced by histamine-type mediators. J. Cell Biol. 42: 647–672, 1969.
598. MALLOV, S.: Effect of hypertension and sodium chloride on vascular reactivity in vitro. Amer. J. Cardiol. 8: 542–548, 1961.
599. MANCINI, R. T. AND GAUTIERI, R. F.: Effect of certain drugs on perfused human placenta. V. Use of α and β adrenergic blocking agents to determine the specific effector site of vasoactive substances. J. Pharm. Sci. 54: 1443–1449, 1965.
600. MANLEY, E. S. AND LAWSON, J. W.: Effect of beta adrenergic receptor blockade on skeletal muscle vasodilatation produced by isoxsuprine and nylidrin. Arch. Int. Pharmacodyn. Thér. 175: 239–250, 1968.
601. MARCHETTI, G., MACCARI, M. AND MERLO, L.: Recherches expérimentales sur les effets de la *l*-adrénaline et de la *l*-noradrénaline sur la circulation coronarienne. Cardiologia 42: 1–26, 1963.
602. MARGOLIUS, H. S., REID, P., MOHAMMED, S. AND GAFFNEY, T. E.: The effect of adrenalectomy and hydrocortisone on responses to norepinephrine and stimulation of the cardioaccelerator nerve. J. Pharmacol. Exp. Ther. 155: 415–421, 1967.
603. MARTIN, P. J. AND SCHILD, H. O.: The antagonism of disulphide polypeptides by thiols. Brit. J. Pharmacol. Chemother. 25: 418–431, 1965.
604. MASON, D. T. AND BRAUNWALD, E.: Studies on digitalis. X. Effects of ouabain on forearm vascular resistance and venous tone in normal subjects and in patients in heart failure. J. Clin. Invest. 43: 532–543, 1964.
605. MASON, D. T. AND MELMON, K. L.: Effects of bradykinin on forearm venous tone and vascular resistance in man. Circ. Res. 17: 1–8, 1965.
606. MASSION, W. H. AND EMERSON, T. E., JR.: Peripheral vascular effects of diethyl ether and methoxyflurane in the isolated forelimb. Anesth. Analg. Curr. Res. 47: 515–521, 1968.
607. MASUYAMA, Y.: Renin-angiotensin system and neurohumoral factors. Jap. J. Nephrol. 7: 23–26, 1965.
608. MAUSKOPF, J. M., GRAY, S. D. AND RENKIN, E. M.: Transient and persistent components of sympathetic cholinergic vasodilatation. Amer. J. Physiol. 216: 92–97, 1969.
609. MAXWELL, G. M.: The cardiovascular effects of octapressin. Arch. Int. Pharmacodyn. Thér. 158: 17–23, 1965.
610. MAXWELL, G. M.: Actions of substance P on the general, pulmonary, and coronary haemodynamics and metabolism of intact dogs. Brit. J. Pharmacol. Chemother. 32: 514–522, 1968.
611. MAXWELL, G. M., ELLIOTT, R. B. AND KNEEBONE, G. M.: Effects of bradykinin on the systemic and coronary vascular bed of the intact dog. Circ. Res. 10: 359–363, 1962.
612. MAXWELL, R. A.: Concerning the mechanism of action of methylphenidate on the responses of rabbit vascular tissue to norepinephrine. J. Pharmacol. Exp. Ther. 147: 289–297, 1965.
613. MAXWELL, R. A.: Concerning the mode of action of guanethidine and some derivatives in augmenting the vasomotor action of adrenergic amines in vascular tissues of the rabbit. J. Pharmacol. Exp. Ther. 148: 320–328, 1965.
614. MAXWELL, R. A., DANIEL, A. I., SHEPPARD, H. AND ZIMMERMAN, J. H.: Some interactions of guanethidine, cocaine, methylphenidate and phenylalkalamines in rabbit aortic strips. J. Pharmacol. Exp. Ther. 137: 31–38, 1962.
615. MAXWELL, R. A., ECKHARDT, S. B. AND WASTILA, W. B.: Concerning the distribution of endogenous norepinephrine in the adventitial and media-intimal layers of the rabbit aorta and the capacity of these layers to bind tritiated norepinephrine. J. Pharmacol. Exp. Ther., 161: 34–39, 1968.
616. MAXWELL, R. A., WASTILA, W. B. AND ECKHARDT, S. B.: Some factors determining the response of rabbit aortic strips to *dl*-norepinephrine-7-H^3 hydrochloride and the influence of cocaine, guanethidine and methylphenidate on these factors. J. Pharmacol. Exp. Ther. 151: 253–261, 1966.

617. MAXWELL, R. A., WASTILA, W. AND ECKHARDT, S. B.: A nonadrenergic musculotropic effect of 2-(cyclohexylamino)-ethylguanidine sulfate (SU-9707) in rabbit aortic strips. J. Pharmacol. Exp. Ther. 158: 248-252, 1967.
618. MAY, M., MORAN, J. F., KIMELBERG, H. AND TRIGGLE, D. J.: Studies on the noradrenaline α-receptor II. Analysis of the "spare-receptor" hypothesis and estimation of the concentration of α-receptors in rabbit aorta. Mol. Pharmacol. 3: 28-36, 1967.
619. MAYER, H. E., ABBOUD, F. M., BALLARD, D. R. AND ECKSTEIN, J. W.: Catecholamines in arteries and veins of the foreleg of the dog. Circ. Res. 23: 653-661, 1968.
620. MAZURKIEWICZ-KWILECKI, I. M.: Antagonistic effects of β-adrenergic blocking agents on responses to adrenaline in vascular smooth muscle. Arch. Int. Pharmacodyn. Thér. 174: 199-209, 1968.
621. MCARDLE, L. AND BLACK, G. W.: The effects of cyclopropane on the peripheral circulation in man. Brit. J. Anaesth. 35: 352-357, 1963.
622. MCARDLE, L., BLACK, G. W. AND UNNI, V. K. N.: Peripheral vascular changes during diethyl ether anaesthesia. Anaesthesia 23: 203-210, 1968.
623. MCCAA, R. E., RICHARDSON, T. Q., LANGFORD, H. G. AND DOUGLAS, B. H.: Circulatory changes following angiotensin administration. Amer. J. Physiol. 212: 565-568, 1967.
624. MCCUBBIN, J. W., DEMOURA, R. S., PAGE, I. H. AND OLMSTED, F.: Arterial hypertension elicited by subpressor amounts of angiotensin. Science 149: 1394-1395, 1965.
625. MCCUBBIN, J. W., KANEKO, Y. AND PAGE, I. H.: Inhibition of neurogenic vasoconstriction by serotonin. Vasodilator action of serotonin. Circ. Res. 11: 74-83, 1962.
626. MCCUBBIN, J. W. AND PAGE, I. H.: Renal pressor system and neurogenic control of arterial pressure. Circ. Res. 12: 553-559, 1963.
627. MCGIFF, J. C., BURNS, R. B. P. AND BLUMENTHAL, M. R.: Role of acetylcholine in the renal vasoconstrictor response to sympathetic nerve stimulation in the dog. Circ. Res. 20: 616-629, 1967.
628. MCGIFF, J. C. AND FASY, T. M.: The relationship of the renal vascular activity of angiotensin II to the autonomic nervous system. J. Clin. Invest. 44: 1911-1923, 1965.
629. MCGIFF, J. C. AND ITSKOVITZ, H. D.: Loss of the renal vasoconstrictor activity of angiotensin II during renal ischemia. J. Clin. Invest. 43: 2359-2367, 1964.
630. MCGINN, F. P., MENDEL, D. AND PERRY, P. M.: The effects of alteration of CO_2 and pH on intestinal blood flow in the cat. J. Physiol. (London) 192: 669-680, 1967.
631. MCGREGOR, D. D.: The effect of sympathetic nerve stimulation on vasoconstrictor responses in perfused mesenteric blood vessels of the rat. J. Physiol. (London) 177: 21-30, 1965.
632. MCGREGOR, D. D. AND SMIRK, F. H.: Vascular responses in mesenteric arteries from genetic and renal hypertensive rats. Amer. J. Physiol. 214: 1429-1433, 1968.
633. MCHEDLISHVILI, G. I., ORMOTSADZE, L. G., NIKOLAISHVILI, L. S. AND BARAMIDZE, D. G.: Reaction of different parts of the cerebral vascular system in asphyxia. Exp. Neurol. 18: 239-252, 1967.
634. MELLANDER, S.: Comparative effects of acetylcholine, butyl-norsynephrine (vasculat), noradrenaline, and ethyladrianol (effontil) on resistance, capacitance, and precapillary sphincter vessels and capillary filtration in cat skeletal muscle. Angiologica 3: 77-99, 1966.
635. MELLANDER, S., JOHANSSON, B., GRAY, S., JONSSON, O., LUNDVALL, J. AND LJUNG, B.: The effects of hyperosmolarity on intact and isolated vascular smooth muscle. Possible role in exercise hyperemia. Angiologica 4: 310-322, 1967.
636. MENDLOWITZ, M., NAFTCHI, N. E., GITLOW, S. E. AND WOLF, R. L.: Vascular responsiveness in hypertensive and hypotensive states. Geriatrics 20: 797-807, 1965.
637. MIELE, E.: Effetti sulla muscolatura liscia e sulla reattività vascolare di diuretici benzotiadiazinici. La Ricerca Scientifica 3: 205-215, 1963.
638. MIELE, E. AND DE NATALE, G.: Modification by guanethidine and nethalide of the pressor effects of bradykinin in the rat. Arch. Int. Pharmacodyn. Thér. 164: 56-66, 1966.
639. MILLER, J. W. AND LEWIS, J. E.: Drugs affecting smooth muscle, Annu. Rev. Pharmacol. 9: 147-172, 1969.
640. MILLIGAN, J. E., ROACH, M. R. AND THALNER, N. S.: Vasomotor responses in the hindlimb of newborn calves. Circ. Res. 21: 237-244, 1967.
641. MILLSON, D. R.: Nicotine and the effect of antisympathomimetic agents on the aorta of the rabbit. Brit. J. Pharmacol. 14: 239-242, 1959.
642. MITOLO-CHIEPPA, D.: Sul meccanismo di una azione vasorilassante della nicotina. Boll. Soc. Ital. Biol. Sper. 44: 892-893, 1968.
643. MOHAMMED, S., GAFFNEY, T. E., YARD, A. C. AND GOMEZ, H.: Effect of methyldopa, reserpine and guanethidine on hindleg vascular resistance. J. Pharmacol. Exp. Ther. 160: 300-307, 1968.
644. MOHAMMED, S., HARDMAN, H. F. AND YARD, A. C.: Mechanism of the vasodilator response to pheniprazine. J. Pharmacol. Exp. Ther. 156: 221-226, 1967.
645. MOOG, E. AND FISCHER, J.: Die Wirkung des Histamins, Serotonins, Bradykinins, Eledoisins und Hypertensins auf isoliert durchströmte Arterien-, Venen- und Bronchienpräparate der Meerschweinchenlunge. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 249: 384-392, 1964.
646. MOORE, P. F.: The effects of diazoxide and benzothiadiazine diuretics upon phosphodiesterase. Ann. N.Y. Acad. Sci. 150: 256-260, 1968.
647. MORAN, J. F., MAY, M., KIMELBERG, H. AND TRIGGLE, D. J.: Studies on the noradrenaline alpha-receptor. I. Techniques of receptor isolation. The distribution and specificity of action of N-(2-bromoethyl)-N-ethyl-1-naphthylemethylamine, a competitive antagonist of noradrenaline. Mol. Pharmacol. 3: 15-27, 1967.
648. MORAN, N. C. (ed.): New adrenergic blocking drugs: their pharmacological, biochemical and clinical actions. Ann. N.Y. Acad. Sci. 139: 541-1009, 1967.

649. MORGAN, T.: The response of the blood pressure to an infusion of angiotensin in patients with essential malignant and renovascular hypertension. Australas. Ann. Med. 16: 168–172, 1967.
650. MORGAN, W. E., III AND MACRI, F. J.: Vascular responses of the posterior segment of the cat eye. Arch. Ophthalmol. 79: 799–784, 1968.
651. MORIWAKI, C., BEILENSON, S. AND SCHACHTER, M.: Sialotonin: vasopressor substance in cat submaxillary saliva. Nature (London) 217: 270–271, 1968.
652. MORIYA, H., MORIWAKI, C., YAMAZAKI, K., AKIMOTO, S. AND FUKUSHIMA, H.: Human salivary kallikrein and liberation of colostrokinin. *In* Hypotensive Peptides, ed. by E. G. Erdös, N. Back and F. Sicuteri, pp. 161–174, Springer-Verlag, New York, 1966.
653. MORKIN, E., LEVINE, O. R. AND FISHMAN, A. P.: Pulmonary capillary flow pulse and the site of pulmonary vasoconstriction in the dog. Circ. Res. 15: 146–160, 1964.
654. MORRISON, J. F. B. AND PICKFORD, M.: A search for a central action of angiotensin. *In* Fourth International Congress on Pharmacology, p. 210, Basel, 1969.
655. MOSS, A. J., EMMANOUILIDES, G. C., ADAMS, F. H. AND CHUANG, K.: Response of ductus arteriosus and pulmonary and systemic arterial pressure to changes in oxygen environment in newborn infants. Pediatrics 33: 937–944, 1964.
656. MULL, R. P. AND MAXWELL, R. A.: Guanethidine and related adrenergic neuronal blocking agents. *In* Antihypertensive Agents, pp. 115–149, Academic Press, New York, 1967.
656a. MURPHY, R. A.: Contractile proteins of vascular smooth muscle: effects of hydrogen and alkali metal cations on actomyosin adenosine-triphosphatase activity. Microvasc. Res. 1: 344–353, 1969.
657. MURPHY, R. A., BOHR, D. F. AND NEWMAN, D. L.: Arterial actomyosin: Mg, Ca, and ATP ion dependencies for ATPase activity. Amer. J. Physiol. 217: 666–673, 1969.
658. MUSCHOLL, E.: B. Indirectly acting sympathomimetic amines. Pharmacol. Rev. 18: 551–559, 1966.
659. NAEYE, R. L.: Effect of alpha-methyl-dopa on heart and pulmonary arteries of hypoxic mice. Amer. J. Physiol. 209: 702–704, 1965.
659a. NAGAOKA, A., KIKUCHI, K. AND ARAMAKI, Y.: Electrolyte pattern of the aorta in the spontaneously hypertensive rats. Jap. J. Pharmacol. 19: 462–464, 1969.
660. NAKANO, J.: Cardiovascular effect of oxytocin in rodents and a marsupial. Proc. Soc. Exp. Biol. Med. 115: 707–709, 1964.
661. NAKANO, J.: Studies on the cardiovascular effects of synthetic eledoisin. J. Pharmacol. Exp. Ther. 145: 71–77, 1964.
662. NAKANO, J.: Effects of synthetic bradykinin on the cardiovascular system. Arch. Int. Pharmacodyn. Thér. 157: 1–13, 1965.
663. NAKANO, J.: Studies on the cardiovascular effects of synthetic vasopressin. J. Pharmacol. Exp. Ther. 157: 19–31, 1967.
664. NAKANO, J.: Effects of prostaglandins E_1, A_1 and F_α on the coronary and peripheral circulations. Proc. Soc. Exp. Biol. Med. 127: 1160–1163, 1968.
665. NAKANO, J. AND FISHER, R. D.: Studies on the cardiovascular effects of synthetic oxytocin. J. Pharm. Exp. Ther. 142: 206–214, 1963.
666. NAKANO, J. AND KUSAKARI, T.: Effect of bradykinin and eledoisin on the regional circulation. Angiology 17 333–337, 1966.
667. NAKANO, J. AND KUSAKARI, T.: Effect of propranolol on the peripheral vascular bed. Nature (London) 209: 923–924, 1966.
668. NAKANO, J. AND MCCURDY, J. R.: Cardiovascular effects of prostaglandin E_1. J. Pharmacol. Exp. Ther. 156: 538–547, 1967.
669. NAKATSU, K. AND REIFFENSTEIN, R. J.: Increased receptor utilization: mechanism of cocaine potentiation. Nature (London) 217: 1276–1277, 1968.
670. NAPODANO, R. J., CALIVA, F. S., LYONS, C., DESIMONE, J. AND LYONS, R. H.: The reactivity to angiotensin of rabbit aorta strips after either alterations of external sodium environment or direct addition of benzydroflumethiazide. Amer. Heart J. 64: 498–502, 1962.
671. NARAHASHI, T. AND MOORE, J. W.: Neuroactive agents and nerve membrane conductances. J. Gen. Physiol. 51: 93–101, 1968.
672. NASH, C. B.: Alteration of vasopressin tachyphylaxis by reserpine pretreatment. Arch. Int. Pharmacodyn. Thér. 155: 90–95, 1965.
673. NASH, C. B., BOYAJY, L. D. AND MANLEY, E. S.: Vasopressin antagonism of adrenergic vasodilation. Arch. Int. Pharmacodyn. Thér. 133: 433–443, 1961.
674. NASH, C. W. AND HEATH, C.: Vascular responses to catecholamines during respiratory changes in pH. Amer. J. Physiol. 200: 755–758, 1961.
675. NASH, C. W., SHIVAK, R. J. AND ENGELHARDT, E. M.: The influence of reserpine on cardiovascular responses to noradrenaline, tyramine, and pitressin during respiratory acidosis. Can. J. Physiol. Pharmacol. 34: 627–638, 1965.
676. NAVA-RIVERA, A., GUTIÉRREZ-LOPEZ, A., FREEE, A. A. AND EISENBERG, J. W.: Influence of procaine, lidocaine and prilocaine on the adrenaline contraction of isolated strips of rabbit aorta. Arch. Int. Pharmacodyn. Thér. 169: 307–311, 1967.
677. NAYLER, W. G., MCINNES, I., SWANN, J. B., RACE, D., CARSON, V. AND LOEW, T. E.: Some effects of the hypotensive drug diazoxide on the cardiovascular system. Amer. Heart J. 75: 223–232, 1968.
678. NAYLER, W. G., RACE, D., PRICE, J. M. AND LOWE, T. E.: Some effects of a cardioactive fraction isolated from human blood plasma on the peripheral circulation of the dog. Circ. Res. 18: 1–9, 1966.

679. Nayler, W. G., Rosenbaum, M., McInnes, I. E., Race, D. and Lowe, T. E.: Effect of adrenergic antagonists on the peripheral constrictor action of kinekard, a cardioactive plasma fraction. Circ. Res. 19: 528–537, 1966.
680. Nayler, W. G., Stone, J., Carson, V., McInnes, I., Mack, V., and Lowe, T. E.: The effect of *beta* adrenergic antagonists on cardiac contractions, myofibrillar ATPase activity, high-energy phosphate stores and lipid-facilitated transport of calcium ions. J. Pharmacol. Exp. Ther. 165: 225–233, 1969.
681. Nedergaard, O. A., Vagne, A. and Bevan, J. A.: Effect of the chelating agents, EDTA, 2,2'-bipyridine, 8-hydroxyquinoline and pyrophosphoric acid, on norepinephrine uptake by rabbit aorta. J. Pharmacol. Exp. Ther. 163: 136–146, 1968.
682. Nedergaard, O. A., Vagne, A. and Bevan, J. A.: Distribution of norepinephrine uptake within rabbit aorta between adventitia and media. Experientia (Basel) 25: 150–151, 1969.
683. Nicolaides, E. D., McCarthy, D. A. and Potter, D. E.: Bradykinin: configurations of the arginine moieties and biological activity. Biochemistry 4: 190–195, 1965.
684. Nonomura, Y.: Myofilaments in smooth muscle of guinea pig's taenia coli. J. Cell Biol. 39: 741–745, 1968.
685. Northover, B. J.: The effect of drugs on the constriction of isolated depolarized blood vessels in response to calcium or barium. Brit. J. Pharmacol. 34: 417–428, 1968.
686. Nusbaum, M., Baum, S., Kuroda, K. and Balkemore, W. S.: Control of portal hypertension by selective mesenteric arterial drug infusion. Arch. Surg. 97: 1005–1013, 1968.
687. O'Donnell, S. R. and Wanstall, J. C.: Actions of phencyclidine on the perfused rabbit ear. J. Pharm. Pharmacol. 20: 125–131, 1968.
688. Oelkers, W., Langholz, H. J., Dissmann, T. and Gotzen, R.: Über den praktischen Wert des Angiotensintests nach Kaplan und Silah für die Erkennung der renovaskulären Hypertonie. Deut. Med. Wochenschr. 93: 18–24, 1968.
689. Offermeier, J.: On the action of 5-hydroxytryptamine on α-sympathetic receptors. Acta Physiol. Pharmacol. Néer. 14: 1–2, 1966.
690. Okamoto, K., Hazama, F., Takeda, T., Tabei, R., Nosaka, S., Fukushima, M., Yamori, Y., Matsumoto, M., Haebara, H., Ichjima, K. and Suzuki, Y.: Pharmacodynamic studies on the cardiovascular system of spontaneously hypertensive rats. Jap. Circ. J. 30: 987–1007, 1966.
691. Olivares, G. J., Smith, N. T. and Aronow, L.: Effect of propranolol on alpha-adrenergic blockade in the dog and isolated rabbit aortic strip. Brit. J. Pharmacol. Chemother. 30: 240–250, 1967.
692. Olmsted, F. and Page, I. H.: Hemodynamic effects of eledoisin, kallidin II, and bradykinin in unanesthetized dogs. Amer. J. Physiol. 203: 951–954, 1962.
693. Olsson, P., Swedenborg, J. and Teger-Nilsson, A.-C.: The role of adenine nucleotides in the peripheral vasodilating effect of thrombin. Acta Physiol. Scand. 76: 137–147, 1969.
694. O'Mahony, D. P.: The pharmacology of isolated venous muscle. Irish J. Med. Sci. 6: 401–406, 1963.
695. Oppelt, W. W. and Ederstrom, H. E.: The comparative sensitivity of isolated coronary and systemic vessels to vasomotor agents. Angiology 10: 153–157, 1959.
696. Page, I. H.: Serotonin (5-hydroxytryptamine); the last four years. Physiol. Rev. 38: 277–335, 1958.
697. Page, I. H.: Serotonin, Yearbook Medical Publishers, Chicago, 1968.
698. Page, I. H. and Bumpus, F. M.: Angiotensin. Physiol. Rev. 41: 331–390, 1961.
699. Palaič, D. and Khairallah, P. A.: Inhibition of noradrenaline uptake by angiotensin. J. Pharm. Pharmacol. 19: 396–397, 1967.
700. Palaič, D. and Khairallah, P. A.: Angiotensin and tyramine tachyphylaxis in isolated rat aorta. Life Sci. 7: 169–172, 1968.
701. Paldino, R. L., Hyman, C. and Lenthall, J.: Bradykinin-induced increase in total and effective blood flow in skeletal muscle. Circ. Res. 11: 847–852, 1962.
702. Pals, D. T. and Fulton, R. W.: Interrelationship between angiotensin and vascular alpha adrenergic receptors. Amer. J. Physiol. 214: 506–512, 1968.
703. Pals, D. T., Fulton, R. W. and Masucci, F. D.: Angiotensin, cocaine and desipramine: comparison of effects on blood pressure responses to norepinephrine, tyramine and phenylephrine in the pithed rat. J. Pharmacol. Exp. Ther. 162: 85–91, 1968.
704. Panigel, M.: Placental perfusion experiments. Amer. J. Obstet. Gynecol. 84: 1664–1683, 1962.
705. Panisset, J. C., Beaulnes, A. and Bois, P.: Effect of thyroxine on the sensitivity of the rat smooth muscle to 5-hydroxytryptamine. Rev. Can. Biol. 25: 155–159, 1966.
706. Panisset, J. C., Bois, P. and Beaulnes, A.: Effet de la désoxycorticostérone et du méthyl-fluorocortisol sur la réponse vasculaire à l'adrénaline. Rev. Can. Biol. 20: 71–73, 1961.
707. Panisset, J.-C. and Bourdois, P.: Effect of angiotensin on the response to noradrenaline and sympathetic nerve stimulation, and on ^{3}H-noradrenaline uptake in cat mesenteric blood vessels. Can. J. Physiol. Pharmacol. 46: 125–131, 1968.
708. Pardee, A. B.: Membrane transport proteins. Proteins that appear to be parts of membrane transport systems are being isolated and characterized. Science 162: 632–637, 1968.
709. Pardo, E. G., Hong, E. and LeLorier, J.: Autoinhibition in rabbit aortic strips after epinephrine. J. Pharmacol. Exp. Ther. 157: 303–310, 1967.
710. Pařízek, J.: Vascular changes at sites of oestrogen biosynthesis produced by parenteral injection of cadmium salts: the destruction of placenta by cadmium salts. J. Reproduct. Fertil. 7: 263–265, 1964.
711. Parker, B. M., Steiger, B. W. and Friedenberg, M. J.: Serotonin-induced pulmonary venous spasm demonstrated by selective pulmonary phlebography. Amer. Heart J. 69: 521–528, 1965.
712. Paterson, G.: The response to transmural stimulation of isolated arterial strips and its modification by drugs. J. Pharm. Pharmacol. 17: 342–349, 1965.

713. PATHAK, C. L.: Action of acetazoléamide (a powerful carbonic anhydrase inhibitor) on isolated perfused amphibian and mammalian blood vessels. Indian J. Med. Sci. 12: 528–530, 1958.
714. PATIL, P. N., TYE, A., MAY, C., HETEY, S. AND MIYAGI, S.: Steric aspects of adrenergic drugs. XI. Interactions of dibenamine and *beta* adrenergic blockers. J. Pharmacol. Exp. Ther. 163: 309–319, 1968.
715. PATIL, P. N., TYE, A. AND NELSON, J. W.: Vasopressin tachyphylaxis. J. Pharm. Sci. 53: 684–686, 1964.
716. PATON, W. D. M.: A theory of drug action based on the rate of drug-receptor combination. Proc. Roy. Soc. (London) 154: 21, 1961.
717. PATON, W. D. M. AND RANG, H. P.: The uptake of atropine and related drugs by intestinal smooth muscle of the guinea-pig in relation to acetylcholine receptors. Proc. Roy. Soc. 163: 1–44, 1965.
718. PEART, W. S.: The renin-angiotensin system. Pharmacol. Rev. 17: 143–182, 1965.
718a. PEASE, D. C.: Structural features of unfixed mammalian smooth and striated muscle prepared by glycol dehydration. J. Ultrastruct. Res. 23: 280–303, 1968.
719. PEIPER, U., WENDE, W. AND WULLSTEIN, H. K.: Der Einfluss von Temperatur, Vorspannung und Propanolol auf die Noradrenalinwirkung am isolierten Gefässstreifen der Rattenaorta. Pflügers Arch. Gesamte Physiol. Menschen Tiere 305: 167–176, 1969.
720. PENEFSKY, Z. J. AND SCHWARTZ, I. L.: Spontaneous electrical and mechanical activity of rabbit aorta. Fed. Proc. 28: 398, 1969.
721. PERKS, A. M.: Pharmacological and chromatographic studies of the neurohypophysial activities of the pituitary of further elasmobranch species. Gen. Comp. Endocrinol. 6: 428–442, 1966.
722. PERRY, H. M., JR., ERLANGER, M., YUNICE, A. AND PERRY, E. F.: Mechanisms of the acute hypertensive effect of intra-arterial cadmium and mercury in anesthetized rats. J. Lab. Clin. Med. 70: 963–972, 1967.
723. PERRY, H. M., JR., SCHOEPFLE, E. AND BOURGOIGNIE, J.: *In vitro* production and inhibition of aortic vasoconstriction by mercuric, cadmium, and other metal ions. Proc. Soc. Exp. Biol. Med. 124: 485–490, 1967.
724. PETTINGER, W. A., SPECTOR, S., HORWITZ, D. AND SJOERSDMA, A.: Restoration of tyramine pressor responses in reserpine-treated animals by methyldopa and its amine metabolites. Proc. Soc. Exp. Biol. Med. 118: 988–993, 1965.
725. PHELAN, E. L., ERYETISHIR, I., DAH, M. AND SMIRK, F. H.: Observations on the responses of rats with spontaneous hypertension and control rats to pressor drugs and to hexamethonium. Circ. Res. 10: 817–824, 1962.
725a. PHELAN, E. L. AND WONG, L. C. K.: Sodium, potassium and water in the tissues of rats with genetic hypertension and constricted renal artery hypertension. Clin. Sci. (London) 35: 487–494, 1968.
726. PICCININI, F. AND POMARELLI, P.: Prostaglandina E_1 (PGE_1) e trasporto del calcio. (Esperienze eseguite *in vitro* secondo uno schema di particolare semplicità). Boll. Soc. Ital. Biol. Sper. 43: 1412–1413, 1967.
727. PICKERING, B. T. AND DYBALL, R. E. J.: Dissociation of the pressor and antidiuretic activities of synthetic arginine vasopressin by heating at pH 10. Nature (London) 216: 584–585, 1967.
728. PICKFORD, M.: Neurohypophysis and vascular reactions. *In* The Pituitary Gland, ed. by G. W. Harris and B. T. Donovan, vol. 3, pp. 399–413, University of California Press, Berkeley, 1966.
729. PIERCE, J. V.: Structural features of plasma kinins and kininogens. Fed. Proc. 27: 52–57, 1968.
730. PISANO, J. J.: Vasoactive peptides in venoms. Fed. Proc. 27: 58–62, 1968.
731. PLIŠKA, V. AND KREJČÍ, I.: The dose-response relation of the antidiuretic and vasopressor activities of 4-asparagine-8-lysine-vasopressin. Arch. Int. Pharmacodyn. Thér. 161: 289–297, 1966.
732. POLÁČEK, I., KREJČÍ, I. AND RUDINGER, J.: The action of oxytocin and synthetic analogues on the isolated mammary-gland myoepithelium of the lactating rat; effect of some ions. J. Endocrinol. 38: 13–24, 1967.
733. PORTZEHL, H., CALDWELL, P. C. AND RÜEGG, J. C.: The dependence of contraction and relaxation of muscle fibres from the carb *Maia squinado* on the internal concentration of free calcium ions. Biochim. Biophys. Acta 79: 581–591, 1964.
734. PRICE, H. L. AND COHEN, P. J. (ed.): Effects of Anesthetics on the Circulation, Charles C Thomas, Springfield, Ill., 1964.
735. PRICE, M. L. AND PRICE, H. L.: Effects of general anesthetics on contractile responses of rabbit aortic strips. Anesthesiology 23: 16–20, 1962.
736. PRIEST, R. E., KOPLITZ, R. M. AND BENDITT, E. P.: Estradiol reduces incorporation of radioactive sulfate into cartilage and aortas of rats. J. Exp. Med. 112: 225–236, 1960.
737. PRUSS, T. P., KOPPANYI, T. AND MAENGWYN-DAVIES, G. D.: Further elucidation of the effect of dichloro-analogs of catecholamines on the aortic strip. Arch. Int. Pharmacodyn. Thér. 141: 163–175, 1963.
738. PRUSS, T. P., MAENGWYN-DAVIES, G. D. AND WURZEL, M.: Comparison of effects of aromatic sympathomimetic amines on rabbit aortic strip and rabbit blood pressure. J. Pharmacol. Exp. Ther. 147: 76–85, 1965.
739. RAAB, W. AND GIGEE, W.: Uptake and breakdown of catecholamines in vascular tissue. Angiology 9: 283–289, 1958.
740. RAMOS, A. O., CHAPMAN, L. F. AND RAMOS, L.: Neurokinin from cerebrospinal fluid. I. Some pharmacological properties. Arch. Int. Pharmacodyn. Thér. 146: 501–506, 1963.
741. RAND, M. J. AND WILSON, J.: The relationship between adrenergic neurone blocking activity and local anaesthetic activity in a series of guanidine derivatives. European J. Pharmacol. 1: 200–209, 1967.
742. RASMUSSEN, H. AND TENENHOUSE, A.: Cyclic adenosine monophosphate, Ca^{++}, and membranes. Proc. Nat. Acad. Sci. 59: 1364–1370, 1968.
743. READ, R. C., JOHNSON, J. A., VICK, J. A. AND MEYER, M. W.: Vascular effects of hypertonic solutions. Circ. Res. 8: 538–548, 1960.
744. REDLEAF, P. D. AND TOBIAN, L.: The question of vascular hyperresponsiveness in hypertension. Circ. Res. 6: 185–193, 1958.
745. REIS, D. J.: Potentiation of the vasoconstrictor action of topical norepinephrine on the human bulbar conjunctival vessels after topical application of certain adrenocortical hormones. J. Clin. Endocrinol. 20: 446–456, 1960.

746. Reite, O. B.: Functional qualities of small blood vessels in tissue injured by freezing and thawing. Acta Physiol. Scand. 63: 111–120, 1965.
747. Reite, O. B.: The evolution of vascular smooth muscle responses to histamine and 5-hydroxytryptamine. I. Occurrence of stimulatory action in fish. Acta Physiol. Scand. 75: 221–239, 1969.
748. Ressler, C. and Rachele, J. R.: Further properties of isoglutamine-oxytocin; inhibition of pressor activity of vasopressin. Proc. Soc. Exp. Biol. Med. 98: 170–174, 1958.
749. Reynolds, D. G. and Imig, C. J.: Segmental vascular reactivity subsequent to sympathectomy. Amer. J. Physiol. 204: 1145–1150, 1963.
750. Reynolds, R. C. and Haugaard, N.: The effect of variations of pH upon the activation of phosphorylase by epinephrine in perfused contracting heart, liver slices and skeletal muscle. J. Pharmacol. Exp. Ther. 156: 417–425, 1967.
751. Ribot, S., Abramowitz, S., Green, H., Small, M. J. and Schwartz, I.: Cardiovascular effects of oxytocin and comparison with related polypeptides. Amer. J. Med. Sci. 248: 61–70, 1964.
752. Ribot, S., Green, H., Small, M. J. and Abramowitz, S.: Cardiovascular effects of vasopressin. Amer. J. Med. Sci. 242: 612–619, 1961.
753. Rice, A. J. and Long, J. P.: An unusual venoconstriction induced by acetylcholine. J. Pharmacol. Exp. Ther. 151: 423–429, 1965.
754. Riniker, B. and Schwyzer, R.: Synthetische Analoge Hypertensins. V. α-L, -β-L-, α-D- und β-D-Asp^1-Val^5-Hypertensin II; Desamino-Val^5-Hypertensin II. Helv. Chim. Acta 47: 2357–2374, 1964.
755. Ritchie, J. M. and Greengard, P.: On the mode of action of local anesthetics. Annu. Rev. Pharmacol. 6: 405–430, 1966.
756. Roberts, D. J.: Chromatographic evidence for the formation as an artifact of an isoprenaline-like substance from adrenaline. Biochem. Pharmacol. 15: 63–69, 1966.
757. Robinson, J. D., Carlini, E. A. and Green, J. P.: The effects of ganglioside preparations on smooth muscle. Biochem. Pharmacol. 12: 1219–1223, 1963.
758. Robison, G. A., Butcher, R. W. and Sutherland, E. W.: Cyclic AMP. Annu. Rev. Biochem. 37: 149–174, 1968.
759. Robleto, J. and Croxatto, H.: Vasoactive substances formed in blood serum by incubation at 37°C at normal pH. *In* International Symposium on Vaso-Active Polypeptides: Bradykinin and Related Kinins, pp. 119–125, Ribeirao Preto, Sao Paulo, Brazil, 1966.
760. Rocha e Silva, M.: Biochemistry and pharmacology of bradykinin. *In* Polypeptides, ed. by M. Schachter, pp. 210–231, Pergamon Press, Oxford, 1960.
761. Rocha e Silva, M. (ed.): Handbook of Experimental Pharmacology, Histamine and Anti-Histaminics. Part I: Histamine. Its Chemistry, Metabolism and Physiological and Pharmacological Actions, Springer-Verlag, New York, 1966.
762. Rocha e Silva, M.: Influence of pH on the interaction of histamine with its receptors in the guinea pig ileum. Arch. Int. Pharmacodyn. Thér. 128: 355–374, 1960.
762a. Rocha e Silva, M., J r. and Rosenberg, M.: The release of vasopressin in response to haemorrhage and its role in the mechanism of blood pressure regulation. J. Physiol. (London) 202: 535–557, 1969.
763. Roddie, I. C.: Electrical and mechanical activity in turtle arteries and veins. Bibl. Anat. 8: 1–4, 1967.
764. Roddie, I. C. and Scott, A. C.: Some effects of oxygen tension on isolated arterial segments. J. Physiol. (London) 179: 59–60, 1965.
765. Roddie, I. C. and Scott, A. C.: Some differences in the responses of arterial and venous smooth muscle to temperature change. J. Physiol. (London) 201: 43P–45P, 1968.
766. Rogers, L. A., Atkinson, R. A. and Long, J. P.: Responses of isolated perfused arteries to catecholamines and nerve stimulation. Amer. J. Physiol. 209: 376–382, 1965.
767. Romero, T. and Talesnik, J.: Influence of nicotine on the coronary circulation of the isolated heart of the cat. J. Pharm. Pharmacol. 19: 322–328, 1967.
768. Rondell, P. and Gross, F.: Method for isometric recording from isolated vessels under various conditions. Helv. Physiol. Pharmacol. Acta 18: 366–375, 1960.
769. Rosas, R., Montague, D., Gross, M. and Bohr, D. F.: Cardiac action of vasoactive polypeptides in the rat. I. Bradykinin. II. Anigotensin. Circ. Res. 16: 150–161, 1965.
770. Rosenberg, P. and Dettbarn, W.-D.: Cholinesterase activity of rabbit aorta. Life Sci. 4: 567–572, 1965.
771. Rosenthal, J., Boucher, R., Rojo-Ortega, J. M. and Genest, J.: Renin activity in aortic tissue of rats. Can. J. Physiol. Pharmacol. 47: 53–56, 1969
772. Rovick, A. A. and Randall, W. C.: Systemic circulation. Annu. Rev. Physiol. 29: 225–258, 1967.
773. Rowe, G. G.: Pharmacology of the coronary circulation. Annu. Rev. Pharmacol. 8: 95–112, 1968.
774. Rowley, D. A.: Venous constriction as the cause of increased vascular permeability produced by 5-hydroxytryptamine, histamine, bradykinin and 48/80 in the rat. Brit. J. Exp. Pathol. 45: 56–67, 1964.
775. Rubin, A. A., Roth, F. E., Taylor, R. M. and Rosenkilde, H.: Pharmacology of diazoxide, an antihypertensive, nondiuretic benzothiadiazine. J. Pharmacol. Exp. Ther. 136: 344–352, 1962.
776. Rubin, B., Waugh, M. H., Laffan, R. J., O'Keefe, E. and Craver, E. N.: Effects on smooth muscle and blood vessels of polypeptides related to bradykinin and to kallidin. Proc. Soc. Exp. Biol. Med. 113: 328–332, 1963.
777. Rubio, R., Berne, R. M. and Katori, M.: Release of adenosine in reactive hyperemia of the dog heart. Amer. J. Physiol. 216: 56–62, 1969.
778. Rudinger, J.: Synthetic analogues of oxytocin: an approach to problems of hormone action. Proc. Roy. Soc. 170: 17–26, 1968.
779. Rudinger, J. and Jöst, K.: A biologically active analogue of oxytocin not containing a disulfide group. Experientia (Basel) 20: 570–574, 1964.

780. RUDINGER, J. AND KREJČÍ, I.: Antagonists of the neurohypophysial hormones. *In* Handbook of Experimental Pharmakologie, vol. 23, pp. 748–801, ed. by B. Berde, Springer-Verlag, New York, 1968.
781. RUDOLPH, A. M., KURLAND, M. D., AULD, P. A. M. AND PAUL, M. H.: Effects of vasodilator drugs on normal and serotonin-constricted pulmonary vessels of the dog. Amer. J. Physiol. 197: 617–623, 1959.
782. RUDOLPH, A. M. AND YAUN, S.: Response of the pulmonary vasculature to hypoxia and H^+ ion concentration changes. J. Clin. Invest. 45: 399–411, 1966.
783. RÜEGG, J. C.: Contractile mechanisms of smooth muscle. *In* Aspects of Cell Motility, Cambridge University Press, Cambridge, 1968.
784. SAAMELI, K.: The circulatory actions of the neurohypophysial hormones and similar polypeptides. *In* Handbook of Experimental Pharmakologie, vol. 23, pp. 544–612, ed. by B. Berde, Springer-Verlag, New York, 1968.
785. SAKAKIBARA, S. AND HASE, S.: Synthesis of an analogue of desamino-lysine-vasopressin containing no disulfide bond. Bull. Chem. Soc. Jap. 41: 2816, 1968.
786. SAKURAI, T. AND HASHIMOTO, Y.: The vasoconstrictor action of angiotensin in relation to catecholamine. Jap. J. Pharmacol. 15: 223–233, 1965.
787. SALEM, E. S., PERMUTT, S., RILEY, R. L. AND JOHNSON, J. W. C.: Effect of respiratory gases on compliance of intrapulmonary arteries and veins. J. Appl. Physiol. 19: 1202–1206, 1964.
788. SALTZMAN, H. A., HART, L., SIEKER, H. O. AND DUFFY, E. J.: Retinal vascular response to hyperbaric oxygenation. J. Amer. Med. Ass. 191: 290–292, 1965.
789. SAMBHI, M. P. AND BARRETT, J. D.: Development of tachyphylaxis to aspartyl and not to asparginyl angiotensin II in the rat. Circ. Res. 21: 327–332, 1967.
790. SAMUELSSON, B.: The prostaglandins. Angew. Chem. Int. Ed. Engl. 4: 410–416, 1965.
791. SANDERS, H. D.: The vasoconstrictor and vasodilator effects of procaine. Can. J. Physiol. Pharmacol. 43: 39–46, 1965.
792. SANDERS, H. D.: Procaine-induced contraction in vein and its modification by drugs. Can. J. Physiol. Pharmacol. 47: 218–221, 1969.
793. SAWYER, W. H.: Neurohypophysial hormones. Pharmacol. Rev. 13: 225–277, 1961.
794. SAWYER, W. H.: Active neurohypophysial principles from a cyclostome (*Petromyzon marinus*) and two cartilaginous fishes (*Squalus acanthias* and *Hydrolagus collei*). Gen. Comp. Endocrinol. 5: 427–439, 1965.
795. SAWYER, W. H.: Evolution of antidiuretic hormones and their functions. Amer. J. Med. 42: 678–686, 1967.
796. SCHACHTER, M.: Some properties of kallidin, bradykinin and wasp venom kinin. *In* Polypeptides which Affect Smooth Muscles and Blood Vessels, ed. by M. Schachter, pp. 232–246, Pergamon Press, New York, 1960.
797. SCHACHTER, M. AND BEILENSON, S.: Mediator of vasodilatation in the submaxillary gland. Fed. Proc. 27: 73–75, 1968.
798. SCHALLY, A. V., BOWERS, C. Y., KUROSHIMA, A., ISHIDA, Y., CARTER, W. H. AND REDDING, T. W.: Effect of lysine vasopressin dimers on blood pressure and some endocrine functions. Amer. J. Physiol. 207: 378–384, 1964.
799. SCHALLY, A. V., KASTIN, A. J., BARRETT, J. F., CARTER, W. H., BOWERS, C. Y. AND WHITE, W. F.: On vasodepressor activity in the hypothalamus. Biochem. Pharmacol. 15: 1805–1811, 1966.
800. SCHAPER, W.: Heart. Coronary circulation. Regulation of coronary blood flow. Annu. Rev. Physiol. 29: 259–312, 1967.
801. SCHAPER, W. K. A., JAGENEAU, A. H. M., XHONNEUX, R., VAN NUETEN, J. AND JANJSEN, P. A. J.: Cinnarizine (R 516), a specific angiotensine-blocking coronary vasodilator. Life Sci. 12: 963–974, 1963.
802. SCHATZMANN, H. J.: Kompetitiver Antagonismus zwischen g-Strophanthin und Corticosteron an isolierten Streifen von Rattenaorten. Experientia (Basel) 15: 73–74, 1959.
803. SCHAYER, R. W.: Enzymatic formation of histamine from histidine. *In* Handbook of Experimental Pharmacology, Histamine and Anti-Histaminics. Part I: Histamine. Its Chemistry, Metabolism and Physiological and Pharmacological Actions, ed. by M. R. Silva, Springer-Verlag, New York, 1966.
804. SCHILD, H. O.: The effect of metals on the S-S polypeptide receptor in depolarized rat uterus. Brit. J. Pharmacol. 36: 329–349, 1969.
805. SCHMAHL, F. W.: Die Wirkung von Adrenalin und anderen gefässaktiven Substanzen auf isolierte Muskel-und Hautarterien im Vergleich mit den Kreislaufreaktionen im Organismus. Z. Biol. 112: 366–379, 1961.
806. SCHMID, P. G., ECKSTEIN, J. W. AND ABBOUD, F. M.: Effect of 9-α-fluorohydrocortisone on forearm vascular responses to norepinephrine. Circulation 34: 620–626, 1966.
807. SCHMID, P. G., ECKSTEIN, J. W. AND ABBOUD, F. M.: Comparison of effects of deoxycorticosterone and dexamethasone on cardiovascular responses to norepinephrine. J. Clin. Invest. 46: 590–598, 1967.
808. SCHMID, P. G., ECKSTEIN, J. W. AND ABBOUD, F. M.: Effect of 9-α-fluorohydrocortisone on forearm venous responses to norepinephrine and tyramine. J. Appl. Physiol. 23: 571–574, 1967.
809. SCHMIDT, L.: Zur Frage der coronarerweiternden Wirkung des Khellins. Klin. Wochenschr. 36: 127–129, 1958.
810. SCHOLTHOLT, J., BUSSMANN, W. D. AND LOCHNER, W.: Untersuchungen über die Coronarwirksamkeit des Adenosin und der Adeninnucleotide sowie ihre Beeinflussung durch zwei Substanzen mit starker Coronarwirkung. Pflügers Arch. Gesamte Physiol. Menschen Tiere 285: 274–286, 1965.
811. SCHRÖDER, E.: Synthese und biologische Aktivität bradykininwirksamer Undeca-, Dodeca- und Tridecapeptide. Experientia (Basel) 21: 271–272, 1965.
812. SCHRÖDER, E. AND HEMPEL, R.: Bradykinin, kallidin, and their synthetic analogues. Experientia (Basel) 20: 529–545, 1964.
813. SCHULZ, H. AND DU VIGNEAUD, V.: Synthesis of 1-L-penicillamine-oxytocin, 1-D-penicillamine-oxytocin, and 1-deaminopenicillamine-oxytocin, potent inhibitors of the oxytocic response of oxytocin. J. Med. Chem. 9: 647–650, 1966.
814. SCHULZ, H. AND DU VIGNEAUD, V.: The effect of replacing one of the hydrogens of the B-carbon of the B-mercap-

topropionic acid residue in deamino-oxytocin by a methyl group on its oxytocic and avian vasodepressor activity. J. Amer. Chem. Soc. 88: 5015–5018, 1966.

815. SCHULZ, H. AND DU VIGNEAUD, V.: Synthesis and some pharmacological properties of 6-L-penicillamine oxytocin. J. Med. Chem. 10: 1037–1039, 1967.

816. SCRIABINE, A.: Some observations on the adrenergic blocking activity of desipramine and amitriptyline on aortic strips of rabbits. Experientia (Basel) 25: 164–165, 1969.

817. SCROOP, G. C. AND WALSH, J. A.: Interactions between angiotensin, noradrenaline and serotonin on the peripheral blood vessels in man. Aust. J. Exp. Biol. Med. Sci. 46: 573–580, 1968.

818. SCROOP, G. C. AND WHELAN, R. F.: The effects of alpha-adrenergic receptor blockade and sympathetic denervation on the pressor action of angiotensin in man. Aust J. Exp. Biol. Med. Sci. 46: 563–572, 1968.

819. SCROOP, G. C. AND WHELAN, R. F.: Vascular reactivity studies in hypertension. Aust. J. Exp. Biol. Med. Sci. 46: 551–561, 1968.

820. SEGURA, E. T., LASCANO, E. F. AND D'AGOSTINO, S.A.: Estrogen-induced arterial hypertension in the hibernating male toad, *Bufo arenarum* Hensel. Amer. J. Physiol. 212: 477–481, 1967.

821. SELLER, H., LANGHORST, P., POLSTER, J. AND KOEPCHEN, H. P.: Zeitliche Eigenschaften der Vasomotorik. II. Erscheinungsformen und Entstehung spontaner und nervös induzierter Gefässrhythmen. Pflügers Arch. Gesamte Physiol. Menschen Tiere 296: 110–132, 1967.

822. SEMLER, H. J., SHEPHERD, J. T. AND SWAN, H. J. C.: Pressor effect of hypertonic saline on pulmonary circulation. Circ. Res. 7: 1011–1017, 1959.

823. SENFT, G., MUNSKE, K., SCHULTZ, G. AND HOFFMANN, M.: Der Einfluss von Hydrochlorothiazid und anderen sulfonamidierten Diuretica auf die 3',5'-AMP-Phosphodiesterase-Aktivität in der Rattenniere. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 259: 344–359, 1968.

824. SETNIKAR, I. AND RAVASI, M.: Inhibition of sensitiveness to nicotine of rabbit aorta by reserpine, hexamethonium, ethyl flavone-7-oxyacetate and other compounds. Nature (London) 183: 898–899, 1959.

825. SEVERS, W. B., DANIELS, A. E., SMOOKLER, H. H., KINNARD, W. J. AND BUCKLEY, J. P.: Interrelationship between angiotensin II and the sympathetic nervous system. J. Pharmacol. Exp. Ther. 153: 530–537, 1966.

826. SHALDON, S., DOLLE, W., GUEVARA, L., IBER, F. L. AND SHERLOCK, S.: Effect of pitressin on the splanchnic circulation in man. Circulation 24: 797–807, 1961.

827. SHANKS, R. G.: The peripheral vascular effects of propranolol and related compounds. Brit. J. Pharmacol. Chemother. 29: 204–217, 1967.

828. SHEMANO, I. AND FALLON, P. C.: Effect of L-3,3',5-triiodothyronine on epinephrine-induced contraction of isolated rabbit aortic strip. Proc. Soc. Exp. Biol. Med. 103: 282–285, 1960.

829. SHIBATA, S.: Effect of prolonged cold storage on the contractile response of strips of rabbit aorta to various agents. Circ. Res. 24: 179–187, 1969.

830. SHIBATA, S. AND BRIGGS, A. H.: Mechanical activity of vascular smooth muscle under anoxia. Amer. J. Physiol. 212: 981–984, 1967.

831. SHIBATA, S. AND CARRIER, O., JR.: Antagonising action of chlorpromazine, dibenamine, and phenoxybenzamine on potassium-induced contraction. Can. J. Physiol. Pharmacol. 45: 587–596, 1967.

832. SHIBATA, S., CARRIER, O., JR. AND FRANKENHEIM, F.: Effect of chlorpromazine, dibenamine and phenoxybenzamine on the contractile response of taenia coli to potassium, acetylcholine, angiotensin and barium. J. Pharmacol. Exp. Ther. 160: 106–111, 1968.

833. SHIDA, H., MEYERS, M. A. AND BARKER, S. B.: Effect of copper in thyroxine potentiation of *in vitro* epinephrine action on smooth muscle. J. Pharmacol. Exp. Ther. 141: 280–284, 1963.

834. SILAH, J. G., STRONG, C. G., NOWACZYNSKI, W. AND GENEST, J.: The angiotensin infusion test and peripheral venous renin activity. Can. Med. Ass. J. 96: 1397–1400, 1967.

835. SILOVE, E. D. AND GROVER, R. F.: Effects of alpha adrenergic blockade and tissue catecholamine depletion on pulmonary vascular response to hypoxia. J. Clin. Invest. 47: 274–285, 1968.

836. SILOVE, E. D., INOUE, T. AND GROVER, R. F.: Comparison of hypoxia, pH, and sympathomimetic drugs on bovine pulmonary vasculature. J. Appl. Physiol. 24: 355–365, 1968.

837. SISSON, J. A.: Smooth muscle-contracting peptide from the rabbit placenta and its comparison to bradykinin. Arch. Int. Pharmacodyn. Thér. 144: 112–119, 1963.

838. SISSON, J. A. AND DAVIES, J.: Some properties of hypotensive smooth muscle contracting principle in placenta of rabbit. Proc. Soc. Exp. Biol. Med. 100: 389–391, 1959.

839. SIVERTSSON, R. AND OLANDER, R.: Aspects of the nature of increased vascular resistance and increased "reactivity" to noradrenaline in hypertensive subjects. Life Sci. 7: 1291–1297, 1968.

840. SKEGGS, L. T., LENTZ, K. E., GOULD, A. B., HOCHSTRASSER, H. AND KAHN, J. R.: Biochemistry and kinetics of the renin-angiotensin system. Fed. Proc. 26: 42–47, 1967.

841. SKINNER, N. S., JR. AND COSTIN, J. C.: Tissue metabolites and regulation of local blood flow. Fed. Proc. 27: 1426–1429, 1968.

842. SKINNER, N. S., JR. AND POWELL, W. J., JR.: Action of oxygen and potassium on vascular resistance of dog skeletal muscle. Amer. J. Physiol. 212: 533–540, 1967.

843. SKINNER, N. S., JR. AND WEBSTER, M. E.: Kinins, beta-adrenergic receptors and functional vasodilatation in the submaxillary gland of the cat. J. Physiol. (London) 195: 505–519, 1968.

844. SKINNER, N. S., JR. AND WEBSTER, M. E.: Submaxilllary gland blood flow: the role of kinins and beta-adrenergic receptors. Fed. Proc. 27: 76–79, 1968.

845. SMITH, D. J. AND VANE, J. R.: Effects of oxygen tension on vascular and other smooth muscle. J. Physiol. (London) 186: 284–294, 1966.

846. SMITH, R. W., MORRIS, J. A., ASSALI, N. S. AND BECK, R.: Effects of chemical mediators on the pulmonary and ductus arteriosus circulation in the fetal lamb. Amer. J. Obstet. Gynecol. 89: 252–260, 1964.

847. SOKOLOFF, L.: The action of drugs on the cerebral circulation. Pharmacol. Rev. 11: 1–85, 1959.

848. SOLTI, F., ISKUM, M., MÁTHÉ, Z., MÁRK, G. AND ÁCS, G.: Effect of procaine on coronary circulation. Acta Physiol. Acad. Sci. Hung. 21: 353–357, 1962.

849. SOMLYO, A. P. AND A. V. SOMLYO: Vascular smooth muscle. I. Normal structure, pathology, biochemistry, and biophysics. Pharmacol. Rev. 20: 197–272, 1968.

850. SOMLYO, A. P. AND SOMLYO, A. V.: Pharmacology of excitation-contraction coupling in vascular smooth muscle and in avian slow muscle. Fed. Proc. 28: 1634–1642, 1969.

851. SOMLYO, A. P. AND SOMLYO, A. V.: Electrophysiological correlates of the inequality of maximal vascular smooth muscle contractions elicited by drugs. *In* Vascular Neuroeffector Systems, ed. by J. A. Bevan, R. F. Furchgott, R. A. Maxwell and A. P. Somlyo, S. Karger, Basel, New York, in press.

852. SOMLYO, A. P. AND SOMLYO, A. V.: Biophysics of smooth muscle excitation and contraction. *In* Airway Dynamics, ed. by A. Bouhuys, Charles C Thomas, Springfield, Ill., pp. 209–228. 1970.

853. SOMLYO, A. P., SOMLYO, A. V. AND WOO, C.-Y.: Neurohypophysial peptide interaction with magnesium in avian vascular smooth muscle. J. Physiol. (London) 192: 657–668, 1967.

854. SOMLYO, A. P. AND VINALL, P. E.: Unpublished observations.

855. SOMLYO, A. P. AND WOO, C.: β-Adrenergic auto-inhibition of the effect of noradrenaline on avian pulmonary artery. J. Pharm. Pharmacol. 19: 59–61, 1967.

856. SOMLYO, A. V. AND SOMLYO, A. P.: Effect of angiotensin and beta-adrenergic stimulation on venous smooth muscle. Amer. Heart J. 71: 568–570, 1966.

857. SOMLYO, A. V. AND SOMLYO, A. P.: Vasotocin-magnesium interaction in vascular smooth muscle of the hagfish (*Eptatretus stoutii*). Comp. Biochem. Physiol. 24: 267–270, 1968.

858. SOMLYO, A. V. AND SOMLYO, A. P.: Unpublished observations.

858a. SOMLYO, A. V., HAEUSLER, G. AND SOMLYO, A. P.: Beta-adrenergic electrogenesis in vascular smooth muscle: effect of theophylline, external potassium, and oligomycin. Fed. Proc., 29: 613 Abs, 1970.

859. SOMLYO, A. V., VINALL, P. AND SOMLYO, A. P.: Excitation-contraction coupling and electrical events in two types of vascular smooth muscle. Microvasc. Res. 1: 354–373, 1969.

860. STAHL, P. D., WAITE, L. C., HEISKELL, C. A. AND KENNEY, A. D.: Thyrocalcitonin preparations: characterization of the depressor contaminant. European J. Pharmacol. 1: 247–253, 1967.

861. STAINSBY, W. N. AND FREGLY, M. J.: Effect of plasma osmolality on resistance to blood flow through skeletal muscle. Proc. Soc. Exp. Biol. Med. 128: 284–287, 1968.

862. STAQUET, M., DEMANET, J.-C. AND BASTÉNIE, P. A.: Étude de la sensibilité vasculaire a la noradrénaline dans l'hypertension artérielle. Rev. Fr. Étud. Clin. Biol. 10: 394–399, 1965.

863. STARR, M. S. AND WEST, G. B.: The effect of bradykinin and anti-inflammatory agents on isolated arteries. J. Pharm. Pharmacol. 18: 838–840, 1966.

864. STASZEWSKA-BARCZAK, J. AND KONOPKA-ROGATKO, K.: Pressor activity and release of catecholamines by angiotensin and some of its analogues. Bull. Acad. Pol. Sci. 15: 503–510, 1967.

865. STEPHENSON, R. P.: A modification of receptor theory. Brit. J. Pharmacol. 11: 379–393, 1956.

866. STEWART, J. M.: Structure-activity relationships in bradykinin analogues. Fed. Proc. 27: 63–66, 1968.

867. STEWART, J. M. AND WOOLLEY, D. W.: Importance of the carboxyl end of bradykinin and other peptides. Nature (London) 207: 1160–1161, 1965.

868. STRONG, C. G. AND BOHR, D. F.: Effects of prostaglandins E_1, E_2, A_1, and $F_{1\alpha}$ on isolated vascular smooth muscle. Amer. J. Physiol. 213: 725–733, 1967.

869. STUDER, A. AND TRIPOD, J.: Verschiedene Reaktivität isolierter Gefässe auf veinengernde und erweiternde Pharmaka. Helv. Physiol Pharmacol. Acta 18: 384–393, 1960.

870. STUDER, R. O. AND CASH, W. D.: Synthesis of 1-acetyl-8-arginine-vasopressin and a study of its effects in the rat pressor assay. J. Biol. Chem. 238: 657–659, 1963.

871. STÜRMER, E.: Bioassay procedures for neurohypophysial hormones and similar polypeptides. *In* Handbook of Experimental Pharmakologie, vol. 23, pp. 130–189, ed. by B. Berde, Springer-Verlag, New York, 1968.

872. STÜRMER, E. AND BERDE, B.: A comparative pharmacological study of synthetic eledoisin and synthetic bradykinin. J. Pharmacol. Exp. Ther. 140: 349–355, 1963.

873. STÜRMER, E., HUGUENIN, R. L., BOISSONNAS, R. A. AND BERDE, B.: Deamino[1]-phenylalanine[3] arginine[8]-vasopressin: a peptide with highly selective antidiuretic activity. Experientia (Basel) 21: 583–586, 1965.

874. SU, C. AND BEVAN, J. A.: Electrical and mechanical responses of pulmonary artery muscle to neural and chemical stimulation. Bibl. Anat. 8: 30–34, 1966.

875. SU, C. AND BEVAN, J. A.: Release of (^{3}H) noradrenaline from vasoconstrictor nerves. J. Pharm. Pharmacol. 19: 625–626, 1967.

876. SULLIVAN, L. J. AND BRIGGS, A. H.: Effects of manganese on the response of aortic strips to angiotensin and norepinephrine contractions. J. Pharmacol. Exp. Ther. 161: 205–209, 1968.

877. SUTHERLAND, E. W., ROBISON, G. A. AND BUTCHER, R. W.: Some aspects of the biological role of adenosine 3′,5′-monophosphate (cyclic AMP). Circulation 37: 279–306, 1968.

878. SUTTER, M. C.: The pharmacology of isolated veins. Brit. J. Pharmacol. 24: 742–751, 1965.

879. SZENTIVÁNYI, M., JUHÁSZ-NAGY, A. AND DEBRECZENI, L.: A new vasoactive substance regulating the metabolic response of the coronaries. Acta Physiol. Acad. Sci. Hung. 31: 9–32, 1967.

880. TAIRA, N., YAMAMOTO, M., SATOH, S. AND HASHIMOTO, K.: Absence of blocking effect of tetrodotoxin on the action of tyramine in the saphenous vascular bed of the dog. Tohoku J. Exp. Med. 97: 97–98, 1969.

880a. TAKASHIMA, H., FRAEFEL, W. AND DU VIGNEAUD, V.: The synthesis and certain pharmacological properties of deamino-oxytocinoic acid methylamide and deamino-oxytocinoic acid dimethylamide. J. Amer. Chem. Soc. 91: 6182–6185, 1969.

881. TAKENAKA, F.: Response of coronary strips to acetylcholine, histamine, 5-hydroxytryptamine and adrenaline. Jap. J. Pharmacol. 9: 55–60, 1959.

882. TAKENAKA, F.: Response of vascular strip preparations to noradrenaline and tyramine. Jap. J. Pharmacol. 13: 274–281, 1963.

883. TAKENAKA, F.: Effects of epinephrine and beta adrenergic blocking agents on coronary circulation and myocardial metabolism. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 252: 407–417, 1966.

884. TALLARIDA, R. J., HARAKAL, C., RUBY, B. F. AND SEVY, R. W.: Theoretical basis for the determination of the molecularity of drug-receptor reactions and affinity of agonists. Curr. Med. Biol. 2: 249–253, 1968.

885. TALLEDO, O. E.: Renin-angiotensin system in normal and toxemic pregnancies. II. Inactivation of angiotensin in normal pregnancy. Amer. J. Obstet. Gynecol. 97: 571–572, 1967.

886. TALLEDO, O. E., CHESLEY, L. C. AND ZUSPAN, Z. P.: Renin-angiotensin system in normal and toxemic pregnancies. IV. Differential sensitivity to angiotensin II and norepinephrine in toxemia of pregnancy. Amer. J. Obstet. Gynecol. 100: 218–221, 1968.

887. TAQUINI, A. C., JR. AND TAQUINI, A. C.: Angiotensin tachyphylaxis in the rat. Acta Physiol. Latinoamer. 13: 159–164, 1963.

888. TEGER-NILSSON, A.-C.: Release of human and horse fibrinopeptides. Acta Chem. Scand. 21: 1879–1886, 1967.

889. TÉTREAULT, L., BEAULNES, A. AND PANISSET, A.: Tachyphylaxie du muscle lisse vasculaire du rat au valyl^{5}-angiotensine II-amide. Rev. Can. Biol. 22: 347–352, 1963.

890. TEXTER, E. C., JR., CHOU, C.-C., MERRILL, S. L., LAURETA, H. C. AND FROHLICH, E. D.: Direct effects of vasoactive agents on segmental resistance of the mesenteric and portal circulation. J. Lab. Clin. Med. 64: 624–633, 1964.

891. THAL, A. P. AND EGNER, W.: The site of action of the Staphylococcus alpha toxin. J. Exp. Med. 113: 67–82, 1961.

892. THILENIUS, O. G., CANDIOLO, B. M. AND BEUG, J. L.: Effect of adrenergic blockade on hypoxia-induced pulmonary vasoconstriction in awake dogs. Amer. J. Physiol. 213: 990–998, 1967.

893. THOENEN, H., HÜRLIMANN, A. AND HAEFELY, W.: Kationenabhängigkeit der Noradrenalinfreisetzung durch Tyramin. Helv. Physiol. Pharmacol. Acta 25: 441–443, 1967.

894. TKACHENKO, B. I., KRASILNIKOV, V. G., POLENOV, S. A. AND CHERNJAVSKAJA, G. V.: Responses of resistance and capacitance vessels at various frequency electrical stimulation of sympathetic nerves. Experientia (Basel) 25: 38–40, 1969.

895. TOBIAN, L. AND CHESLEY, G.: Calcium content of arteriolar walls in normotensive and hypertensive rats. Proc. Soc. Exp. Biol. Med. 121: 340–343, 1966.

896. TOBIAN, L., MARTIN, S. AND EILERS, W.: Effect of pH on norepinephrine-induced contractions of isolated arterial smooth muscle. Amer. J. Physiol. 196: 998–1002, 1959.

897. TOBIAN, L., OLSON, R. AND CHESLEY, G.: Water content of arteriolar wall in renovascular hypertension. Amer. J. Physiol. 216: 22–24, 1969.

898. TORIKAI, T.: On the humoral factors in arterial hypertension. Jap. Circ. J. 30: 184–185, 1966.

899. TRABER, D. L., GARY, H. H. AND GARDIER, R. W.: The involvement of the sympathetic nervous system in the pressor response to vasopressin. Arch. Int. Pharmacodyn. Thér. 168: 288–295, 1967.

900. TRENDELENBURG, U.: I. Mechanisms of supersensitivity and subsensitivity to sympathomimetic amines. Pharmacol. Rev. 18: 629–640, 1966.

901. TRENDELENBURG, U., MUSKUS, A., FLEMING, W. W. AND GOMEZ ALONSO DE LA SIERRA, B.: Modification by reserpine of the action of sympathomimetic amines in spinal cats; a classification of sympathomimetic amines. J. Pharmacol. Exp. Ther. 138: 171–180, 1962.

902. TRIPOD, J. AND BEIN, H. J.: Modification de la réactivité vasculaire périphérique dans l'hypertension renale du rat. Helv. Physiol. Pharmacol. Acta 18: 394–403, 1960.

903. TSAKIRIS, A., HAEMMERLI, U. P. AND BÜHLMANN, A.: Reduction of portal venous pressure in cirrhotic patients with bleeding from oesophageal varices, by administration of a vasopressin derivative, phenylalanine^{3}-lysine^{8}-vasopressin. Amer. J. Med. 36: 825–839, 1964.

904. TUPPY, H.: The influence of enzymes on neurohypophysial hormones and similar peptides. *In* Handbook of Experimental Pharmakologie, vol. 23, pp. 67–129, ed. by B. Berde, Springer-Verlag, New York, 1968.

905. TÜRKER, R. K., KARAHÜSEYINOGLU, E.: Interaction of cocaine with angiotensin and tyramine on the isolated rabbit aortic strips. Experientia (Basel) 24: 921–922, 1968.

906. TÜRKER, R. K. AND KHAIRALLAH, P. A.: Action of eledoisin on isolated vascular strips. Experientia (Basel) 22: 696–699, 1966.

907. UCHIDA, E., BOHR, D. F. AND HOOBLER, S. W.: A method for studying isolated resistance vessels from rabbit mesentery and brain and their responses to drugs. Circ. Res. 21: 525–536, 1967.

908. UHLENBROCK, K. AND SCHWEER, M.: Zur Frage der coronarerweiternden Wirkung des Khellins. Arzneimittel-Forschung 10: 293–297, 1960.

909. UVNÄS, B.: Cholinergic vasodilator nerves. Fed. Proc. 25: 1618–1622, 1966.

910. VACCA, C., ROSATI, F. AND VACCA, L.: Osservazioni isto-fisiologiche sul circolo polmonare del coniglio sottoposto ad ossigenazione iperbarica acuta a 3 atmosfere assolute. Riv. Med. Aeronaut. Sp. 30: 23–40, 1967.

911. VALETTE, G., COHEN, Y. AND BRALET, J.: Action de l'éphédrine sur l'aorte du rat *in vitro*: étude à l'aide de noradrenaline ^{14}C. Biochem. Pharmacol. 15: 177–185, 1966.

912. VALETTE, G., PEYROUX, C. AND JACQUOT, C.: Influence du temps de conservation à basse température de l'aorte isolée de lapin sur l'apparition de la tachyphylaxie à la tyramine. C. R. Séances Soc. Biol. 161: 1043–1045, 1967.

913. VALTIN, H.: Hereditary hypothalamic diabetes insipidus in rats (Brattleboro strain). Amer. J. Med. 42: 814–827, 1967.
913a. VAN BREEMAN, C.: Blockade of membrane calcium fluxes by lanthanum in relation to vascular smooth muscle contractility. Arch. Int. Physiol. Biochim. 77: 710–716, 1969.
914. VANDONGEN, R. AND GORDON, R. D.: A pressor agent in human stable plasma protein solutions. Circ. Res. 23: 397–400, 1968.
915. VAN DYKE, H. B. AND YEOH, T. S.: Effects of arginine vasotocin and other pharmacologically active substances on the cardiovascular system of the frog, *Rana macrodon*. Endocrinology 77: 716–724, 1965.
916. VANE, J. R.: The release and fate of vaso-active hormones in the circulation. Brit. J. Pharmacol. 35: 209–242, 1969.
917. VANHOUTTE, P.: Influence de variations du pH sur la réactivité de fragments de veines isolées du chien. C. R. Séances Soc. Biol. 161: 2318–2320, 1967.
918. VANHOUTTE, P. AND CLEMENT, D.: Effect of pH and pCO_2 changes on the reactivity of isolated venous smooth muscle. Arch. Int. Physiol. Biochim. 76: 144–146, 1968.
919. VANHOUTTE, P., CLEMENT, D. AND LEUSEN, I.: The reactivity of isolated veins to electrical stimulation. Arch. Int. Physiol. Biochim. 75: 641–657, 1967.
920. VANHOUTTE, P. AND LEUSEN, I.: Influence des concentrations des ions Ca, Na et H sur la réactivité de fragments de veines isolées du chien. C. R. Belge Soc. Biol. 162: 800–802, 1968.
921. VANHOUTTE, P. AND LEUSEN, I.: The reactivity of isolated venous preparations to electrical stimulation. Pflügers Arch. Gesamte Physiol. Menschen Tiere 306: 341–353, 1969.
922. VANHOUTTE, P. M. AND SHEPHERD, J. T.: Effect of temperature on reactivity of isolated cutaneous veins of the dog. Amer. J. Physiol., 218: 187–190, 1970.
923. VARMA, D. R. AND MCCULLOUGH, H. N.. Dissociation of the supersensitivity to norepinephrine caused by cocaine from inhibition of H^3-norepinephrine uptake in cold-stored smooth muscle. J. Pharmacol. Exp. Ther. 166: 26–34, 1969.
924. VÁVRA, I., MACHOVÁ, A., HOLEČEK, V., CORT, J. H., ZAORAL, M. AND SŎRM, F.: Effect of a synthetic analogue of vasopressin in animals and in patients with diabetes insipidus. Lancet 1: 948–952, 1968.
925. VICK, J. A.: Bioassay of the prominent humoral agents involved in endotoxin shock. Amer. J. Physiol. 209: 75–78, 1965.
926. VILES, P. H. AND SHEPHERD, J. T.: Relationship between pH, pO_2, and pCO_2, on the pulmonary vascular bed of the cat. Amer. J. Physiol. 215: 1170–1176, 1968.
927. VIVEROS, O. H., GARLICK, D. G. AND RENKIN, E. M.: Sympathetic beta adrenergic vasodilatation in skeletal muscle of the dog. Amer. J. Physiol. 215: 1218–1225, 1968.
928. VIZI, E. S.: The inhibitory action of noradrenaline and adrenaline on release of acetylcholine from guinea-pig ileum longitudinal strips. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 259: 199–200, 1968.
929. VOGT, W.: Pharmacologically active acidic phospholipids and glycolipids. Biochem. Pharmacol. 12: 415–420, 1963.
929a. WADDELL, W. J. AND BATES, R. G.: Intracellular pH. Physiol. Rev. 49: 285–329, 1969.
930. WÅHLIN, Å.: The action of succinylcholine on the peripheral blood vessels of the cat. Acta Anaesthesiol. Scand. 4: 21–31, 1960.
931. WALASZEK, E. J., HUGGINS, C. G. AND SMITH, C. M.: Drugs that modify actions of pharmacologically active polypeptides. Ann. N.Y. Acad. Sci. 104: 281–289, 1963.
932. WALLENTIN, I.: Studies on intestinal circulation. Acta Physiol. Scand. 69: 3–38, 1966.
933. WALSH, J. A.: Antagonism by methysergide of vascular effects of 5-hydroxytryptamine in man. Brit. J. Pharmacol. Chemother. 30: 518–530, 1967.
934. WALTER, P. AND BASSENGE, E.: Wirkung von ATP, A-3, 5-MP, Adenosin und Dipyridamol an Streifenpräparaten der A. coronaria, A. renalis und der V. portae. Pflügers Arch. Gesamte Physiol. Menschen Tiere 299: 52–65, 1968.
935. WALTER, P. AND BASSENGE, E.: Effect of angiotensin on vascular smooth muscles. Pflügers Arch. Gesamte Physiol. Menschen Tiere 307: 70–82, 1969.
936. WALTER, R. AND SCHWARTZ, I. L.: 5-Valine-oxytocin and 1-deamino-5-valine-oxytocin. J. Biol. Chem. 241: 5500–5503, 1966.
937. WARD, C. O. AND GAUTIERI, R. F.: Effect of certain drugs on perfused human placenta. VI. Serotonin antagonists. J. Pharm. Sci. 55: 474–478, 1966.
938. WARD, C. O. AND GAUTIERI, R. F.: Effect of certain drugs on perfused human placenta. VIII. Angiotensin-II antagonists. J. Pharm. Sci. 57: 287–292, 1968.
939. WAUD, D. R.: Pharmacological receptors. Pharmacol. Rev. 20: 49–88, 1968.
940. WEBB-PEPLOE, M. M.: Cutaneous venoconstrictor responses to local cooling in the dog. Unexplained by inhibition of neuronal re-uptake of norepinephrine. Circ. Res. 24: 607–615, 1969.
941. WEBB-PEPLOE, M. M. AND SHEPHERD, J. T.: Peripheral mechanism involved in response of dogs' cutaneous veins to local temperature change. Circ. Res. 23: 701–708, 1968.
942. WEBSTER, M. E. AND SKINNER, N. S., JR. AND POWELL, W. J., JR.: Role of the kinins in vasodilatation of skeletal muscle of the dog. Amer. J. Physiol. 212: 553–558, 1967.
943. WEEKS, J. R., SEKHAR, N. C. AND DUCHARME, D. W.: Relative activity of prostaglandins E_1, A_1, E_2 and A_2 on lipolysis, platelet aggregation, smooth muscle and the cardiovascular system. J. Pharm. Pharmacol. 21: 103–108, 1969.
944. WEIDMAN, W. H., TITUS, J. L. AND SHEPHERD, J. T.: Effect of chronic hypoxia on the pulmonary circulation of cats. Proc. Soc. Exp. Biol. Med. 118: 1158–1164, 1965.
945. WEINER, R. AND ALTURA, B. M.: Serotonin-bradykinin synergism in the mammalian capillary bed. Proc. Soc. Exp. Biol. Med. 124: 494–497, 1967.
946. WEINER, R. AND KALEY, C.: Influence of prostaglandin E_1 on the terminal vascular bed. Amer. J. Physiol. 217: 563–566, 1969.

947. WEINER, R. AND ZWEIFACH, B. W.: Effect of proteolytic enzyme inhibitors on contractile responses of the aortic strip. Amer. J. Physiol. 211: 735–738, 1966.
948. WEINER, R. AND ZWEIFACH, B. W.: Influence of *E. coli* endotoxin on serotonin contractions of the rabbit aortic strip. Proc. Soc. Exp. Biol. Med. 123: 937–939, 1966.
949. WEINER, R. AND ZWEIFACH, B. W.: Vasoinhibitory action of proteolytic enzyme inhibitor in the capillary bed. Amer. J. Physiol. 211: 725–729, 1966.
950. WEINSTEIN, H., BERNE, R. M. AND SACHS, H.: Vasopressin in blood: effect of hemorrhage. Endocrinology 66: 712–718, 1960.
951. WELLENS, D. AND WAUTERS, E.: Norepinephrine induced reflex vasodilation and vascular effects of serotonin. Arch. Int. Pharmacodyn. Thér. 164: 140–149, 1966.
952. WENDLING, M. G., ECKSTEIN, J. W. AND ABBOUD, F. M.: Cardiovascular responses to carbon dioxide before and after beta-adrenergic blockade. J. Appl. Physiol. 22: 223–226, 1967.
953. WERLE, E., HOCHSTRASSER, K. AND TRAUTSCHOLD, I.: Studies of bovine plasma kininogen, ornitho-kallikrein, and ornitho-kinin. *In* Hypotensive Peptides, ed. by E. G. Erdös, N. Back and F. Sicuteri, pp. 105–115, Springer Verlag, New York, 1966.
954. WERLE, E. AND LEYSATH, G.: Über das Molekulargewicht des Plasmakinins von Vögeln. Hoppe-Seyler's Z. Physiol. Chem. 348: 352–353, 1967.
955. WERLE, E., SCHMAL, A. AND ZACH, H. P.: Identifizierung des blutdrucksteigernden Prinzips des Colostrums als Nucleotid. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 259: 45–55, 1967.
956. WESEMANN, W. AND ZILLIKEN, F.: Adamantanamines and their derivatives as sensitising agents for 5-hydroxytryptamine-induced contraction of smooth muscle. J. Pharm. Pharmacol. 19: 203–207, 1967.
957. WIEDEMAN, M. P.: Effect of denervation on diameter and reactivity of arteries in the bat wing. Circ. Res. 3: 618–622, 1955.
958. WIEDERHIELM, C. A.: Effects of temperature and transmural pressure on contractile activity of vascular smooth muscle. *In* 4th European Conference on Microcirculation, S. Karger, Basel, New York. pp. 321–327, 1966.
959. WILKENFELD, B. E. AND LEVY, B.: Adrenergic blocking properties of MJ1999 and butoxamine on cardiac and vascular *beta*-receptors. Arch. Int. Pharmacodyn. Thér. 176: 218–232, 1968.
960. WILL, D. H., ALEXANDER, A. F., REEVES, J. T. AND GROVER, F. R.: High altitude-induced pulmonary hypertension in normal cattle. Circ. Res. 10: 172–177, 1962.
961. WILLARD, P. W.: Tissue electrolyte alterations with hypertension induced by L-triiodothyronine and salt. Life Sci. 7: 27–33, 1968.
962. WILLIAMSON, A. W. R. AND MOORE, F. D.: Norepinephrine sensitivity of isolated rabbit aorta strips in solutions of varying pH and electrolyte content. Amer. J. Physiol. 198: 1157–1160, 1960.
963. WITHRINGTON, P. AND ZAIMIS, E.: The reserpine-treated cat. Brit. J. Pharmacol. 17: 380–391, 1961.
964. WOHL, A. J., HAUSLER, L. M. AND ROTH, F. E.: Studies on the mechanism of antihypertensive action of diazoxide: *in vitro* vascular pharmacodynamics. J. Pharmacol. Exp. Ther. 158: 531–539, 1967.
965. WOHL, A. J., HAUSLER, L. M. AND ROTH, F. E.: Mechanism of the antihypertensive effect of diazoxide: *in vitro* vascular studies in the hypertensive rat. J. Pharmacol. Exp. Ther. 162: 109–114, 1968.
966. WOO, C.-Y. AND SOMLYO, A. P.: Interaction of magnesium with vasopressin in intestinal smooth muscle. J. Pharmacol. Exp. Ther. 155: 357–366, 1967.
967. WOOLEY, P.: The effect of posterior lobe pituitary extracts on blood pressure in several vertebrate classes. J. Exp. Biol. 36: 453–458, 1959.
968. WOOLEY, P. AND WARING, H.: Responses of the perfused fowl leg to posterior lobe pituitary extracts. Aust. J. Exp. Biol. Med. Sci. 36: 447–456, 1958.
969. WURZEL, M.: Serotonin receptor in rabbit artery. Amer. J. Physiol. 211: 1424–1428, 1966.
970. WURZEL, M., BACON, R. C., KALT, R. B. AND ZWEIFACH, B. W.: Vasoactive properties of plasma protein fractions. Amer. J. Physiol. 206: 923–925, 1964.
971. WURZEL, M., BERNHEIMER, A. W. AND ZWEIFACH, B. W.: Staphylococcal α-toxin-induced contraction of isolated arterial smooth muscle. Amer. J. Physiol. 210: 360–364, 1966.
972. WURZEL, M., BLAIR, D. C., ZWEIFACH, B. W., CRAIG, L. C. AND TAYLOR, W. I.: Blood-Borne Factors Affecting Vascular Tone. Experientia (Basel) 23: 486–492, 1967.
973. WURZEL, M., PRUSS, T. P., KOPPANYI, T. AND MAENGWYN-DAVIES, G. D.: Dichloroisoproterenol blockade of the rabbit aortic strip. Arch. Int. Pharmacodyn. Thér. 141: 153–162, 1963.
974. WURZEL, M. AND ZWEIFACH, B. W.: Contracting principles of arterial smooth muscle in rabbit and dog plasma. Arch. Int. Pharmacodyn. Thér. 162: 1–19, 1966.
975. YAJIMA, G., MASUGI, Y., SUZUKI, T., OOAMI, H. AND ITO, S.: An adult case of primary pulmonary hypertension; as compared with an adult case of patent ductus Botalli and experimental vasopressin pulmonary thromboarteriopathy of the rabbit. Acta Pathol. Jap. 13: 107–117, 1963.
976. YAMABAYASHI, H. AND HAMILTON, W. F.: Effect of sodium ion on contractility of the dog's aortic strip in response to catecholamines. Amer. J. Physiol. 197: 993–996, 1959.
977. YAMAMURA, H. I. AND HORITA, A.: Effect of propranolol on the blockade of *alpha* adrenergic receptors. J. Pharmacol. Exp. Ther. 164: 82–89, 1968.
978. YAMASHIRO, D., GILLESSEN, D. AND DU VIGNEAUD, V.: Oxytoceine and deamino-oxytoceine. Biochemistry 5: 3711–3720, 1966.
979. YATES, C. M. AND GILLIS, C. N.: The response of rabbit vascular tissue to electrical and drug stimulation. J. Pharmacol. Exp. Ther. 140: 52–59, 1963.
980. YATES, F. E., KIRSCHMAN, R. AND OLSHEN, B.: Analysis of adenohypophysial blood flow in the rat by radioisotope washout: estimate of the vasomotor activity of vasopressin in the anterior pituitary. Endocrinology 79: 341–351, 1966.

981. YONG, M. S. AND MARKS, G. S.: Studies of the chemical nature of the α-adrenergic receptor. IV. Labeling studies on nerve-free rabbit aortic strips. Biochem. Pharmacol. 18: 1619–1626, 1969.
982. YUR'EV, V. A.: Muscle proteins of blood vessel walls, and changes in their composition during hypertensive disease. Bull. Exp. Biol. Med. 51: 569–572, 1961.
983. ZAIMIS, E.: Pharmacology of the autonomic nervous system. Annu. Rev. Pharmacol. 4: 365–400, 1964.
984. ZEMPLÉNYI, T.: Enzyme Biochemistry of the Arterial Wall as Related to Atherosclerosis, Lloyd-Luke (Medical Books) Ltd., London, 1968.
985. ZIEGLER, M., RINIKER, B. AND GROSS, F.: Nature of the pressor substance in rabbit placenta. Biochem. J. 102: 28–32, 1967.
986. ZIMMERMAN, A. M. AND HARRIS, L. S.: Microcirculation: effects of guanethidine and reserpine. J. Pharmacol. Exp. Ther. 142: 78–82, 1963.
987. ZIMMERMAN, B. G.: Evaluation of peripheral and central components of action of angiotensin on the sympathetic nervous system. J. Pharmacol. Exp. Ther. 158: 1–10, 1967.
988. ZIMMERMAN, B. G. AND GISSLEN, J.: Pattern of renal vasoconstriction and transmitter release during sympathetic stimulation in presence of angiotensin and cocaine. J. Pharmacol. Exp. Ther. 163: 320–329, 1968.
990. ZIMMERMAN, B. G. AND WHITMORE, L.: Effect of angiotensin and phenoxybenzamine on release of norepinephrine in vessels during sympathetic nerve stimulation. Int. J. Neuropharmacol. 6: 27–38, 1967.
991. ZSOTÉR, T. T.: Effect of hypoxia on the vascular response to isoproterenol and norepinephrine. Amer. Heart J. 77: 498–505, 1969.
992. ZSOTÉR, T., REVESZ, C. AND BANDERMANN, L.: Effect of ovariectomy on vascular reactions. Acta Endocrinol. 34: 33–37, 1960.
993. ZSOTÉR, T. AND TOM, H.: Adrenoceptive sites in the veins. Brit. J. Pharmacol. Chemother. 31: 407–419, 1967.
994. ZUBERBUHLER, R. C. AND BOHR, D. F.: Responses of coronary smooth muscle to catecholamines. Circ. Res. 16: 431–440, 1965.
995. ZWEIFACH, B. W.: The behavior of the vascular barrier during tissue injury. Bibl. Anat. 4: 21–31, 1964.