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Review Article

Drug-Induced Cardiomyopathies

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WHILE FREQUENT REFERENCE is made to the toxicity of drugs for the myocardium, and at least one major symposium has dealt with the subject of cardiomyopathies (1), there has been no general review of the drug-induced condition. The lack of well-defined and universally-employed criteria for cardiomyopathies necessitated some latitude when interpreting reports of myocardial drug toxicity. For the purpose of this review the terms degeneration, fatty degeneration, necrosis, primary myocardial disease, myocardial injury or lesions, calcification, fibrosis, or myocarditis were accepted as being synonymous with a cardiomyopathy. Obviously, some of these are not necessarily related to a true cardiomyopathy. Myocarditis, for example, while frequently preceding, accompanying, or following degeneration, is essentially an inflammatory rather than a degenerative process. While drugs acting primarily on the coronary vasculature were included in this review, the mechanism was indicated whenever it was apparent. Alterations in biochemical, electrical, or hemodynamic functions may accompany, or even precede, morphologic evidence of injury to the myocardium, but such changes were not included as cardiomyopathies unless accompanied by evidence of physical alterations.

Degeneration of the heart muscle can result from a wide variety of causes. In this country the most common causes are cardiovascular diseases which result in acute or chronic impairment of coronary circulation. These include coronary artery disease, hypertension, heart-lung disease (*corpulmonale*), valvular heart disease, and congenital heart disease. As practically all adult males in the United States are believed to have some degree of coronary artery disease, the incidence of minimal myocardial degeneration must be considerable. For this reason an assessment of drugs in human degenerative heart disease must include the possibility of an interaction with impaired coronary circulation. While it is possible to experimentally distinguish between drugs producing primary toxic or allergic lesions of the myocardium and those producing similar end effects through alterations in coronary blood flow, such differentiation is often not possible on the basis of clinical reports. In fact, some drugs, of which the catecholamines are an outstanding example, probably produce their degenerative effects through both mechanisms.

Primary myocardial disease may also result from a variety of infections, nutritional and metabolic disturbances, and allergies, and in some cases may have a genetic component. Once again, superimposing the effect of a drug upon such underlying conditions would be expected to intensify the response. Most drugs which produce primary cardiomyopathies are believed to interfere with the metabolic activity of the cell, probably by poisoning enzyme systems. The remaining drugs act through an allergic mechanism, either by a direct effect on the myocardium or secondary to coronary vasculitis. In addition to the possibility that some drug cardiomyopathies seen in the human are related to predisposing

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factors, it may be argued that myocardial lesions may occur with almost any drug if administered in a large enough dose and for a sufficient length of time. Despite the use of unphysiologic doses in many of the reported animal experiments, these data were included in order to present a complete picture. Drugs having a low order of intrinsic activity on the normal heart would be expected to demonstrate their toxicity on hearts already damaged or otherwise rendered susceptible.

SYMPATHOMIMETIC AMINES

The earliest evidence relating the sympathomimetic amines to necrotic lesions of the myocardium as cause and effect was in a report on epinephrine by Josué in 1907 (2). Since then this observation has been repeated many times with epinephrine and other sympathomimetic amines. A variety of mechanisms have been postulated to explain the pathogenesis of these lesions. Proposed mechanisms include: a direct oxygen wasting action (3–29); altered permeability of the myocardial cell membrane through elevation of plasma nonesterified fatty acids (30); impairment of venous drainage of the heart (31); potassium depletion (32); constriction of the coronary arteries (33); dilatation of precapillary shunts between coronary arteries and veins (34); damage to the coronary endothelial cells (35); increased myocardial oxygen requirements plus alterations of systemic circulation (36); and combinations of three different effects including myogenic, physical, and metabolic mechanisms (37).

Raab and his co-workers were the earliest and have been the principal proponents of a mechanism by which the amines increase myocardial oxygen consumption and cardiac work without a corresponding increase in energy production (3–29). It has been repeatedly demonstrated that following administration of the catecholamines the oxygen consumption of the heart greatly exceeds the normal energy requirements (38–46). Raab not only proposed a mechanism by which endogenous neurohormones or administered sympathomimetic amines produce myocardial degeneration, but he seriously challenged the classical concept of occlusive coronary artery disease as *the* cause of myocardial degeneration. It is notable that even in defining the term infarction, as applied to the myocardium, recognition is now given to the fact that arterial obstruction or insufficiency is not the sole cause (47). Since the early study of Herrick (48), demonstrating the effects of coronary occlusion, and the subsequent emphasis by Keefer and Resnik (49) on the role of myocardial oxygen deprivation in the symptoms of angina pectoris, relatively little attention has been given to the nonocclusive mechanisms. While there can be little doubt that coronary occlusion is a major factor in the production of myocardial necrosis, it is also probable that the primary cardiomyopathies constitute a significant factor.

Of the known mechanisms by which the sympathomimetic amines may act, oxygen wastage is at least of theoretical importance. This mechanism appears to be related to mitochondrial function. Following the admnistration of catecholamines the mitochondria become swollen (50) and undergo uncoupling of oxidative phosphorylation (51). This effect is apparently unrelated to hypoxia, congestive heart failure, or the accumulation of free fatty acids, and does not occur when catecholamines are added to the mitochondria *in vitro* (51). The lack of an *in vitro* action suggests a preliminary *in vivo* effect. Possible *in vivo* mechanisms include the reduction of myocardial potassium by the catecholamines (52, 53) because potassium has an essential role in mitochondrial metabolism (54). Still another possible explanation is the *in vivo* conversion of catecholamines to adrenochrome, a metabolite with a demonstrated capacity to uncouple oxidative phosphorylation in mitochondria (55). Some investigators have concluded that the catecholamine-induced increase in myocardial oxygen consumption is the result of hemodynamic changes rather than of a direct metabolic action (56). To reach this conclusion, the heart was arrested by potassium, which in addition to preventing hemodynamic changes would also modify any potassium-depleting effect of the catecholamines. In the isolated rat heart it was shown, however, that the increase in oxygen uptake produced by epinephrine still occurred following arrest by potassium (57), citrate, or procainamide (57, 58). These results suggest that if uncoupling of oxidative phosphorylation is the cause of the observed increase in oxygen consumption, the uncoupling is not the result of potassium depletion. Hauge and Øye (58) concluded that part of the effect of epinephrine on the arrested heart was due to an increased utilization of ATP by several separate reaction systems. They found that this increase in oxygen consumption was blocked by a β-adrenergic receptor blocking agent, propranolol, but not by phentolamine, an α-adrenergic receptor blocking agent.

While the relative importance of the various mechanisms is still unresolved, there is direct evidence that the adrenergic receptors responsible for the myocardial toxicity of the catecholamines are alpha in character rather than beta. The intravenous administration of epinephrine to dogs has been shown to produce a fatty degeneration of the

myocardium associated with elevated serum levels of several myocardial enzymes (59–61). These effects are prevented by the administration of an α- receptor blocking agent (62–64). In a study with rats, it was found that the myocardial damaging effects of epinephrine, norepinephrine, or phenylephrine were prevented by the α-adrenergic receptor blocking agent, phentolamine, but the β-adrenergic receptor blocking agent, pronethalol, did not add to the effectiveness of the phentolamine, nor was it effective alone (65). In fact, with low doses of isoproterenol and with high doses of epinephrine the pronethalol added to the toxicity. The β-receptor blocking agents prevent phosphorylase activation and hyperglycemia (66) without affecting hyperkalemia (67). Alpha-receptor blocking agents, on the other hand, prevent the loss of myocardial potassium without appreciably affecting hyperglycemia (68). As previously suggested, potassium depletion is a likely causal mechanism by which the catecholamines are toxic to the heart. Among the known consequences of potassium depletion is interference with mitochondrial metabolism (54, 69). It has been suggested that this effect is based upon the importance of potassium in transphosphorylation reactions (70) as shown by the potassium dependence of enzymes involving phosphate transfer, such as fructokinase (71, 72), pyruvic phosphoferase (73–75), phosphotransacetylase (76), and acetate activating enzyme (77). Still other potential potassium-related effects are the requirements for high concentrations of this element in protein synthesis (78) and the fall in muscle pH produced by potassium deficiency (79). Numerous studies have demonstrated the production of myocardial necrosis by potassium depletion as well as the loss of potassium following myocardial injury (80–85). The extent to which hemodynamic effects are responsible for the myocardial lesions produced by the sympathomimetic amines is still conjectural. To summarize the vascular effects of the three principal catecholamines: isoproterenol is almost entirely a vasodilator; epinephrine produces both vasoconstriction and vasodilation; while norepinephrine is almost entirely a vasoconstrictor. It has been suggested that at least part of the toxicity of isoproterenol for the myocardium is related to the marked decrease in systemic blood pressure (86, 87). Just as a marked fall in peripheral vascular resistance may result in embarrassment to the myocardial circulation, an intense rise in peripheral pressure produced by the pressor amines would be expected to produce an increase in the myocardial work load.

The role of the coronary vessels in the production of myocardial necrosis by the sympathomimetic amines may be significant yet variable. The cardiovascular effects of the catecholamines are usually accompanied by marked compensatory dilatation of the coronary vessels, provided that they are not sclerotic (88, 89). The nature of the response appears to depend upon vessel size and the amount of catecholamine. Norepinephrine was found to produce good relaxation of the small coronary arteries, but somewhat less relaxation resulted from equal doses of epinephrine (90). This dilatation was blocked by pronethalol. Larger coronary vessels tend to be contracted by the catecholamines, and this effect is blocked by phenoxybenzamine hydrochloride[1] (90). The over-all myocardial circulation, as measured by coronary flow, is improved by epinephrine or norepinephrine, while after β-adrenergic receptor blockade these same sympathomimetic amines produce coronary constriction (91). The predominant effects of low doses of catecholamines are seen upon the myocardium and coronary circulation, while large doses produce greater peripheral effects (92). Furthermore, isoproterenol in large doses actually produces a pressor response which is blocked by α-adrenergic receptor blocking agents (93).

A factor of great importance in the action of sympathomimetic amines as myocardial necrotizing agents is their interaction, either as drugs or hormones, with other agents capable of producing cardiomyopathies. Because such unplanned interactions are probably common in the human, results obtained with sympathomimetic amines in normal animals may give an unrealistic impression of a low order of toxicity.

Epinephrine—Myocardial injury ranging from edema to massive necrosis can be produced by the injection of epinephrine. The nature of these effects and their severity are dependent upon the dose of epinephrine and the species tested. Cats appear to be most susceptible, demonstrating necrosis after the intravenous administration of moderate doses (94, 95). Larger doses are usually necessary to produce equivalent lesions in dogs (60, 61, 96, 99), rabbits (100), and rats (65, 86, 101–103). The importance of interacting factors is demonstrated by the fact that a dose of epinephrine producing no lesions alone (104, 105) consistently causes myocarditis when combined with low doses of caffeine (104–108), sparteine, or strophanthidin (105–106). A similar interaction with caffeine has been observed with guinea pigs (109) and dogs (104, 110). While the sensitivity of the human

[1] Trademarked as Dibenzylamine by Smith Kline & French Laboratories, Philadelphia, Pa.

myocardium is not known, large doses of epinephrine have been reported to produce functional evidence of lesions (111).

Norepinephrine—High mortality rates resulting from the use of norepinephrine in the treatment of cardiogenic shock or shock-like states prompted the initial studies of its myocardial toxicity (112). It was found that patients dying after treatment with norepinephrine or those with pheochromocytoma presented evidence of morphologic changes in the myocardium similar to those obtained by treating dogs with therapeutic doses of norepinephrine (113, 114). Lesions observed ranged from myocarditis to necrosis and/or focal fibrosis. It has been suggested that the mortality in cardiogenic shock would be reduced if lower doses of norepinephrine were employed (115). A hazard in the use of norepinephrine was demonstrated by the marked cardiac toxicity resulting from its administration to patients receiving iproniazid (116).

Focal myocarditis, patchy, fatty, degenerative changes, necrosis, and hemorrhages of the myocardium were produced in dogs by the intravenous administration of therapeutic doses of norepinephrine (60, 61, 112, 113). Rats were similarly susceptible to single or repeated subcutaneous injections (65, 86, 117–123). Doses producing minimal lesions when administered alone resulted in severe lesions when combined with dihydrotachysterol and calcium acetate (120), with a low potassium diet (121) or with cold stress (117).

Isoproterenol—In terms of the extent of its use, isoproterenol has become the reference standard for producing experimental myocardial necrosis. The rat has generally been the species of choice. Since the first studies (87, 124) using isoproterenol to produce lesions resembling those resulting from human myocardial infarction, a wide variety of factors have been studied in order to determine the pathogenesis of cardiopathies in general. The significance of such factors has been reviewed (125). Different strains of rats, as well as animals from the same strain but from different colonies, have significantly altered sensitivities to isoproterenol (126). Large animals were found to be more susceptible than small ones, while age and sex were not significant factors in this study as long as body weights were equal (126). Treatment of rats with conjugated equine estrogen or progesterone (125), ACTH (127), or glucocorticoids (127) failed to influence the cardiotoxicity of isoproterenol. Factors increasing isoproterenol-induced necrosis were: estrone (125), testosterone (125), hyperthyroidism (128), mineralocorticoids (127), a low-potassium diet (52), a high-sodium diet (52), isolation or cold stress (129), increased body fat (130), and nicotine (131). Factors providing some protection were: hypothyroidism (128), a high potassium diet (52), a low sodium diet (52), starvation (125), and, contrary to a report indicating a potentiation of the effects of norepinephrine in the human (116), monoamine oxidase inhibitors (132–134).

The hamster has also been used in studies to determine the mechanism by which isoproterenol affects the heart (33, 34). From these studies it was initially concluded that isoproterenol produced its effects by dilating the precapillary shunts of the coronary arteries (34); however, it was later concluded that the effects were those of ischemia resulting from coronary vasoconstriction (33).

Other studies of isoproterenol to follow were performed with rats unless otherwise indicated. These studies demonstrated: histochemical and electron microscopic changes (50); the relationship of the lesions to the loss of myocardial aspartate aminotransferase (135); the effect of adrenergic blocking agents on isoproterenol-induced biochemical changes in the myocardium (65, 136, 137); the similarity of isoproterenol-induced myocardial lesions to those occurring naturally in breeder rats (138); hemodynamic changes during the acute (139) and chronic (140) phases of the myocardial damage; the presence of impaired venous drainage as a possible cause of myocardial injury (31); the rate at which necrotic areas heal (36); a correlation of the lesions with hemodynamic and electrocardiographic changes in the dog (141); comparative effects with other sympathomimetic amines (86); a correlation between the disappearance of myocardial glycogen and potassium (142); detailed histological effects (143, 144); lack of protection from cardiac glycosides, monoamine oxidase inhibitors (145), or adrenergic blocking agents (65, 145); and a series of studies in which hemodynamic and metabolic effects were correlated with the histopathologic responses of rats to several sympathomimetic amines including isoproterenol (30, 37, 146).

Other Sympathomimetic Amines—Surprisingly few studies have been performed to evaluate the potential of other sympathomimetic amines in the production of cardiomyopathies. In early studies the oral administration of ephedrine each day for 1 to 2 years produced foci of calcification in the myocardium of guinea pigs (147). Following treatment with xanthine compounds in rabbits, ephedrine was found to produce myocarditis (106). Obviously ephedrine is much less potent in terms of its capacity to produce myocardial necrosis than are the catecholamines. The amount of ephedrine required to produce minimal

gross myocardial lesions in the rat is approximately 1,000 times the amount of epinephrine required, 700 times that of norepinephrine, and 4,400 times that of isoproterenol (86). Ephedrine also failed to produce myocardial injury when it was repeatedly injected in chickens and rabbits, both with and without the administration of sparteine (148).

Tyramine has also been shown to produce myocarditis in rabbits following administration of xanthine alkaloids (106). Methamphetamine administered daily for long periods to mice or rabbits resulted in myocardial degeneration (149). Phenylephrine, a sympathomimetic amine usually regarded as a specific stimulant for α-adrenergic receptors, produced myocardial necrosis, accompanied by loss of myocardial aspartate aminotransferase activity in rats, equivalent to the changes produced by epinephrine or norepinephrine when given in approximately twice the dose (65).

Nicotine—Nicotine has notable pharmacodynamic activities other than those of an indirect-acting sympathomimetic amine, but its principal effects upon the heart are probably mediated through stimulation of the sympathetic nervous system and the release of epinephrine and norepinephrine. Tobacco has long been suspect as a major etiologic factor in the increased mortality from cardiovascular disease of smokers, and nicotine is probably the active agent (150). Chronic administration of nicotine to rats (151–155), or rabbits (156, 157) did not produce myocardial lesions when used by some workers, yet others have produced ischemic changes (158) and necrotic areas of the myocardium (159) with rats. As large doses of nicotine produce death by respiratory arrest, it is not expected that myocardial necrosis would be seen with acute nicotine poisoning, yet myocardial effects have been seen in humans (160, 161) and horses (162). As was suggested from evidence with the catecholamines, however, there are indications that nicotine may owe much of its potential myocardial toxicity to interactions with other agents. It was observed, for example, that while nicotine or bovine serum administered daily to rabbits did not produce myocarditis, this effect resulted when the two agents were combined (163–167). Similarly, nicotine administered to the rat in doses approximating the intake of an average smoker does not produce lesions of the myocardium, yet it significantly intensifies the lesions produced by isoproterenol (131) or corticosteroid–electrolyte-stress treatment (53). Furthermore, when nicotine, ergometrine, and a hypercholesterolemic diet were administered to rabbits, as separate treatments or as any pair of treatments, there was no evidence of morphologic damage to the myocardium. When the three treatments were combined, fatty degeneration of the myocardium accompanied by thickening and fibrosis of the coronaries resulted (168, 169). Because of the multiplicity of the direct and indirect effects of nicotine on the myocardium, the nature of its interacting mechanism(s) can only be speculative at this time.

CORTICOSTEROIDS

In 1942 Miller and Darrow administered repeated doses of desoxycorticosterone to rats and produced necrosis of the myocardium which was indistinguishable from that produced by a low potassium diet (170). These effects were preventable by the administration of potassium chloride in the drinking water. Darrow later observed that a low potassium diet intensified the necrosis produced by this steroid (171). Others have reproduced these effects with desoxycorticosterone (172, 173), and have further observed that the coadministration of sodium chloride potentiates its damaging action (174–184). It was also demonstrated that the myocardial lesions were intensified by experimental hypertension (180, 182), uninephrectomy (177, 181, 183, 184), adrenalectomy (185), growth hormone (176), methandriol (186), digitalis in patients with congestive heart failure (187), hydrocortisone and calciferol (183), and cortisone or hydrocortisone (188). The lesions produced by desoxycorticosterone were reported to be reduced or prevented by promethazine (174), adrenalectomy (185), corticotropin or cortisone (177), or a sodium-free diet (182). Contrary to previous reports concerning the potentiation of the effect of desoxycorticosterone by sodium chloride, the administration of sodium chloride has also been reported to prevent the lesions in unilaterally nephrectomized and adrenalectomized rats (189). A further conflicting report is that the coadministration of cortisone does not influence the response to desoxycorticosterone (190). The guinea pig was also shown to be sensitive to the steroid-induced necrosis (191) as were humans treated for arthritis (192).

Not only are necrotic lesions of the myocardium produced by injections of desoxycorticosterone, but by corticotrophin (193–197, 206), cortisone (188, 194, 198–203), hydrocortisone (195, 201, 204, 205), corticosterone (206), and prednisone (207). The toxic effects of corticotropin for the myocardium were reported in the treatment of asthma (193, 194) and when used in conjunction with tetanus antitoxin (197). Prednisone produced myocardial infarctions in two of 63 tuber-

culous patients treated with average doses of prednisone and antitubercular drugs (207). The toxicity of the glucocorticoids, like that of desoxycorticosterone, was potentiated in rats by sodium chloride in the drinking water (199–201), by a low potassium diet (202), and by coadministration with desoxycorticosterone in doses which produced no effects alone (188). It is interesting that infarcts produced in dogs by ligating a branch of a coronary artery were made worse by the administration of desoxycorticosterone and improved over the controls by the administration of hydrocortisone (208). However, corticosteroid therapy of acute myocardial infarctions of the human has proven to be ineffective (209).

In 1957 Selye and Renaud (210) tested a new corticosteroid for its effectiveness in the production of cardiomyopathies. This compound, 2α-methyl-9α-chlorocortisol, when combined with the oral administration of sodium phosphate, was most effective in producing lesions in the rat heart. Since then a number of similar halogen-substituted steroids have been tested with a variety of other agents and treatments (118, 119, 210–228). Details of the speculations concerning the nature of the numerous interactions between corticosteroids, salts, stressors, and miscellaneous compounds can be found in books by Selye (229, 230). The mechanism of the toxicity has been the subject of considerable speculation and some disagreement. These lesions referred to as "electrolyte-steroid-cardiopathy with necrosis" (ESCN) by Selye's group were prevented by treatment with potassium (32). Their causation was said to be related to an undefined interaction between so-called "activating" anions, specifically phosphate, sulfate, and perchlorate, and certain halogenated corticosteroids. The answer to the question of mechanism begins with the clearly demonstrated activity of either mineralocorticoids or glucocorticoids in producing myocardial necrosis. Such activity has been shown to be intensified by the combination of glucocorticoid and mineralocorticoid activities whether as two separate compounds (14, 19, 53) or as a single highly active halogenated corticosteroid with both effects in a single molecule. In those few cases where an investigator has been unable to produce cardiac necrosis in the rat with desoxycorticosterone (231, 232), it might be concluded that doses, animals, or treatments were not optimal. In an attempt to resolve this seemingly confused picture, Nickerson and co-workers (84) studied the mechanisms of corticosteroid and the so-called "activating" anion. They determined that the "activating" anions were simply producing potassium-depletion through what they felt was catharsis, coupled with the potassium depleting effect of the halogenated steroid. The hypothesis of simple potassium depletion as the causative mechanism was later rejected by Prioreschi (231, 232) because he was unable to produce necrosis with desoxycorticosterone alone, because he seemingly protected the animals by the administration of chlorides other than potassium, and because not all animals with a low cardiac potassium developed necrosis. These apparent discrepancies in the low potassium hypothesis were later examined by Tucker and co-workers (233). They found that necrosis of the heart muscle was associated with a high metabolic alkalosis, an increase in intracellular sodium, and a decrease in skeletal muscle potassium. It was concluded that sodium phosphate as well as the other "activating" anions increased the rate of potassium excretion by their action on the kidney rather than by catharsis. Furthermore, the apparent protection by chlorides described by Prioreschi was interpreted as lack of potentiation rather than protection. The lack of a clear relationship between depletion of myocardial potassium and necrosis was found to result from the protective effect of potassium in skeletal muscle. Lack of a positive effect of desoxycorticosterone, in Prioreschi's studies, was related to the use of liberal amounts of potassium in the diet he fed his rats.

VASOCONSTRICTORS

Although the sympathomimetics include many agents with vasoconstrictor activity, they were treated separately because of their multiple actions and their over-all significance in terms of cardiomyopathies. As is the case with drugs classified as antihypertensives or vasodilators, the vasoconstrictors are assumed to produce myocardial injury through hemodynamic changes rather than direct myocardial toxicity.

The ergot alkaloids produce severe anginal symptoms in the presence of hyperthyroidism, syphilitic aortitis, deformities of the aortic valve, or stenosis of the coronary ostia (234, 235). Electrocardiographic changes, coronary thrombosis, and/or myocardial infarction have also been shown to follow therapy with ergot derivatives (236–238). The effect of the ergot alkaloids on the coronary vessels is seen in the electrocardiographic alterations during the ergonovine (ergometrine) stress test (239). Such ECG alterations occur when the drug is administered in the presence of pathologic changes of the coronary arteries (240, 241). In addition to being employed clinically, this test has been used to obtain evidence of restricted coronary flow in the living animal (242–244). The coronary constriction produced by

ergometrine in the rabbit receiving a hypercholesterolemic diet and chronic nicotine in the drinking water was sufficient to produce electrocardiographic alterations, thickening and fibrosis of the small branches of the coronaries, and myocardial necrosis (245, 246).

Vasopressin is another major vasoconstrictor drug shown to produce myocardial lesions. The earliest indication of its effects on the myocardium were reports by Scheps in 1934 (247, 248). He treated rabbits and guinea pigs with intramuscular injections of vasopressin and observed myocardial ischemia, hyperemia, edema, and necrosis. Others have repeated this observation using rabbits (249), dogs (250, 251), rats (252, 253), and cats (254), with effects ranging from hemorrhage to necrosis. Several cases of infarction and sudden death have been reported from the use of vasopressin in the human (255, 256). The marked reduction of coronary flow by vasopressin in normal, noninfarcted hearts (257) with no evidence of direct toxicity leaves ischemia as the probable mechanism. Vasoconstriction produced by posterior pituitary[2] has been combined with altered blood coagulability (thrombin administration) and/or coronary atherosclerosis (hypercholesterolemic diet) in rabbits (258). Infarction resulted from the combination of posterior pituitary and thrombin, while more severe necrosis was produced by the addition of hypercholesterolemia to the regimen.

VASODILATORS AND ANTIHYPERTENSIVES

Vasodilators or antihypertensives are not usually considered to be precipitating factors in myocardial degeneration, although they may induce ischemia through severe hypotension accompanied by prolonged tachycardia. A shortened diastolic interval coupled with diminished venous return in the presence of aortic stenosis or coronary sclerosis may be sufficient to produce localized ischemia to the point of necrosis. In the absence of evidence suggesting a direct toxic effect, one must assume a hemodynamic mechanism for such drugs.

Ganglionic blocking agents have been found to produce myocardial lesions when employed for the treatment of hypertension (259–266). Specific agents have been: tetraethylammonium chloride (259–261), hexamethonium chloride (264), pentamethonium bromide (263), pentolinium tartrate (262), and mecamylamine hydrochloride (266). In all cases the basis for the development of infarction appeared to be the administration of single or repeated hypotensive doses of the drug to arteriosclerotic patients. In one series, infarctions were produced in 7 hypertensive patients following the daily aministration of antihypertensive agents for periods of 4 days to 9 months (265). It was concluded that these drugs should not be used for elderly patients with systolic hypertension and especially not in the presence of angina pectoris. Other drugs reported to produce myocardial lesions when used for the treatment of hypertension include reserpine (267–269) and hydralazine (270, 271).

While the nitrites are used to treat the symptoms of angina pectoris, they have been reported to increase the incidence of infarction when administered chronically in large doses to patients with arteriosclerosis (272). Degenerative changes of the rat myocardium have been produced by the oral administration of erythritol tetranitrate (273).

THYROID HORMONE

While the term "thyroid hormone," is used throughout this section the actual substances are crude thyroid extract, thyroxin, or thyroid-stimulating hormone. In 1913 Farrant (274) reported that the administration of large doses of desiccated thyroid to the rat produced scattered areas of necrosis in the myocardium. Many others have since repeated his observations on experimental animals (103, 275–294) which have included cats (285, 288, 289, 293), rabbits (280–284, 286, 287, 290), guinea pigs (278), rats and pigeons (291, 292). Histologic changes in the various studies ranged from minor fatty degeneration to frank necrosis of the muscle fibers with exudative cellular infiltration. In some cases fibroblasts were described as replacing myocardial bundles. Not all investigators were able to demonstrate specific myocardial lesions in animals with experimental hyperthyroidism (295–298). Thyroid hormone alone is relatively ineffective in producing focal myocardial lesions in the cat, but when it is combined with otherwise nontoxic doses of digitalis, potentiation results (293).

Treatment with various stressors has failed to produce myocardial necrosis in rats pretreated with thyroid hormone (229). Although clinicians have reported histopathological changes in the hearts of patients with hyperthyroidism (299–305), and it is common to find swollen myocardial fibers in patients with hyperthyroidism, myocarditis or myocardial necrosis are said to be comparatively rare (306).

The mechanism by which thyroid hormone can produce lesions of the myocardium is not known.

[2] Trademarked as Pituitrin by Parke Davis and Co., Detroit, Mich.

It has been observed that, when administered to young growing rats, it produces an increase in the magnesium requirements accompanied by a decreased efficiency of oxidative-phosphorylation by the cardiac mitochondria (307). A similar impairment of oxidative phosphorylation by cardiac mitochondria is observed following magnesium deprivation (308).

CARDIAC GLYCOSIDES

The fact that the cardiac glycosides are capable of producing injury to the myocardium in addition to their positive inotropic action has been observed clinically and experimentally, yet this phenomenon has received relatively little attention. Perhaps the earliest report of this toxic effect was in the doctoral thesis of Lewitzky (309). In his studies with rabbits, dogs, and cats he observed that large doses of digitalis extract produced myocardial necrosis followed by inflammation. Since this study, other investigators and clinicians have confirmed and extended his data with various cardiac glycosides including: crude digitalis (310–318), convallaria (315), digitoxin (319–327), digitalin (319), gitalin (319, 321), lanatoside-C (328, 329), oleandrin (324, 326), ouabain (319), and strophanthin (330, 331).

Myocardial lesions have been reported following the administration of therapeutic (311, 317, 318) or toxic doses (310, 322) to humans. In one case death occurred from a combination of cortisone, corticotropin, antibiotics, meralluride, ammonium chloride, and digitalis (316). Most investigators studying the toxicity of the cardiac glycosides have employed the cat because of its sensitivity (312, 313, 315, 319–321, 323–328, 331, 332). In one comparative study, cats were found to develop focal myocardial necrosis from a single intravenous injection of digitoxin while dogs or rabbits required repeated injections (320). Other studies have confirmed the relative resistance of the dog (314, 328, 329). The rabbit when bled was found to be more susceptible to the cardiac glycosides (330). It is probable that the effect of bleeding acted as a stressor.

While the mechanism by which the cardiac glycosides produce lesions of the myocardium is not known, the evidence is in favor of potassium depletion. The positive correlation between depletion of myocardial potassium and digitalis toxicity is well documented (333–335). The problem is complicated by conjoint factors which increase the potassium loss. Congestive heart failure, the condition for which digitalis is usually employed, results in increased secretion of aldosterone with an accompanying increase in sodium retention and potassium excretion. Potent diuretics, used either for the treatment of congestive heart failure or hypertension, may aggravate myocardial toxicity through potassium depletion. The importance of interacting factors is demonstrated by the production of myocardial lesions with otherwise nontoxic doses of digitalis when administered with thyroid hormone (293).

EMETINE

The therapeutic value of emetine in the treatment of amebic dysentery is limited by the considerable toxicity of the drug. This toxicity has been demonstrated upon the heart, skeletal muscle, and intestine (336), although reports of polyneuritis and nervous involvement are not unusual (337). Evidence of its toxicity for the myocardium in humans treated for amebiasis has been frequently reported (338–348). In addition to the myocardial lesions resulting from emetine, alterations in the electrocardiogram (349), ventricular fibrillation (350), diminished systolic force (351), and tachycardia (352) have been observed following its therapeutic use.

A number of investigators have noted the production of fatty degeneration and necrosis of the myocardium following administration of emetine to rabbits (353–356), dogs (356), and pigeons (357). Its toxic effects for the myocardium have been said to be lessened by the administration of inositol or pyridoxine (358) and intensified by physical exercise (359, 360) or psychological stress (361).

A number of studies have been conducted to determine the biochemical mechanism by which emetine produces cardiomyopathies (361–369). It has been suggested that emetine may act to interfere with the enzyme system by which the heart converts glycogen to useful energy (370). A single dose of 10 to 20 mg./Kg. was found to cause a rapid fall of liver glycogen in the rat (362). In testing this theory Diamant (367) concluded that the synthesis, rather than the utilization, of glycogen was significantly depressed by emetine. He found that emetine depressed the activities of both aldolase and phosphorylase and suggested these effects as causes of the reduced glycogen synthesis. Emetine was shown to have no effect on the synthesis of cocarboxylase by the rat liver (366), and its effects on the heart were not blocked by the administration of nicotinamide adenine dinucleotide (368). The metabolism of vitamin A, riboflavin, nicotinic acid, or biotin were unaffected by the administration of emetine while smaller amounts of folic acid and thiamine were stored in the livers of pair-fed rats (364).

In studies with heart homogenate or mitochondrial preparations, emetine decreased the oxygen uptake in the presence of glucose, pyruvate, malate, fumarate, or without added substrates (365), and with butyrate or β-hydroxybutyrate (371). Oxygen uptake was augmented by succinate (365). Evidence was presented that the enhancement of succinate oxidation may have resulted from inhibition of malic dehydrogenase (369). As liver homogenates from emetine-poisoned rats did not demonstrate an impaired ability to oxidize any of the previously mentioned substrates (372), and as the liver accumulates a far higher concentration of emetine than does the heart (373), it was apparent that the toxicity to the heart was the result of a susceptibility of one or more still unidentified metabolic processes in this organ. The similarity of the effects of emetine to those of thyroxin on heart homogenates and to the toxicity of thyroxin for the myocardium has been noted (369).

METALLIC COMPOUNDS

Arsenic—Toxic interstitial myocarditis and related symptoms have been reported during the use of arsenicals in the treatment of syphilis (374, 375) and in acute or chronic arsenic poisoning (376–378).

Antimony—The usual cause of antimonial toxicity to the myocardium is its use in the treatment of schistosomiasis. Electrocardiographic abnormalities are common and morphologic alterations of the heart are frequently seen when sudden death ensues. These alterations are similar to the findings with arsenic poisoning. The myocardial toxicity of both the older and newer forms of antimonials has been the subject of several reports (379–381).

Other Metallic Compounds—Bismuth has been reported to produce a toxic myocarditis similar to that observed with arsenic or antimony (382, 383). Myocardial toxicity from the mercurials has produced sudden death from ventricular fibrillation or severe abnormalities of the electrocardiogram (384–388). Similar effects with morphologic changes of the myocardium have been demonstrated with animals (389–391).

While the mechanism by which the metallic compounds induce cardiopathies is not known, the protection against their over-all toxicity by dimercaprol suggests inhibition of sulfhydryl enzymes as a general mechanism (392).

ANTIMALARIALS

The earliest indication that the antimalarials may produce myocardial damage was in a report by Chopra and Wahed in 1934 (393). In treating malarial patients with a combination of pamaquine and quinacrine they observed evidence of myocardial injury, including tachycardia, palpitation, ECG changes, and signs of heart failure. It was apparent that the combination was considerably more toxic than either drug alone. It has since been found that quinacrine interferes with the metabolic degradation of the 8-aminoquinolines thus increasing their concentration in the plasma from five to tenfold (394). Quinine has been reported to produce myocardial damage when it was injected intravenously each day for the treatment of malaria (395).

Studies with rats have demonstrated a severe myocardial toxicity for the experimental antimalarial, plasmocid 8-(3-diethylaminopropylamino)-6-methoxyquinoline (117–119, 121, 396). Quinacrine has produced necrosis and fibrosis of the myocardium of rats, mice, or hamsters when administered as a single LD_{50} (397). Dogs, however, appeared to be refractory to this effect. The addition of small amounts of chloroquine to the diet of rats for periods up to 2 years resulted in fibrosis of the myocardium (398).

PSYCHOTHERAPEUTIC AGENTS

The different classes of psychotherapeutic agents are grouped for convenience of reference rather than to imply a common mechanism. Their potential myocardial toxicity was first reported following the intravenous administration of large doses of chlorpromazine to mental patients (399, 400). A deleterious cardiac action of promethazine was also suggested when it was employed for the production of "deep sleep" therapy for infarction (401). While promethazine, combined with chlorpromazine and meperidine, was said to be useful for suppressing the symptoms of myocardial infarction, heart damage was observed when it was used to treat patients in a state of severe collapse or older patients (402). Further indication of the phenothiazine's myocardial toxicity was suggested from the marked quinidine-like effect of thioridazine (403). In these cases the electrocardiographic changes resembled those of severe hypokalemia. With large doses, circulatory collapse and ventricular tachycardia had occurred, terminating in death. At necropsy, however, nonspecific changes were observed in the myocardium. In another instance, 30% of a group of patients under therapy with chlorpromazine or perphenazine had significant ECG abnormalities (404). About this time a number of unexpected deaths associated with chlorpromazine therapy were reported (405–407). In one 2,000-

bed neuropsychiatric hospital at least two cases of sudden, unexplained deaths had occurred each year since 1957 (408). A detailed histochemical analysis of the hearts from 12 such patients who had received phenothiazine therapy revealed lesions in the arterioles and myocardial muscle which were not present in a control group. Focal lesions of the myocardium, although less extensive, were observed in 70% of tranquilized patients dying from other causes. This effect of the phenothiazines was later demonstrated by the same authors using experimental animals subjected to chronic physical stress.

Evidence that imipramine may possess myocardial toxicity is seen in a report of infarction during its use for the treatment of depression (409) and evidence of cardiac complications during treatment with and poisoning by the drug (410).

Isoniazid (411) and iproniazid (412) have been reported to produce myocardial infarction in patients being treated for tuberculosis. Iproniazid has also been thought to damage the myocardium in patients to whom the drug was being administered for angina pectoris (413).

ALCOHOL

The toxicity of alcohol for the myocardium is infrequently noted, possibly because of the more obvious liver damage. Nevertheless, as early as 1873 an association was observed between alcohol and heart disease (414). These effects were described as..."a localized form of cirrhosis occurring in the myocardial wall and *trabeculae carneae* in the absence of impaired coronary circulation." The term "Munchen Bierherz" was introduced in 1884 to describe the cardiac dilatation and hypertrophy observed in Munich brewery workers who consumed excessive amounts of beer (415). This subject was recently revived following the deaths of 17 people in the U. S. and 20 in Canada from what authorities have called "Beer Drinkers Heart Disease" (416). In 1895 alcoholic myocarditis was observed in alcoholics with liver disease (417) and in 1902 the term "Alcoholic Heart Disease" was used to describe the general cardiac symptoms associated with chronic alcoholism (418). The similarity of alcoholic heart disease to beriberi was observed as early as 1906 (419). While later investigators also noted the similarity between these conditions (420), some reported that patients with alcoholic heart disease responded poorly to thiamine therapy (421). A number of investigators have documented the electrocardiographic abnormalities in chronic alcoholics and often noted that these alterations were reversible when alcohol was withheld for a sufficiently long period (422–424). Still others have observed low cardiac output, gallop rhythm, left ventricular failure, and a gradual refractoriness to thiamine therapy (425–427). Pathological changes ranging from microscopic areas of fibrosis to large confluent areas of fibrosis have been reported (428). A detailed study of 50 very heavy drinkers over a 10-year period revealed the usual functional changes of the heart with 10 deaths (429). At postmortem examination macroscopic fibrosis was found in the left ventricles with scattered areas of muscle degeneration and some fibrosis in all chambers. The lesions were said to resemble those produced by hypokalemia. It was suggested that they may have resulted from magnesium depletion, an effect known to occur with heavy drinking (430). The possibility that excessive alcohol consumption may have triggered an autoimmune reaction was also considered. In 10 patients examined for this purpose there were none of the usual reactions such as persistent fever, serositis, raised ESR, or arthropathy, but two of the 10 demonstrated anti-heart antibodies (429). Myocardial lesions have been reported to occur as a consequence of acute intoxication, although there was no evidence that chronic alcoholism was not a factor (431). An attempt has been made to correlate hemodynamic and biochemical changes in a group of hospitalized alcoholics (432). Hemodynamic changes were accompanied by the leakage of myocardial enzymes into the blood suggesting biochemical and physical alterations of the myocardium.

Electron microscope studies have demonstrated swelling of the mitochondria, a decrease in intramitochondrial enzymes, and deposition of lipid in myocardial cells from animals treated with alcohol (433). In chronic studies with alcoholic rats, impaired functioning of the citric acid cycle was observed with increased levels of pyruvate and lactate (434). Such changes were thought to be related to the myocardial lesions of chronic alcoholics (432). Dogs, to whom alcohol was administered for 12 weeks, demonstrated a marked and sustained increase in triglycerides, lipid phosphorus, and total cholesterol with a decrease in free fatty acids (435). The significance of these changes was related to the organ damage produced during chronic alcoholism. Recently, the question of whether chronic alcoholism produces myocardial damage through nutritional deficiencies was studied with pair-fed rats (436). Rats to whom alcohol was administered suffered from functional changes of the heart including arrhythmias following either epinephrine or mechanical

stress. These effects did not occur in the pair-fed animals, nor were they prevented by vitamin supplements. It was concluded that the myocardial toxicity of alcohol was not the result of nutritional deficiencies and it was speculated that alcohol may produce its effect through a reserpine-like action on the heart, an effect which has been previously reported (437, 438). The degeneration observed in the sympathetic neurons of chronic alcoholics (439) may also relate to catecholamine depletion.

DRUGS PRODUCING HYPERSENSITIVITY REACTIONS

It is not always clear whether a hypersensitivity reaction of the myocardium to drugs is the result of a direct injury to the myocardial cells or whether it is secondary to vasculitis. Interstitial and occasionally granulomatous myocarditis are the usual pathological lesions of the heart in these cases, although occasionally necrosis has resulted.

The sulfanamides are prone to produce such injury. The clinical administration of sulfanilamide was first demonstrated to produce myocarditis in 1939 (440). Since then this myocardial hypersensitivity has been reported again clinically (441–443) and been demonstrated using mice, rats, or rabbits (444, 445). The effect is not limited to sulfanilamide (440, 442, 444), but has been reported to occur with sulfapyridine (442, 444), sulfathiazole (441–445), sulfadiazine (441), and sulfasuxidine (442).

Myocarditis as a result of hypersensitivity to other drugs has been noted with chloramphenicol (446–449), chlortetracycline (450), streptomycin (451), carbutamide (452), and phenylbutazone (453). Penicillin sensitivity has been found to result in cardiomyopathies. Since 1950 a number of cases of minor myocardial reactions (454–460) and infarctions (461–466) have been reported.

Allergic myocardial reactions to vaccines, sera, and toxins have also been observed. The nature of the electrocardiographic changes produced by such agents was studied by Criep in 1931 (467). He postulated that the disturbances were the result of anoxia. Diphtheria (468–472) or typhoid (473) toxins were shown to produce fatty degeneration and necrosis of the myocardium in rabbits (469, 470, 473), guinea pigs (468, 470, 472, 473), rats (473), cats (471), or mice (473). Myocarditis and/or myocardial infarction have since been reported to result from the therapeutic administration of tetanus antitoxin (474, 475), rabies vaccine (476), and smallpox vaccine (477, 478).

ANDROGENS

A number of androgens were tested and found to be relatively nontoxic to the myocardium in rats (479) and guinea pigs (191) sensitized with monobasic sodium phosphate. When the rats were further sensitized by uninephrectomy and a high salt diet, or with other treatments, a greater degree of myocardial degeneration was produced (181, 480, 481). Adrenalectomy protected against such treatments, suggesting that at least part of the effect was related to the release of catecholamines and/or corticosteroids (482).

ANTICOAGULANTS

Anticoagulants continue to be a principal form of therapy for myocardial infarction, but there have been reports suggesting that they aggravate the condition (483, 484), retard healing of infarcts (485), and even produce fatal myocarditis due to a sensitivity reaction (486). Prolonged administration of bishydroxycoumarin in the diet of mice resulted in myocardial fibrosis, necrosis, and hemorrhage (487). These lesions were identical in appearance to those produced by the addition of sulfaguanidine to the diets of rats and were prevented by the administration of vitamin K.

HISTAMINE

While histamine is seldom used medicinally, its release from endogenous stores plays an important role in a number of pathological states. Following injury, locally released histamine is responsible for the initiation of an inflammatory response (488, 489). The administration of polymyxin B, a histamine-releaser, has been shown to produce severe myocardial necrosis in rats (490). A number of investigators have produced degenerative lesions in the hearts of experimental animals by the administration of histamine (94, 491–494). The pharmacodynamic and pathologic effects of histamine have been reviewed (495).

INSULIN

The administration of large doses of insulin to experimental animals has produced myocardial changes ranging from edema to disseminated necrotic patches (496–498). Other workers administering insulin for prolonged periods have been unable to demonstrate such lesions (499, 500). It has been suggested that the release of catecholamines and corticosteroids by insulin overdosage is the probable mechanism of toxicity (501). Insulin has been found to produce myocardial infarction during its routine use in the treatment of

diabetes (502–508) or when employed for shock therapy in schizophrenia (509, 510).

LOCAL ANESTHETICS

Large doses of local anesthetics have occasionally been observed to produce myocardial necrosis. The nature of this action has not been studied although, in most instances, it is probable that a marked fall in blood pressure was responsible. In one instance infarction followed procaine infiltration of the stellate ganglion (511). In other cases, injury was reported during the instillation of tetracaine into the urethra (512). Procaine–epinephrine has produced fatal infarction following its administration (513). The production of myocardial injury during spinal anesthesia has been reviewed by Gross *et al.* (514).

VITAMIN D

The administration of large doses of vitamin D has been shown to injure the myocardium of rachitic children (515) and of parathyroid patients (516). Myocardial calcium deposits were observed in patients using excessive amounts of vitamin D in conjunction with alkaline inorganic salts (517). Such effects have since been amply demonstrated in experimental animals (117–121, 183, 225, 518–523). The fact that such effects are difficult to produce except when vitamin D is combined with a potassium-depleting regimen strongly implicates low-potassium as the causative mechanism. In fact, a hypercalcemic nephropathy is produced by large doses of vitamin D, which in turn impair renal conservation of potassium (524).

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