CARDIOVASCULAR PHARMACOLOGY[1]

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The search of literature dealing with cardiovascular pharmacology published during the past year resulted in a completely unexpected problem, namely, to find all important articles pertaining to cardiovascular drugs. In addition to pharmacology journals, the survey had to include journals dealing with physiology, clinical cardiology, anesthesiology, internal medicine and surgery. The second volume of the *Index-Handbook of Cardiovascular Agents* (1) was an invaluable aid. It lists 195 journals which, in the opinion of Dr. I. D. Welt of the Cardiovascular Literature Project, contain almost all important articles on cardiovascular agents. For the period 1931 to 1950, over 18,000 articles were indexed in this handbook. The *Index-Handbook* covering the period 1951 to 1955 appeared earlier (2), citing over 13,000 articles from 400 journals. These statistics indicate that the annual average of 900 articles in the first period (1931 to 1950) has increased to 2600 in the second period (1951 to 1955), and is undoubtedly still increasing. The rising number of published articles in medicine, in general, and in cardiovascular research, in particular, has been referred to as "the publication explosion" by Schmidt in a recent editorial (3).

The present reviewer has examined only a fraction of the 400 journals suggested by the *Index-Handbook*. From 40 journals, 144 articles were selected for inclusion in this review, on the basis of their contributions to the following aspects of cardiovascular pharmacology: antihypertensive drugs, pressor drugs, vasodilators for special vascular beds, and cardiac drugs. The latter are covered in terms of the hemodynamic effects of cardiotonic and antiarrhythmic agents. Marks has reviewed elsewhere in this volume the effects of drugs on the properties of the heart muscle (4).

Antihypertensive Drugs

No important new drugs for the treatment of essential hypertension were introduced during the past year. However, the hemodynamic effects and modes of action of previously introduced drugs have been more clearly defined.

Guanethidine.—This drug is proving to be the most widely investigated prototype of an agent which blocks reflex-induced, but not chemically

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induced, hypertension. The blockade of the former has been demonstrated in two types of preparations. Gaffney, Bryant & Braunwald (5) showed blockade by guanethidine of venoconstriction induced by various reflexes in the dog. Kahler, Gaffney & Braunwald (6) measured the hemodynamic responses to muscular exercise in human subjects, and observed that the administration of guanethidine reduced the augmentation in cardiac output which accompanies muscular exercise. Such a reduction may partly be due to blockade of the cardiac sympathetic nerves but the blockade of venoconstriction which may occur during muscular exercise is another possible mechanism.

The mechanism for blockade of peripheral sympathetic nerves has been extensively investigated using the heart. Gaffney, Chidsey & Braunwald (7) showed that the blockade by guanethidine of adrenergic transmission by the cardiac sympathetics was independent of depletion of adrenergic transmitter. The release of norepinephrine from the canine heart (8) and the rodent heart (9), resulting in a detectable depletion of catecholamine stores, can occur following the administration of guanethidine but such a release is not the principle mechanism for blockade of cardiac nerves.

The role of catecholamine depletion in explaining the antihypertensive action of guanethidine has been questioned by Cohn, Liptak & Freis (10). Their query is based on the observation that patients showing the antihypertensive action of guanethidine still revealed a pressor response to tyramine, a sympathomimetic amine dependent on catecholamine stores for its pressor action. If the hypotension is largely due to vasodilatation, the observations of Abboud & Eckstein (11) are pertinent. In the perfused limb of the dog, the vasodilatation induced by guanethidine was not mediated by release of catecholamines, histamine or acetylcholine. They postulate stimulation of *beta* adrenergic receptors or other dilator receptors which are blocked by dichloroisoproterenol. Excised aortic strips do not respond to guanethidine by relaxation; Maxwell et al. (12) noted a small, slowly developing and sustained contraction.

The clinical efficacy of guanethidine has been repeatedly and perhaps unduly stressed. The articles by Grenfell, Briggs & Holland (13 to 15) contain the results of a double-blind study of various antihypertensive agents which lasted for seven years. Guanethidine administered orally caused a decrease in systolic and diastolic blood pressures not significantly different from that after the administration of placebo. Whether true pharmacologic effect will continue after the placebo effect disappears remains to be seen.

Bretylium.—The antihypertensive effects of bretylium, a drug which blocks the peripheral sympathetic nerves, have been described (16, 17). Gardner (18) observed that bretylium effectively lowered the incidence of arteriolar necrosis and of arteritis in steroid hypertensive vascular disease in the rat. It is difficult to exclude the additional possibility that bretylium may induce a local cellular change, independent of its action to reduce blood pressure.

Reserpine.—Most of the experiments involving guanethidine reported above have been extended to include reserpine with essentially similar results

(5, 7, 8, 11, 15). The only important difference appears to be in the mechanism of depletion of norepinephrine in the heart, in the period immediately after administration of the blocking drug. Reserpine caused a reduction of norepinephrine content of atrial appendage by an average of 65 per cent in control values, whereas guanethidine reduced it by 24 per cent (8). Yet, the latent period of blockade of the latter is shorter than the former. This observation supports the conclusion discussed above, that adrenergic nerve blockade by drugs is independent of depletion of catecholamines. Booker et al. (19) observed a catecholamine release in adrenalectomized dogs during carotid clamping. The source of norepinephrine is believed to be in the brain, and the release is blocked by reserpine but not by bretylium. No explanation for the action of reserpine on the brain has been offered. Reusch (20) observed an increase in cardiac output during the administration of reserpine in hypertensive patients.

Mebutamate.—This drug (2-methyl-2-sec-butyl-1,3-propanediol dicarbamate) has been shown by Margolin, Plekss & Fedor (21) to be a spinal interneuronal blocking agent in cats and dogs with selective inhibition of spinal vasoconstrictor tracts. Theoretically, such a drug would be ideal in the treatment of essential hypertension because it would reduce the generalized increase in systemic vascular resistance. The hemodynamic studies in dogs by Rowe et al. (22) showed that mebutamate induced tachycardia with an increase in cardiac output and myocardial oxygen consumption, an undesirable feature in an antihypertensive drug. Clinical trials have shown mebutamate to be primarily a sedative or tranquilizer, and that any effect the drug may have on hypertension is due to sedation (23, 24). A selective blockade of the spinal vasoconstrictor tracts by drugs has therefore not yet been achieved.

Chlorothiazide.—An extensive search has been made for the mechanism of the hypotensive effects of this diuretic drug. In the anesthetized dog, Gillenwater, Scott & Frohlich (25) noted that injections of isosmotic solution of chlorothiazide failed to influence renal vascular resistance, but did acutely attenuate the constriction produced by intra-arterial injection of levarterenol and epinephrine. Eckstein, Abboud & Pereda (26) observed a similar reduction in the vasoconstrictor effect of norepinephrine on peripheral blood vessels. On the other hand, the rabbit aortic strip did not show any alteration in response to angiotensin (27). Daniel (28) suggested that in rats with experimentally induced hypertension, the alteration in cardiac function is not due to a decrease in intracellular sodium. Some changes in other ionic constituents may be responsible for the alteration in ventricular function.

In hypertensive patients, Villareal et al. (29) reported that the reduction in blood pressure brought about by chlorothiazide was accompanied by a reduction in filtration rate, and an increase in osmotic clearance, both of which were encountered in normotensive subjects without a reduction in blood pressure. The observed alterations in renal function in hypertensive subjects are therefore unrelated to changes in blood pressure. The same group of investigators (30) also measured the hemodynamic effects following acute and long-term administration of chlorothiazide. Whereas with long-term use

the fall in blood pressure was due to reduction in total peripheral resistance, the acute administration caused a fall largely by reduction in cardiac output. The accepted practice is to administer hydrochlorothiazide to reduce the dose of guanethidine in the treatment of hypertension (31). The clinical uses of chlorothiazide and selected compounds have been reviewed recently by Laragh (32), and Fuchs (33).

Diazoxide.—This analogue of benzothiadiazine was discovered by Rubin, Roth & Winbury in 1960 to be nondiuretic but antihypertensive. Subsequent reports by this group have confirmed this pharmacological profile for diazoxide in various animal preparations. In the anesthetized dog, the intraaterial injection of the drug caused increase in flow in the coronary, renal, mesenteric and femoral vascular beds (34, 35). In the forelimbs, the major sites for the reduction in the resistance were the small vessels rather than the large vessels (36). The increase in cardiac output brought about by diazoxide in both the anesthetized dog (36) and hypertensive patients (37, 38) is difficult to explain on the basis of a pure local vasodilatation. The most probable explanation is a reflex stimulation of the heart from the initial reduction in blood pressure, but appropriate denervation studies are necessary for confirmation. The possibility of pancreatic toxicity, a side effect during benzothiadiazine administration, should be carefully examined for diazoxide (39).

Miscellaneous compounds.—An inhibitor of monoamine oxidase (*dl*-serine-N^2-isopropylhydrazide; RO 4-1038) has been administered to hypertensive patients with favorable results. Maxwell et al. (40) described hypotension attributable almost solely to decreased total peripheral resistance, and unrelated to minor changes in cardiac output, blood volume, and sodium space.

An inhibitor of decarboxylase, *alpha* methyl dopa, has been shown by Onesti et al. (41) to cause hypotension by a combination of peripheral vasodilatation and reduction in cardiac output. The latter action is probably secondary, but additional studies are required to exclude a direct cardiac depression. The early clinical reports on trichlormethiazide have been favorable (42, 43).

Pressor Drugs

Angiotensin. The most important mechanism for the pressor action of angiotensin is vasoconstriction. This has been shown in the anesthetized dog with measurement of cardiac output and total systemic vascular resistance (44), and in the perfused hindlimb of the rat (45) and the dog (46). Zimmerman (46) observed that the vasoconstrictor response to angiotensin in the limb was reduced significantly after acute sympathectomy, ganglionic blockade with hexamethonium, or cervical spinal transection. The basic cause for this reduction in sensitivity is not known. Ganglion blocking drugs enhance the pressor response to angiotensin largely by bringing about an increase in cardiac output during the infusion of angiotensin (47). One important cause for the increase in cardiac output is the elimination by ganglionic blockade of the reflex bradycardia. The infusion of angiotensin into conscious rabbits

elicited a reflex slowing of the heart but this disappeared in spite of continuous infusion. Alexander & DeCuir (48) concluded that in the presence of continuously elevated arterial pressure, the mechanism for the reflex cardiac slowing can adjust within a relatively short time, probably by a resetting of the mechanism within the central nervous system.

Norepinephrine.—Most of the reports deal with the factors responsible for the augmentation and reduction of the pressor action of norepinephrine. Page & McCubbin (49) have investigated in the dog the mechanisms contributing to the increased responsiveness to norepinephrine and other pressor drugs, caused by ganglioplegic agents. They have identified three, namely: (*a*) elimination of parasympathetic reflexes; (*b*) elimination of sympathetic compensatory reflexes; and (*c*) direct sensitization of blood vessels, similar to that produced by surgical denervation. A phenomenon similar to (*c*) was observed by Mawji & Lockett (50) in cats, rats, and pigeons; potentiation of norepinephrine by ganglioplegic drugs could occur in doses too low to influence transmission in autonomic ganglia. The phenomenon was not modified by acute adrenalectomy or spinal transection, but was absent after pretreatment with reserpine. Guanethidine has been shown by Alper & Schmier (51) to potentiate the chronotropic potency of norepinephrine in the heart-lung preparation. Sambhi, Weil & Udhoji (52) have excluded adrenal cortical hormones as possible causes for potentiation of norepinephrine in normal subjects. The conclusion does not necessarily apply to patients in shock.

The development of tolerance to norepinephrine administered by continuous infusion was systematically studied by Rosenthale & DiPalma (53). In the anesthetized normotensive dog the development of tolerance to norepinephrine was unaltered by adrenalectomy, splenectomy, ganglioplegic drugs, and atropine and was accompanied by hemoconcentration, acidosis, decreased blood volume, and decreased cardiac output. The administration of plasma expanders at the height of tolerance temporarily restored normal sensitivity to norepinephrine, but did not affect the acidosis. Eich et al. (54) noted a variability in response to norepinephrine infusion in both the control subjects and those with labile hypertension. The response was similar at the initial infusion rate, but increasing the dose resulted in a fall in total peripheral resistance. The relation of these vascular responses to alteration in blood volume will require further study. The contribution of enzymatic process by which norepinephrine is inactivated in the heart has been studied (55) but analogous studies in vessels are wanting.

Epinephrine.—The development of refractoriness to epinephrine has been investigated by Wood, Manley & Woodbury (56). The pressor action of epinephrine was more resistant than the depressor or vasodilator action to suppression by acidosis. Failure to eliminate the pressor response cannot be attributed to the persistence of the positive inotropic action of epinephrine during severe acidosis. The vasoconstrictor action of epinephrine persisted even during acidosis. Hilton (57) investigated the opposite phenomenon, i.e. potentiation of pressor action of epinephrine by ganglioplegic agents. His observations in the dog allowed him to postulate that potentiation is not by

sensitization of the vessels to epinephrine, but by lowering the level of catecholamines available to the receptor sites (as a result of autonomic blockade), and shifting the dose-response curve to the left. This suggestion will require direct proof on a simpler preparation than the entire animal.

Tyramine.—This amine has been widely used in the laboratory as a prototype of a sympathomimetic drug with actions dependent on the release of catecholamines. There are still no reports of its clinical use as a pressor agent probably because of the availability of numerous sympathomimetic pressor drugs. In the dog heart-lung preparation, tyramine induced positive inotropic and chronotropic effects, but not in preparations from animals pretreated with reserpine (58). The repeated administration of tyramine to the isolated perfused guinea pig heart caused a gradually diminishing inotropic response, paralleled by a decrease in norepinephrine content of the heart (59). In the isolated atria, a depletion of 50 per cent in the stores by reserpine had little effect on the response to tyramine but a depletion to about 10 per cent of normal reduced the response to 50 per cent (60). These results are consistent with the view expressed by Crout, Muskus & Trendelenburg (60) that norepinephrine stores in the atria exist in two compartments, the smaller of which is important for the action of tyramine.

Amines with predominant vasoconstrictor action.—Methoxamine and phenylephrine were shown by Zimmerman, Abboud & Eckstein (61) to constrict the vessels of the perfused foreleg of the dog. The potency of both amines with respect to total vasconstrictor activity was about equal, but less than norepinephrine and greater than tyramine. The venoconstrictor action of both methoxamine and phenylephrine was relatively small compared to that of other amines. Bender, Larsen & Horvath (62) noted an increase in splanchnic vascular resistance during infusion of phenylephrine in the anesthetized dog. The lack of a positive inotropic action of methoxamine has been applied in one clinical situation: Patients with idiopathic hypertrophic subaortic stenosis showed a disappearance of the gradient between left ventricle and aorta due to the reduction in the severity of obstruction. Braunwald & Ebert (63) have suggested the use of the drug in exertional syncope in such patients.

Pressor amines with predominant cardiac action.—Li, Shimosato & Etsten (64) studied human subjects receiving a constant infusion of mephentermine. During the first 5 to 20 min, the increase in arterial pressure was primarily the outcome of the increase in cardiac output, and in the later period, the increase in total peripheral resistance. These observations raise several questions regarding the cause of the increase in total peripheral resistance because mephentermine has been known to be a weak vasoconstrictor and even a vasodilator. It is possible that the delayed appearance of the vasoconstriction is a secondary response, perhaps to a persistent release of catecholamines. Additional studies are wanting. The pressor actions of *t*-butylamine (65) and of chlorphentermine (66), with predominant cardiac actions, have been described in animals but actual clinical trial has not been reported.

Ganglion stimulants.—The possible clinical use of ganglion stimulants to

treat hypotensive states has not been reported. In 1961, Roszkowski described the pressor effect of compound no. McN-A-343 [4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride], a unique ganglion stimulant whose action was blocked by atropine but not by the usual ganglioplegic agents. Several confirmatory studies have appeared during the past year. The pressor action appears to be due to a combination of excitation of sympathetic ganglionic innervation to blood vessels (67, 68) and to an action on the heart with an increase in phosphorylase a activity (69). On the other hand, this compound has no important stimulatory actions on the aortic body chemoreceptors and adrenal medulla (70). It appears that compound no. McN-A-343 is the closest approach to a selective stimulant of the autonomic ganglia, as compared to lobeline and DMPP (1, 1-dimethyl-4-phenylpiperazinium). Its pressor action in animals does not offer a distinct advantage over that of norepinephrine and epinephrine because acidosis reduces the pressor action of the ganglionic stimulant as conspicuously as that of the amines (70).

Hemodynamic Effects of Cardiac Drugs

Digitalis.—The widely accepted concept that digitalis should be administered only to treat patients in congestive heart failure has been challenged by a number of recent reports. Kahler et al. (71) observed that some patients who have cardiac disease and enlarged hearts without signs or symptoms of heart failure can be benefited by digitalization. The accumulation of a smaller oxygen debt following exercise, while these patients were receiving digoxin, indicated that the functional status of their circulatory system was improved. Rodman & Pastor (72) have reviewed the "prophylactic use" of digitalis in patients about to undergo surgery or delivery, with impaired myocardial reserve.

The direct effects of digitalis on the heart muscle have been reviewed elsewhere in this volume (4). The reviewer cannot help but comment on the successful direct perfusion of the sinus node *in situ*, as described by James & Nadeau (73). The digitalizing dose by direct perfusion (1/1000 the systemic dose) has resulted in the appearance of chronotropic effects of digitalis, both bradycardia and tachycardia. If these studies were extended to include hemodynamic measurements, it would become possible to differentiate a pure cardiac sinus action from other cardiac and extracardiac actions of digitalis.

Quinidine.—The hemodynamic events during toxicity of quinidine in the dog were studied by Luchi, Helwig & Conn (74). The administration of large doses of quinidine resulted in a reduction in cardiac output, mean aortic blood pressure, and total systemic vascular resistance. In an attempt to reverse the toxicity, they reported that the infusion of angiotensin and disodium calcium versenate proved to be more effective than the infusion of angiotensin alone. Gottsegen & Ostor (75) have proposed isoproterenol to counteract the lethal effect of quinidine. The prolongation of conduction time in the ventricle, and the depression of myocardial contractility were pre-

vented by simultaneous administration of isoproterenol. Thus, the toxicity of quinidine can be significantly reduced without any considerable curtailment of antifibrillatory effectiveness.

Dichloroisoproterenol and nethalide.—Moran et al. (76) described an antiarrhythmic action of dichloroisoproterenol in the dog. A desirable action was exerted on arrhythmias induced by ouabain and the ventricular fibrillation produced by the combined use of the substituted propiophenone (U-0882) and isoproterenol. One undesirable feature of dichloroisoproterenol is its sympathomimetic action, as demonstrated by James & Nadeau by direct perfusion of the canine sinus node (77). A low concentration of dichloroisoproterenol elicited a slight positive chronotropic effect, but higher concentrations had a negative chronotropic effect, related to blockade of the acceleration from adrenergic nerve stimuli. There were other reported effects (77, 78) but those just mentioned are pertinent to the introduction of a new compound which retains the blockade of nerve stimulation but is free of any sympathomimetic action. Black & Stephenson (79) have introduced nethalide [2-isopropylamine-1-(2-naphthyl) ethanol hydrochloride] for this specific purpose. Dornhorst & Robinson (80) observed that normal subjects and patients with ischemic heart disease receiving nethalide showed an increase in exercise tolerance with cardiac slowing, instead of the usual tachycardia of effort. The measurement of cardiac output in two normal subjects receiving the drug indicated that the normal exertional increase in stroke volume was not inhibited. Confirmatory studies are necessary to determine the exact place of this drug in therapy of exertional tachycardia and other forms of arrhythmias which are brought about by increase in cardiac accelerator activity.

Inhalation anesthetics.—The hemodynamic effects of general anesthetics are discussed under cardiac drugs because of their known cardiotoxicity, and because of their importance during cardiac surgery. Shimosato, Li & Etsten (81) observed that the canine heart was able to perform work efficiently in the presence of decreased myocardial contractility during halothane anesthesia. The depression of contractility was partially improved by digitalization, and they concluded that the incomplete recovery does not justify the use of digitalis during hypotension of prolonged halothane anesthesia (82). Flacke & Alper (83) succeeded in reversing the cardiac depression of halothane on the canine heart-lung with norepinephrine. The reversal was not simple nor complete because myocardial excitability to norepinephrine-induced arrhythmias was increased during halothane anesthesia (84, 85). One logical pressor amine to test would be mephentermine with its unique antiarrhythmic action which, however, has been recently challenged (86).

Drugs and Coronary Circulation

Nitrites and nitrates.—Favorable results in relieving angina have been reported for the following: isosorbid dinitrate (87, 88), pentaerythritol tetranitrate (89), erythrol tetranitrate (90) and etrynil [1-hydroxy-2,2(bishydroxymethyl) butanitrate] (91). None of the reports has contributed an

answer to the fundamental question as to how nitrites and nitrates relieve angina: by coronary dilatation or by reduction in cardiac work. The introduction by Hollander, Madoff & Chobanian (92) of radioiodide clearance from the myocardium of an exercising dog may help solve the problem. So far, in the dog without coronary artery disease, the clearance is a reliable index of local myocardial blood flow. The administration of nitrites failed to increase radioiodide removal if there was an associated fall in blood pressure.

Other drugs reducing cardiac work.—Wendt et al. (93) have added some favorable results for 2,6-bis(diethanolamino)4,8-dipiperidinopyrimido-(*5,4-d*)-pyrimidine (Persantin) to the growing literature on this drug. In nine patients, the intravenous injection of the drug reduced cardiac work, increased coronary blood flow and brought about a decline in ratio of left ventricular work to myocardial oxygen consumption. The latter was believed to be the result of an action on cellular metabolism. West & Foltz (94) administered protoveratrine in dogs with renal hypertension. A therapeutically beneficial effect was derived from its ability to decrease the work of the heart (lowering elevated blood pressure) and the coronary vascular resistance while maintaining coronary blood flow and cardiac output within normal levels. Rowe et al. (95) administered triamterene (2,4,7-triamino-6-phenyl pteridine) in normotensive subjects; there was a decrease in cardiac output and left ventricular work but no change in coronary blood flow and myocardial oxygen consumption.

Drugs that increase cardiac work.—Ouabain has been observed by Goksel, Katz & Feinberg (96) to possess a primary coronary dilator action in a canine heart in which work is kept constant. In the intact heart, this action would supplement the coronary dilatation initiated by the increase in cardiac work. Rowe et al. (97) administered adenosine, and its triphosphate and diphosphate salts in the anesthetized dog. There was an increase in coronary blood flow, cardiac output and cardiac work but a reduction in coronary vascular resistance to the extent that the coronary bed received a strikingly greater percentage of the cardiac output.

Coronary vasodilators.—Charlier et al. (98, 99) reported a series of modifications of 2-butyl-3-(4′-β-N-diethylaminoethoxyl-3′,5′-diiodobenzolyl) benzofuran. They have reported an increase in activity for coronary vasodilation for some compounds which are awaiting clinical trial. Blake et al. (100) showed a relaxation of the excised swine coronary artery by warfarin and bishydroxycoumarin. They believe that the anticoagulant doses of these drugs used clinically are sufficient to have an action on coronary vessels. Antonio & Rocha-e-Silva (101) observed a coronary dilatation in the heart by bradykinin. The possibility that bradykinin is a mediator in the coronary dilatation produced by epinephrine has been presented.

Vasodilators for Special Vascular Beds

Vasodilators for limb.—Clinical reports have described relief of peripheral arterial insufficiency by cyclandelate (102), phenylbutazone (103), and bro-

melain (104). The clinical use of older drugs has been reviewed by Juergens (105).

A few reports pertain to the measurement of limb blood flow following the administration of drugs. Abramson et al. (106) administered histamine by ion transfer to the hand and forearm of normal subjects and observed a marked increase in blood flow, not only in the applied extremity, but also in the other extremities. Histamine administered by ion transfer is absorbed into the systemic circulation to affect distant vascular structures. In the limb of the anesthetized dog, Frohlich (107) observed that adenosine mono-, di-, and triphosphate induced dilatation primarily of the arterioles. McCubbin, Kaneko & Page (108) investigated the vasodilatation in the limb of the dog induced by 5-hydroxytryptamine. They concluded that the vasodilatation was brought about by stimulation of adrenergic vasodilator receptors largely in the small arteries and veins.

Cerebral vasodilators and vasoconstrictors.—Pierce et al. (109) measured cerebral blood flow in normal subjects under thiopental anesthesia. They described significant and nearly proportional reductions in cerebral metabolic rate and cerebral blood flow but an increase in cerebral vascular resistance. Under profound thiopental anesthesia, the reactivity of cerebral blood vessels to carbon dioxide (constriction during hyperventilation) was preserved. In the anesthetized dog, Carpi, Ursillo & Bovet (110) tested the reactions of cerebral vessels to epinephrine at varying blood levels of oxygen and carbon dioxide. The local vasoconstrictor action was reduced during cerebral hypoxia and hypercapnia. In the anesthetized rabbit, Ikeda et al. (111) described a local constrictor action for angiotensin both in the intracranial and extracranial vessels. To date, a drug with a selective action for cerebral vessels has yet to be discovered.

Histamine and splanchnics.—The action of histamine on the splanchnic vascular bed was investigated in the anesthetized dog. Chien & Krakoff (112) observed a reduction in splanchnic blood flow, proportionate to the reduction in blood pressure. The unchanged splanchnic vascular resistance was ascribed to a combination of arteriolar dilatation and hepatic venoconstriction, the latter indicated by the increase in the wedged hepatic venous pressure in the face of a decreased flow. During histamine shock, there was a shift of blood from the hepatic veins to the capillaries, and the subsequent reduction in venous return contributed to the observed fall in cardiac output. Kowalewski & Wisniewski (113) sampled blood from the portal vein during histamine shock and observed a marked reduction in oxygen content and pH. They believe the stagnant anoxia to be an important etiologic factor responsible for post-histaminic gastric lesions.

Drugs and Pulmonary Circulation

During the past year, the action of drugs on the circulation of the lungs has attracted considerable attention. The proceedings of the Symposium on the Action of Drugs
national Pharmacological Meeting, has appeared (114). This volume re-

viewed the effects of drugs on the pulmonary and bronchial circulation, as well as bronchial smooth muscles. The general conclusion at this meeting was that there are numerous drug-sensitive mechanisms in the lungs which are either harmful (produce pulmonary hyptertension and pulmonary edema) or otherwise. The actions of the drugs discussed in this section will support this conclusion.

Acetylcholine.—Yu et al. (115) administered acetylcholine directly into the pulmonary artery of patients with heart disease and pulmonary hypertension and noted active vasodilatation, evidenced by a decrease in pulmonary arterial pressure and an increase in pulmonary blood volume. The dilatation persisted while the patients were subjected to the pulmonary vasoconstrictor action of anoxia. Behnke, Williams & White (116) noted a similar dilatation in patients with pulmonary emphysema, even while the patients were subjected to muscular exercise. Schlant et al. (117) observed a reduction in arterial oxygen saturation, even during inhalation of oxygen. They believe that this effect of acetylcholine is due to disruption (or vasodilatation) of the local protective vasoconstrictor action in poorly ventilated areas. Such an explanation assumes that anoxia is a local vasoconstrictor of the lungs, but this has not yet been generally accepted.

Isoproterenol.—Several reports have mentioned pulmonary vasodilatation induced by isoproterenol in the following situations: patients with mitral valvular disease (118), heart disease (119, 120), and pulmonary hypertension (121). McGaff et al. (120) observed that the dilatation was extensive enough to increase the pulmonary blood volume. The latter can be brought about by a concomitant increase in pulmonary blood flow, since isoproterenol is a powerful cardiac stimulant. Halmagyi et al. (122) reported a successful reduction by isoproterenol in pulmonary arterial pressure in the sheep with experimental embolization. Clinical confirmation has been difficult because patients with acute pulmonary embolism are too ill to be subjected to catheterization.

Miscellaneous sympathomimetics.—The past controversies on the effects of norepinephrine and epinephrine on the pulmonary circulation were continued during the past year. The conspicuous effect of norepinephrine on the heart has been regarded as more important than the known pulmonary vasoconstrictor action (123, 124). The cardiac stimulatory effect of epinephrine was utilized to prevent pulmonary congestion and edema in infants with large left to right shunts (125). The rise in pulmonary arterial pressure in patients with mitral stenosis following phenylephrine has been described (126) as due not to cardiac action but to local pulmonary vasoconstriction.

Autonomic blocking drugs.—The generalized ganglionic blockade induced by trimethidinium methosulfate was observed by Afonso et al. (127) to be accompanied by a reduction in pulmonary vascular resistance in dogs. The primary cause for this fall is blockade of the sympathetic nerves but sympathetic nerve blocking drugs have produced some results that are superficially confusing. Widimsky et al. (128) noted a reduction in pulmonary vascular resistance in patients with chronic pulmonary disease following injection of

reserpine. Bevan (129) introduced an isolated preparation of the pulmonary artery with its sympathetic nerve supply and showed a definite blockade of sympathetic nerve by reserpine. The injection of bretylium in the dog initiated a rise in pulmonary vascular resistance, a constriction which cannot be explained by blockade of sympathetic nerves (130). It is probably a manifestation of a transient sympathomimetic action, known to occur with bretylium (see page 140).

5-Hydroxytryptamine.—Several important details on the pulmonary vasoconstriction action of 5-hydroxytryptamine became known during the past year. Ring, Kurbatov & Smith (131) injected various sizes of microspheres to identify two reactive areas in the lungs: venules which block microspheres 5 μ or larger in diameter, and arterioles which block microspheres less than 5 μ. Both sites were constricted by 5-hydroxytryptamine but the former was dilated by acetylcholine, the latter constricted by norepinephrine. Young et al. (132) measured capillary blood volume in the canine lung and concluded that 5-hydroxytryptamine caused capillary congestion largely by venous constriction. Although pulmonary vasoconstriction is an important cause for the pulmonary hypertensive action of 5-hydroxytryptamine, there is a second contributory factor, an increase in pulmonary blood flow (133) not due to a direct cardiac stimulation. The increase in pulmonary blood flow elicited by 5-hydroxytryptamine in the intact dog is reduced by thoracic sympathectomy (134). It has been suggested that the rise in pulmonary blood flow is mostly a sympathetic reflex initiated by the initial pulmonary vasoconstriction.

Endotoxin.—Bacterial endotoxin is a known effective agent to induce constriction of the pulmonary veins. Kuida and his collaborators have offered additional evidence that the venous constriction is mediated through the release of vasoactive agents such as histamine and 5-hydroxytryptamine. The pretreatment with an antihistaminic drug, promethazine, blocked some of the systemic but not the pulmonary vascular effects of endotoxin (135). Pretreatment with an inhibitor of the synthesis of 5-hydroxytryptamine (*alpha* methyl dopa) caused a significant reduction of the pulmonary arterial hypertension (136), and the combined use of both abolished the pulmonary vascular effects of endotoxin (137).

Bradykinin.—Rowe et al. (138) described a reduction in pulmonary vascular resistance in dogs following the administration of bradykinin. The observed fall in pulmonary arterial blood pressure is brought about not only by the vasodilatation but also by a reduction in cardiac output as described by Olmsted & Page (139). Both actions are unrelated to a third action, i.e. causation of pulmonary edema. Di Mattei (140) observed that concomitant administration of bradykinin with subthreshold doses of epinephrine in rabbits terminated in pulmonary edema. He postulated the participation of circulating active kinins in the production of pulmonary edema.

Reflexes induced by drugs.—Takasaki (141) demonstrated the stimulation of pulmonary receptors by nicotine and veratrum alkaloids, which initiated bradycardia and systemic depressor response. Rosenstein & Borison (142)

described a similar reflex from the lung induced by injection of large doses of sodium salicylate. The normal function of these pulmonary receptors continues to arouse interest. Guazzi, Libretti & Zanchetti (143) feel that these pulmonary receptors supplied by the vagus have tonic inhibitory influences on vasomotor centers controlling systemic blood pressure. The role of pulmonary receptors in the regulation of structures in the lungs have been recently discussed (144). It is possible that the pulmonary receptors participate in the nervous control of the smooth muscles of the tracheobronchial tree and pulmonary blood vessels. Experiments to demonstrate specific intrinsic reflexes in the lungs have led to mixed results probably because of the participation of a secondary humoral mechanism which antagonizes the primary reflex response. The humoral mechanism may or may not be present, depending on the experimental situation, so that the divergent results are understandable.

Concluding Remarks

The reviewer has attempted to cover advances in our knowledge of cardiovascular pharmacology during the past year. The articles on cardiovascular pharmacology are published in approximately 400 journals (2), a tenth of which were scrutinized in the preparation of this review. The selection of the 144 articles discussed was hopefully performed in an unprejudiced way from twice as many articles dismissed as simple duplication of previous efforts. The reviewer sincerely believes that the duplication in effort is unintentional on the part of the investigators but is the natural outcome of the publication explosion alluded to in the Introduction. It indicates that reliance on abstract journals and the monthly *Index Medicus* is not universally successful. The *Index Handbook of Cardiovascular Agents* (1, 2) may solve the problem provided that it can be updated and become immediately available on a monthly basis to those who are interested in cardiovascular pharmacology.

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