Meetings

Cardiomyopathies

The term cardiomyopathy designates disease processes which affect the myocardium but spare, or only minimally involve, other cardiovascular structures. This definition excludes such common etiological categories as coronary, hypertensive, pulmonary, and valvular heart diseases. Nevertheless, cardiomyopathies are not necessarily "primary myocardial diseases," although the two terms are often used interchangeably. Cardiomyopathy may occur in the absence of any underlying primary disease elsewhere (primary cardiomyopathy or primary myocardial disease) or in association with systemic diseases including endocrinopathies, hemochromatosis, beri-beri, and muscular dystrophy (secondary cardiomyopathy). Thus, the cardiomyopathies comprise a large group of hereditary and acquired conditions, diseases of known and unknown etiology, degenerative and inflammatory processes, and a wide variety of aberrations characterized by idiopathic cardiac enlargement and heart failure. All these diseases are essentially metabolic (nonocclusive) forms of heart-muscle disease. Experimental studies have revealed that such metabolic cardiomyopathies can be induced in laboratory animals by many techniques.

The exploration of interesting parallels and confusing dissimilarities between experimental and human cardiomyopathies was the purpose of an international conference held in New York City under the auspices of the New York Academy of Sciences (9–11 January 1967). An interdisciplinary group of 74 basic research workers and clinical investigators presented their observations and views on experimental metabolic cardiomyopathies and their relationship to human heart-muscle diseases.

Following a review of the ultrastructural characteristics of normal heart muscle by E. Lindner (Kiel) and an attempt by C. E. Challice (Calgary) to correlate electrophysiologic properties with the microstructure of "specialized" tissue in the mammalian heart, the fine structural effects of several unrelated agents upon the myocardium were discussed. These included K deficiency, Mg deficiency, phosphorous poisoning, plasmocid, sympathomimetic amines, and stressor agents. The observations of H. A. Heggtveit (Ottawa), R. Poche (Düsseldorf), W. H. Hauss (Münster), V. J. Ferrans, R. G. Hibbs, J. J. Walsh, and G. E. Burch (New Orleans), and others, have indicated that cellular necrosis, from an ultrastructural point of view, may evolve along a number of different pathways. Thus, various metabolic and physicochemical disturbances may induce quite dissimilar morphological alterations in the affected myocardial cells. Conversely, certain disparate pathogenic agents may damage the subcellular organelles in similar fashion, thus suggesting common pathways of cellular injury.

According to the electron microscopic studies of G. Korb and V. Totovic (Marburg), ischemia causes two kinds of necrobiosis. In the center of the ischemic area the edematous cardiac muscle cells gradually undergo cytolysis, while in the periphery of the affected region the morphologic changes begin with a contraction of portions of the myofibrils and terminate in coagulation necrosis. Interestingly, in the majority of other types of cardiomyopathies, the myofibril has proved to be one of the organelles most resistant to injury.

In every situation reported thus far, except in K deficiency, the mitochondria were structurally severed; the sarcoplasmic reticulum was also easily damaged by numerous stimuli. In fact, an evaluation of the data in functional terms, and within our present conceptual restraints, suggests that the part of the muscle cell most sensitive to injury probably is the electrolyte-dependent sarcoplasmic reticulum, and next, the organizer, or nucleus, and the intracellular nutrition and energy mechanism-conducting system, the mitochondrion, in that order. According to D. Lehr (New York), such early, discernible ultrastructural changes as enlargement of the tubules of sarcoplasmic reticulum, as well as swelling and degeneration of mitochondria, are already associated with significant changes in myocardial electrolyte concentrations consisting of Na and Ca accumulation, Mg depletion, and a drop in PO_4 content.

In general, the importance of electrolytes in the genesis, treatment, and prevention of cardiomyopathies was emphasized by several other speakers. H. A. Hochrein (Würzburg) presented evidence indicating that electrolyte shifts—decrease of intracellular K and Mg and increase of Na, Cl, and PO_4—which can be observed in heart failures induced by either hypoxia or mechanical overload, are not the consequence but, rather, the cause of myocardial insufficiency. Thus, ionic alterations appear to be vital components of the disturbance in cardiac metabolism which, in the final analysis, expresses itself as reduced energy production in the case of hypoxia-induced heart failure and as a defect in the utilization of energy-supplying substrates in the case of failure due to overload.

E. Bajusz, J. R. Baker, P. Bogdonoff, and F. Homburger (Cambridge, Massachusetts) observed that the development of a spontaneous, hereditary, congestive heart failure which occurs in an inbred strain of hamsters can be prevented by prophylactic administration of certain K-salts (K-aspartate and K-orotate), but not with others (KCl and K-citrate). Data pertinent to this finding were presented by C. T. G. Flear (Newcastle-upon-Tyne), who demonstrated that K depletion is already present in patients with chronic heart disease who have not been in congestive failure. During the development of myocardial insufficiency changes do take place in the characteristics of cell membranes and also in the amount of intracellular ionic and organic constituents, but there is as yet no direct evidence that these changes alone cause cell malfunction in heart failure.

H. Selye (Montreal) pointed out that development of the various pluricausal cardiomyopathies normally induced in the rat by exposure to stressor agents, administration of corticoids and Na- or Ca-salts, vitamin-D derivatives, and other methods, all can be prevented by pretreatment with K- and/or Mg-

salts. K depletion plays a contributory role in the pathogenesis of some of these experimental heart-muscle diseases, but not in others. W. Raab (Burlington) has reviewed data which seem to indicate that in the pathogenesis of ischemic degenerative heart diseases, derangements of the cellular electrolyte balance play a crucial role by causing structural lesions, by inducing distortions of ion gradients which elicit potentially fatal conduction disturbances, and by reducing myocardial cell contractility. A loss of K and Mg ions from myocardial cells, accompanied by uptake of extra Na, was assumed to result from a deficiency of micro- or macrofocally distributed myocardial oxygen. The potentially hypoxiating action of sympathetic overactivity, an atherosclerotic impairment of coronary compensatory dilatability, and an increased secretion of K-depleting corticoids (for example, under various stresses) would appear to be among the most important factors eliciting this hypoxic electrolyte alteration. D. Sodi-Pallares (Mexico City) suggested the correction of K depletion by the administering of K-salts together with glucose and insulin (by the so-called polarizing solution) could be of therapeutic value in degenerative heart diseases. According to the observations of R. J. Bing (Detroit), the rate of reparative processes in hypoxia-damaged myocardial cells is increased by the polarizing solution, as adduced from the rate of incorporation of glycine-2-C^{14} into protein and nucleic acid and that of glucose-1-C^{14} into lipids. Insulin alone, ascorbic acid, and anabolic hormones exerted similar effects in this respect.

The frequent observance of myocardial degeneration in patients with various brain lesions was demonstrated by R. C. R. Connor (Glasgow). M. A. Klouda (Amherst) and G. Brynjolfsson (Hines) induced myocardial pathology by electric stimulation of the stellate ganglia in the dog, while the observations of K. I. Melville (Montreal) in monkeys following central neural excitation suggested the participation of a centrally mediated adrenergic component in the pathogenesis of ischemic heart-muscle lesions. The histochemical studies of E. T. Angelakos, R. W. Millard, and M. P. King (Boston) provided an insight into the regional distribution and localization of catecholamines in the heart. However, the functional significance of these neurohormones in the myocardium is still under debate. E. Braunwald, E. H. Sonnenblick, J. F. Spann, Jr., and R. Buccino (Bethesda) presented evidence to indicate that, while cardiac stores of norepinephrine are not fundamental for maintaining the intrinsic contractile force of muscle fibers, the thyroid state exerts direct action in this respect.

One of the most widely used experimental models of cardiac necrosis is that induced by isoproterenol, although other synthetic vasoactive amines also elicit similar heart-muscle lesions in laboratory animals. D. S. Kahn, G. Rona, and C. I. Chappel (Montreal) postulated that degeneration induced by isoproterenol results from a relative myocardial ischemia caused by the combination of increased myocardial oxygen requirement and decreased coronary blood flow. G. Jasmin (Montreal) believes that an impairment of veinous drainage and the peripheral circulatory shock caused by excessive administering of vasoactive amines are crucial factors in the genesis of this form of cardiac pathology.

According to A. M. Martin, Jr. (Washington), D. B. Hackel, and M. L. Entman (Durham), the basic mechanism for development of myocardial degeneration in hemorrhagic shock lies in the nature of the compensatory response of the heart to this situation, namely tachycardia, increased force of contraction, and decreased ventricular volumes. Interestingly, as shown by R. B. Jennings, H. M. Sommers, and P. B. Herdson (Chicago), the structural and chemical manifestations of cell death are greatly accelerated in states of transient ischemia, thus suggesting that diminished blood flow and impaired diffusion contribute to the delay in the development of overt necrosis in an area of permanent ischemia. The studies of these authors on mitochondria isolated from myocardium injured by ischemia support the concept that mitochondrial failure plays an important role in causing myocardial cells to enter a state of irreversible injury.

J. N. P. Davies (Albany) dealt with the pathology of the various forms of cardiomyopathies common to tropical regions and occasionally seen in temperate areas. Endomyocardial fibrosis is one of the most common diseases among this group, with totally obscure etiology. An experimental model resembling the last-mentioned condition was induced by M. Spatz (Bethesda) in guinea pigs maintained on a diet deficient in tryptophan. A. Laufer and A. M. Davis (Jerusalem) discussed the immunologic aspects of experimental and spontaneous cardiomyopathies by suggesting that hypersensitivity reactions may be responsible for the development of certain types of heart-muscle diseases. W. H. Abelman (Boston) showed the adverse effect of muscular exercise and alcohol consumption on the progression of experimental Chagas' myocarditis.

G. Rona and D. S. Kahn (Montreal) obtained evidence which suggests that healing processes in the heart are influenced by factors independent of the extent of the original injury. Furthermore, studies of E. Bajusz, J. R. Baker, C. W. Nixon, and F. Homburger (Cambridge, Massachusetts) on a spontaneous myocardial degeneration which regularly occurs in a genetically afflicted hamster strain indicate that the normal healing processes are significantly altered by concurrent development of cardiac hypertrophy and ventricular dilatation. In these animals, minor structural changes are usually the only recognizable remnants of an earlier severe myocardial degeneration. These findings suggest that the presence of a few foci of fibrosis and small linear scars, often seen in hearts of patients dying of chronic heart diseases and usually regarded as insignificant from a functional point of view, may be of primary etiologic importance concerning the development of congestive heart failure.

Although disappointingly little progress has been made in understanding the etiology and pathogenesis of experimental and spontaneous cardiomyopathies, the many new observations disclosed at this conference strengthened the conclusion that most cardiotoxic agents and conditions are potential pathogens, their adverse effects upon the heart muscle largely depending upon other (sensitizing and desensitizing) factors. While the pathogenic action and interaction of such factors as heredity, endocrines, neurohormones, emotional and physical stress, nutrition, and electrolyte imbalance are apparent, the precise mechanisms which govern the cardiac muscle's resistance versus susceptibility to diseases remain unclarified.

Moreover, with most of the basic problems still unresolved, the increased interest in cardiomyopathies has augmented the confusion, so that experimentalists, pathologists, and clinicians often find it difficult to understand one another. As emphasized by W. B. Wart-

man (Chicago), the lack of criteria for the pathologic differentiation of a primarily degenerative process from a primarily inflammatory process constitutes one of the greatest obstacles to progress. A disease which at its inception is purely degenerative may, in a matter of a few days, assume the appearance of an inflammatory disease due to the occurrence of natural reparative processes. Conversely, myocarditis (true inflammation) may eventually result in degeneration of muscle fibers. Many observations, concurring with the results of D. Reichenbach and E. P. Benditt (Seattle), show that in a number of cardiomyopathies there is a characteristic morphologic finding of myofibrillar degeneration, or myolysis. This distinct form of degeneration is usually, although not always, accompanied by interstitial mononuclear-cell proliferation, but by little if any polymorphonuclear-cell invasion. Even such a primarily degenerative lesion was repeatedly designated as myocarditis during the conference, as it is customarily done by pathologists elsewhere. It is, of course, very misleading to diagnose an inflammation secondary to myocardial degeneration as myocarditis; this term implies an infectious process to the clinician.

The use of the term myocardial infarction, which is one of the commonest designations entered on death certificates today, also requires reevaluation in the light of recent developments. In accordance with generally accepted views, myocardial infarct applies to an ischemic necrosis of the heart muscle secondary to mechanical obstruction of a coronary artery (thrombosis, formation of atherosclerotic plaques, or stenosis). However, ischemic necroses may develop through a variety of other mechanisms, and the limitations of light and electron microscopy in the study of myocardial ischemia have long been apparent. Furthermore, thrombosis may be, at least theoretically, the consequence rather than the cause of myocardial degeneration. This possibility was emphasized by the observations of G. Baroldi (Milan) on 696 autopsy specimens. No correlation between coronary thrombosis and myocardial degeneration could be found in 90 percent of the cases clinically diagnosed as "acute myocardial infarct"; in 98 percent of the sudden unexpected "coronary death" cases; and in 100 percent of the sudden but not unexpected "coronary death" cases. The use of the term myocardial infarct was ob-

viously incorrect in these cases. There are no currently available methods for determining, in the absence of a recent occlusion, whether coronary atherosclerosis and myocardial degeneration in a particular patient are cause-and-effect related. In fact, investigators are beginning to interpret the pathogenesis of all forms of cardiomyopathies as sequelae of metabolic derangements in the heart muscle influenced by electrolytes, hormones, hypoxia, and other sensitizing and desensitizing factors.

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Calendar of Events

Courses

Integrated Circuit Engineering, Univ. of Arizona, 17 July–18 Aug. A 200-hour program which combines theory with the practical considerations required to design a functional integrated circuit. Fee, $500. (R. H. Mattson, Electrical Engineering Dept., Univ. of Arizona, Tucson 85721)

School Librarian Workshop, Drexel Inst. of Technology, 17–28 July (Miss M. Warrington, Graduate School of Library Science, Drexel Inst. of Technology, Philadelphia, Pa. 19104)

Analysis and Design for Automatic Control, Carnegie Inst. of Technology, 18–28 July. Includes 70 hours of classroom work, laboratory projects, and special lectures. Fee, $375. (W. W. Ellis, Post-College Professional Education, Carnegie Univ., Pittsburgh, Pa. 15213)

Non-Equilibrium Processes in Astrophysics, Univ. of Manchester, 24–28 July. Lectures at postgraduate level. (J. Hazlehurst, Astronomy Dept., Univ. of Manchester, Manchester 13, England)

Engineering Summer Conferences, Univ. of Michigan, 31 July–4 Aug. Designed for engineers, scientists, and technical writers in order to increase the clarity of technical communication by intensive training in expression and organization. Registration 1 month before course begins is required. Fee, $175. (Engineering Summer Conf., West Engineering Bldg., Univ. of Michigan, Ann Arbor)

Neutron Activation Analysis, State Univ. at Buffalo, 31 July–11 Aug. No previous experience with nuclear techniques required. The course is applicable to industry, law enforcement, and laboratories. (Office of Continuing Education, State Univ. at Buffalo, 3435 Main St., Buffalo, N.Y. 14214)

Workshop on Microscopy, Chicago, Ill., 11–14 Sept. Sponsored by Paper Physics Committee of Technical Assoc. of Pulp and Paper Industry. Registration limited to first 75 persons who apply. Fee, $100. (T. S. McConnell, TAPPI, 360 Lexington Ave., New York 10017)