COMPLICATED and even contradictory concepts concerning the biochemical and physiological aspects of cardiac hypertrophy are less enigmatic if we first discern whether the type of hypertrophy analyzed is physiological or pathological; i.e., whether factors secondary to the process of hypertrophy have induced the heart to augment or depress its mechanical function. In this review physiological hypertrophy is defined as hypertrophy accompanied by a normal or augmented contractile state in which the maximum rate at which myosin hydrolyzes ATP and the maximum velocity of muscle shortening are either normal or elevated. Pathological hypertrophy, on the other hand, is associated with depressed contractility without necessarily concordant heart failure, in which case the rate of myosin ATPase activity and the velocity of muscle shortening are decreased. Both types of hypertrophy may be considered compensatory in that the heart biochemically and physiologically adjusts to cellular alterations that occur according to the severity of the workload. Thus, our definition is not the same as that provided by Meerson (1976), since he did not distinguish between the two types of hypertrophy described here.

To understand better the evolution of the cardiac hypertrophy process into physiological or pathological hypertrophy, this review is concerned with the immediate inciting stimuli of cardiac hypertrophy, the mechanism of its development, the various stages in its development, and its regional localization. We also are concerned with the dependency of the type of hypertrophy that evolves on the interdigitation or combination of such major determinants as the degree of ventricular wall stress, the duration of such stress, and the nature of the inciting stimulus, as well as the species, age, and health of the animal.

Early Stages of Myocardial Hypertrophy

Both in the developing and adult animal, the workload is an important determinant of ventricular mass (Zak, 1973; Wikman-Coffelt et al., 1976). The muscle fiber loses mitotic activity shortly after birth; myocardial cell enlargement then becomes the principal process by which the heart as a whole enlarges. For example, the canine muscle cell diameter normally increases approximately 3-fold from birth to adult life (Zak, 1973); an additional increase of 60% in diameter is possible with cardiac hypertrophy produced by pressure overload (Laks et al., 1974). Likewise, ventricular wall thickness increases by addition of sarcomeres in series and parallel (Laks et al., 1974), causing augmentation in cell length and width and resulting in less tension per sarcomere. Since muscle mass increases with workload, the heart physiologically responds to such demands by increasing its number of sarcomeres. Involved in such cell growth are the intercalated discs which proliferate with the hypertrophic process and from which new sarcomeres are laid down (Adomian et al., 1974). Although the mechanism of sarcomere genesis has not been fully elucidated, two microanatomical areas have been hypothesized as locations for new sarcomere production, the intercalated discs (Adomian et al., 1974) and the Z bands (Legato, 1970).

Excessive ventricular systolic pressure or volume overload leads to increased wall tension per sarcomere and greater stretch of muscle fibers, thus resulting in augmentation of end-diastolic sarco-
mere length (Laks et al., 1974); this in turn activates the growth process of myocardial hypertrophy. Pressure per se (Schreiber et al., 1978), or simply stretch of muscle fibers (Vandenburgh and Kaufman, 1979) occurring with pressure or volume overload, appears to activate the genetic apparatus of the myocardial cell, resulting in enhanced nucleic acid (Fanburg and Posner, 1968; Morkin and Ashford, 1968), protein (Schreiber et al., 1966), and myosin (Zak et al., 1976) synthesis and possibly induction of new genetic expressions, such as the appearance of new myosin isoenzymes (Flink et al., 1979; Schwartz et al., 1978), which characterize hypertrophy of muscle fibers. Increases in deoxyribonucleic acid content may be a possible consequence of polyplody of myofibers (Leclercq and Swynghedauw, 1978), as well as hyperplasia of interstitial and vascular endothelial cells (Nair et al., 1968; Zak et al., 1976; Kompman et al., 1966; Bishop and Melsen, 1976). [For difficulties involved in analyses of proliferation of interstitial and vascular endothelial cells, see Laurent et al. (1978)]. Furthermore, a relationship has been established between increased volume of isolated myocytes and augmented left ventricular mass during experimentally induced hypertrophy, thus providing evidence consistent with growth by hypertrophy without necessitating replication (Korecky and Rakusan, 1978).

The sequence of events leading to increased protein synthesis in the stressed heart has been investigated both in vivo and in vitro. Although an increase in the ribonucleic-to-deoxyribonucleic acid ratio is used as an index of hypertrophy, this measure provides an assessment of hypertrophy of all the cells constituting heart muscle and not simply myocytes. The heart possesses a relatively high ribonucleic-to-deoxyribonucleic acid ratio as compared to other organs. In addition, this ratio increases during hypertrophy (Winick and Noble, 1965). Furthermore, there is an altered base composition in the ribonucleic acids of hypertrophied hearts (Meerson et al., 1966). Present evidence suggests that, within the first 30 minutes to 1 hour after the onset of an elevated workload, there is increased myocardial polyamine content (Caldarera et al., 1971; Russell et al., 1971) and an increased adenyl cyclase activity (Schreiber et al., 1971) associated with rises in ribonucleic acid synthesis in the myocardium. However, it is important to point out that increased adenyl cyclase activity is not always associated with increased cyclic adenosine 3',5'-monophosphate (cAMP) content. In response to ventricular wall stress and with the time required for transcribing messenger RNA (mRNA) (Busch and Smetana, 1970), there is increased mRNA synthesis within 1 hour after elevated workload (Schreiber et al., 1968); and within the time required for extranuclear transport of mRNA (Busch and Smetana, 1970), there follows (within 2 hours) an increase in specific mRNA types based on augmented synthesis of large-sized polysomes (Schreiber et al., 1968), presumably coding for large molecular weight proteins. There then follows an increase in myocardial protein biosynthesis (Schreiber et al., 1968).

Hemodynamic overload thus is followed within a few hours by increased protein synthesis (Schreiber et al., 1966). This is probably one of the most accurate and sensitive estimates of hypertrophy, especially where methods of continuous infusion of labeled precursors over short periods of time are used and where there is a steady state labeling of the free amino acid pool (Everett et al., 1977). The proteins translated in early stages following stress are products of selective synthesis; they do not include all of the cardiac proteins (Schreiber et al., 1970). Microsomes from the overloaded heart show increases in microsomal protein synthesis as early as 1 hour following wall stress (Schreiber et al., 1967).

In addition to the above-described changes, there is also preferential synthesis and accumulation of mitochondrial proteins during the early phases of cardiac hypertrophy (Albin et al., 1973; Zak et al., 1976), as well as increased labeling and concentration of mitochondrial RNA and DNA (Rabinowitz and Zak, 1975). Mitochondria increase both in number and size with progression of hypertrophy (Schreiber et al., 1973), thus helping to alleviate the augmented energy demand placed on the hypertrophying myocardium. The process of hypertrophy may impose a reduction of the ATP:ADP ratio, which may in turn serve as a feedback mechanism causing an increase in mitochondrial protein synthesis in the stressed tissue by inducing the following salutary sequential changes: increased ADP concentration leads to augmented oxidative phosphorylation, which elevates mitochondrial substrate uptake, thereby resulting in increased energy production, improved coronary blood flow, and greater myocardial oxygen consumption (Meerson, 1969). It is recognized that substantiation of the evolution of these events is incomplete, since the normal inciting stimulus of mitochondrial neo-genesis is not substantiated at this time (Gevers, 1972), and the ability of a decline in high energy phosphate compounds to stimulate synthesis of mitochondrial proteins, an endergonic process, has not been established (Gevers, 1972).

After the early microsomal and mitochondrial adjustments in myocardial hypertrophy in response to wall stress, there is also an increased myosin biosynthesis approximately 3 hours following the work overload (Schreiber et al., 1966); in contrast, myoglobin, measured directly, and collagen synthesis, assessed indirectly, appear unchanged at this time (Schreiber et al., 1970).

Important alterations occur in protein synthesis during the process of hypertrophy, whereas protein
degradation remains constant (Laurent et al., 1978; Everett et al., 1977). (Such synthesis is assessed by incorporation of labeled precursors into proteins; since protein degradation is occurring simultaneously, allowing for reutilization of labeled precursors, accurate analyses become difficult.) In the studies of Schreiber et al. (1973) in which the effects of reutilizable amino acids were minimized by including a protein synthesis inhibitor, puromycin, in the incubation system, protein degradation remained constant during the first few hours of acute pressure overload. A retardation of protein degradation in the myocardium during the initial few days after aortic banding was reported (Zak et al., 1971, 1976). Consistent with these findings, a similar slowing of protein degradation has been observed during the early stages of exercise-induced skeletal muscle hypertrophy (Goldberg, 1969). In more recent studies using continuous infusion of an isotopically labeled protein precursor and during which reutilization of amino acids was minimal due to short labeling periods, there was no apparent change in protein degradation during early stages of cardiac hypertrophy in the dog (Everett et al., 1977). It remains to be resolved at this time whether the rate of protein degradation is different in physiological and pathological hypertrophy.

Because we have not distinguished between physiological and pathological cardiac hypertrophy in the past, there are insufficient data to determine if molecular alterations occurring during the early stages of hypertrophy are the same for the two types of hypertrophy. There may be asynchronous synthesis of certain cardiac proteins; e.g., a disproportional synthesis of mitochondrial to myofibrillar proteins may occur in one type of hypertrophy relative to the other, causing the compensatory mechanism characteristic of each type to be different. Such possible changes in the early stages of cardiac hypertrophy eventually may lead to a normal or elevated velocity of muscle shortening in physiological hypertrophy and a depressed velocity of muscle shortening in pathological hypertrophy.

Progression of Myocardial Hypertrophy

The mitochondrial cytochrome content per gram of tissue (Caldarera et al., 1971) and the relative volume occupied by the mitochondria in the cardiac fiber begin to decrease in relation to enhanced myofibrillar accumulation, depending on the animal model, e.g., 3–10 days after aortic banding in rats. As a result, myofibrillar content increases substantially so that the myofibrillar:mitochondrial ratio increases considerably (Wollenberger and Schultz, 1962; Wollenberger et al., 1966). Thus, mitochondrial and myofibrillar masses respond to work overload differentially. Similarly, as hypertrophy proceeds, there is an increase in muscle mass and enlargement of individual muscle fibers (Geha et al., 1966); thereby, the cell surface-to-cell volume ratio may decrease as proposed for the hypertrophying dog heart (Wikman-Coffelt et al., 1975b), which thus may limit efficient exchange of metabolites and tissue gases.

Myocardial hypoxia occurs following increased ventricular wall stress (Honig and Bourdeau-Martini, 1974) and serves as a stimulus for collagen synthesis. Collagen synthesis is augmented in animals that are undergoing cardiac hypertrophy and are subjected at the same time to hypoxic conditions (Bartosova et al., 1969). In other studies, mild hypoxia was found by mass spectrometric tissue gas analyses 3–6 weeks after pulmonary artery banding in dogs (Stewart et al., 1978). The lowered myocardial tissue PO2 (Stewart et al., 1978) appears to result from an elevated myocardial respiratory rate (Whalen et al., 1973), despite the coronary dilation evoked by decreased PO2.

In the ensuing periods (1 to 3 weeks, depending on the animal model) of the process of hypertrophy, the heart enlarges and other biochemical alterations appear. The cAMP levels in the pressure-overloaded ventricle decrease if analyses are based on cardiac tissue weight (Stewart et al., 1978). In addition, myocardial norepinephrine is diminished (Mason et al., 1971; Kramer et al., 1968). Accompanying the decrease in cAMP, there may be a concomitant reduction in RNA polymerase activity [in contrast to the early elevations in this enzyme (Schreiber et al., 1969)], which may result in return to a normal rate of protein synthesis as reported by Everett et al. (1977). This eventually could cause a stabilization of ventricular weight at its increased load or a moderate decrease in weight (Wikman-Coffelt et al., 1975a, 1975b, 1976). Due to the circumstances detailed below, partial or complete reversal of hypertrophy may occur depending on the nature, degree, and duration of the initial stimulus, as well as the health and age of the animal and the species studied. Interestingly, in experimental animals at the later stage of hypertrophy, a disparity between cAMP levels and contractile state has been observed (Stewart et al., 1978).

For a complete review of the role of cyclic nucleotides, see Rasmussen and Goodman (1977).

The maximum fiber size attained with myocardial hypertrophy is restricted partially by the ability of component organelles and other subcellular particles to increase in number proportionate to the demands of altered cellular dimensions, i.e., an increase in the cell volume:cell surface ratio, and proportionate to mechanical demands for maintaining circulatory integrity. The maximum cell volume attained may vary both with species and type of hypertrophy. Although the heart's inherent use of the hypertrophy process serves the useful mechanical and hemodynamic purpose of maintaining circulatory integrity and alleviating the stress placed on single sarcomeres, the increase in contractile
hypertrophy from the onset of hemodynamic stress, dogs, the left ventricle usually develops pathological whereas the pressure-overloaded right ventricle generally exhibits physiological before pathological hypertrophy (Wikman-Coffelt and Mason, 1977). It is important to emphasize, however, that, after prolonged stress on the ventricular wall with the eventual development of cardiac failure, pathological hypertrophy is characteristic of both the hemodynamically stressed and nonstressed ventricle. It is reasoned that the initial differential response between the stressed right ventricle and the stressed left ventricle in the adult is the result of the right ventricle normally operating at a lower contractile state than the left ventricle (Salel et al., 1972). Therefore, the right ventricle possesses a greater contractile reserve than the left ventricle in the face of excessive hemodynamic load.

A mild but prolonged stimulus produced by pulmonary artery banding is capable of eliciting physiological hypertrophy. Thus, under this condition, myosin ATPase activity is temporarily increased (Wikman-Coffelt, et al., 1975b, 1975c), whereas contractile function remains normal (Meerson, 1969) or even is elevated (Meerson, 1969; Stewart et al., 1978). An increase in contractile state of the nonstressed ventricle was also associated with hypertrophy of this chamber in experimentally induced systemic hypertension (Pool et al., 1976). It is possible that this type of physiological hypertrophy may gradually return to normal metabolic and mechanical activity. Physiological hypertrophy produced by moderate pulmonary artery banding (Stewart et al., 1978) or by thyroid hormone administration (Strauer and Scherpe, 1975, Goodkind et al., 1974) has produced even greater elevations in myosin ATPase activity and enhancement of contractility.

It is important to emphasize that, when the stimulus to hypertrophy is particularly prolonged and intense, excessive cell growth is elicited with disproportionate biosynthesis of organelles and contractile proteins, as well as other subcellular structures, thereby leading to the evolution of pathological hypertrophy. Pathological hypertrophy may occur not only in chronic situations but may take place immediately, such as in severe experimentally induced pulmonic or aortic stenosis (Wikman-Coffelt et al., 1975a, 1976). Pathological hypertrophy is characterized by decreased myosin ATPase activity (Wikman-Coffelt et al., 1975a, 1976), diminished cAMP content, and depressed contractile function (Meerson, 1969), as observed with severe pulmonary artery banding (Wikman-Coffelt et al., 1975a) or aortic banding (Wikman-Coffelt et al., 1976). These metabolic and mechanical features of pathological hypertrophy may be the result of tissue acidity (Poole-Wilson, 1978).

Regional Differences in the Ventricular Hypertrophy Process

The proliferation of ventricular nonmuscle components appears to be linked to conditions causing hypertrophy of the muscle fibers. Thus, in the pressure-overloaded ventricle, collagen concentration...
increased in the endocardium (Buccino et al., 1969) where hypoxia would be expected to be relatively more severe than in the epicardium. Collagen appears to increase, particularly in areas surrounding coronary vessels in response to ventricular pressure overload (Harkness, 1968), thus preventing distension of such vessels with increased workload. In addition, diastolic compliance becomes reduced with cardiac hypertrophy (Dodge et al., 1962). It is recognized that assessment of collagen synthesis is difficult both because of analytical techniques and also because of differences which may occur in collagen synthesis accompanying physiological vs. pathological hypertrophy (Bartosova et al., 1969).

Disproportionately greater hypertrophy appears to take place in the inner, relative to the middle, portion of the right ventricular wall in dogs after pulmonic stenosis (Morady et al., 1973). Spotnitz et al. (1966) have demonstrated a decreasing spectrum of sarcomere length from the inner to outer wall of the normal left ventricle. The sarcomere length is consistent with the calculated and measured decrease in radial wall stress from the inner to outer wall. Following 17-40 weeks of pulmonary artery banding in dogs, the sarcomere lengths in the midportion of the right ventricular wall were significantly greater than in the inner wall, suggesting greater tension per sarcomere in the middle wall (Morady et al., 1973). Thus, greater hypertrophy and an increase in number of sarcomeres may take place in the inner wall after pulmonic stenosis, accounting for an eventual reduction in wall stress and sarcomere length in that layer of the heart (Morady et al., 1973).

The degree of hypertrophy varies according to the region of the ventricle. Regions of the heart subjected to greater tension, such as the inner wall, hypertrophy to a greater extent than other locations. The hypertrophy process begins at the base of the ventricle in pressure overload and progresses apically (Laks et al., 1969; Morady et al., 1973). Sarcomere length becomes the same at basal and apical sites in volume overload (Laks et al., 1969). Stress induced by pulmonic banding in dogs elicited greater hypertrophy, as measured by wall thickness and cell length, in the base of the right ventricle than in the apex of the same chamber following pulmonic stenosis in dogs (Laks et al., 1969). The nonstressed left ventricle reflected this same response but to a lesser degree (Laks et al., 1969). Along with increases in wall thickness and cell length, there also was an increase in fiber width but not sarcomere length (Laks et al., 1974).

Myosin Activity as an Index of Physiological Vs. Pathological Cardiac Hypertrophy

The sarcomere is comprised principally of thick and thin filaments. The thick filaments consist of an assembly of the three proteins, actin, troponin, and tropomyosin. Actin is a globular protein which polymerizes into a double helical configuration. Tropomyosin consists of a long linear molecule which rests in the double helix of the actin molecules. Troponin is a globular molecule containing three subunits affixed near the end of each tropomyosin molecule, designated, I, C, and T. Troponin I, like tropomyosin, has the ability to regulate the interaction between actin and myosin (Perry et al., 1972). Troponin T primarily serves to bind the troponin complex to tropomyosin. Troponin C binds available Ca$^{2+}$ and thus releases the inhibitory action of troponin I; this action forces tropomyosin into a configurational change, thereby allowing interaction between actin and myosin to commence (Cohen et al., 1972). The biochemical and biophysical interaction between the myosin molecules of the thick filaments and the polymerized actin of the thin filaments produce force and shortening during ventricular systole. Hydrolysis of ATP by myosin ATPase produces angulation in the myosin heads, thus resulting in a force which pushes the thin filaments together toward the center of the sarcomere. There is a direct relationship between the rate of Ca$^{2+}$-activated myosin ATPase activity and the maximum velocity of muscle shortening (Barnay, 1967).

Accompanying myocardial hypertrophy, there occur new isozymes of myosin, which demonstrate, in the case of physiological hypertrophy, an increased rate of ATP hydrolysis, an increased rate of ATP hydrolysis (Flink and Morkin, 1977) and, in the case of pathological hypertrophy, a decreased rate of ATP hydrolysis (Schwartz et al., 1978). In support of the theory that such new genetic expressions could occur during hypertrophy, isozymes of myosin have been shown to be present in the atria (Long et al., 1977; Flink et al., 1978) and are reflected in high V$_{max}$ contractility indices (Korecky and Michael, 1974). Substantiating that an increased workload may incite synthesis of a myosin isozyme, it has been shown that synthesis of isozymes of skeletal muscle myosin are influenced by the nature of the automatic innervation (Amphlett et al., 1975). Subsequent studies using electrical stimulation have demonstrated that these isozyme alterations are due to the degree of stimulation. It has been shown further in skeletal muscle that more than one isozyme of myosin can exist in a single muscle fiber (Gauthier and Lowey, 1977).

The decrease in myosin ATPase activity in failing hemodynamically stressed hypertrophied hearts is associated with alterations in the sulfhydryl groups of myosin involved in the active site (Thomas and Alpert, 1977). A disparity in stoichiometry of light chains accompanying alterations in myosin ATPase activity was reported for the hypertrophied canine left ventricle (Wikman-Coffelt et al., 1976). These variations may be due to contamination (Fabian et al., 1977). A disproportionate increase in heavy chain synthesis was shown to occur with pulmonic
stenosis in guinea pigs (Evans et al., 1978). Variances in Ca\(^{2+}\) binding of myosin have also been reported (Wikman-Coffelt et al., 1976); however, these differences appear to be in the low-affinity Ca\(^{2+}\)-binding sites (Fabian et al., 1977). In further studies, it has been shown that there is no relation to alterations in myosin ATPase activity and the Ca\(^{2+}\)-binding light chain LC\(_1\) (Higuchi et al., 1978b). Differences in myosin ATPase activity between normal and hypertrophied myocardium also may be due to variances in degree of charge modification of light chain LC\(_1\) (Wikman-Coffelt et al., 1975c); however, this type of light chain is reflected in actin-activated myosin ATPase activity (Wagner and Weeds, 1977; Wikman-Coffelt and Srivastava (in press)), whereas variances in the heavy chains are reflected in myosin ATPase activity. An increased synthesis of myosin light chains relative to heavy chains has been reported in cardiac hypertrophy accompanying severe stenosis in the rat (Zak, 1977); however, this was not true with moderate stenosis in the guinea pig (Evans et al., 1978).

Supporting the occurrence of such preferential myosin subunit synthesis, a disparate turnover of light and heavy chains has been established for normal cardiac myosin (Wikman-Coffelt et al., 1973).

A direct relationship has been observed between the V\(_{\text{max}}\), contractility index of velocity of muscle shortening and the rate at which myosin hydrolyzes ATP (Alpert et al., 1974; Stewart et al., 1978). In comparative studies of animal species, a direct relationship has been described between the rate of myosin ATPase activity and the velocity of contractile element shortening (Henderson et al., 1970; Delcayre and Swynghedauw, 1975; Higuchi et al., 1978a). The velocity of contractile element shortening has been shown to be elevated with mild and moderate pulmonic stenosis in dogs (Wikman-Coffelt et al., 1975c; Stewart et al., 1978); in mild pulmonic stenosis, the increase in myosin ATPase activity was transitory, lasting from 3 to 6 weeks after pulmonary artery banding (Wikman-Coffelt et al., 1975b).

**Determinants of Physiological Vs. Pathological Cardiac Hypertrophy**

Biochemical and mechanical alterations of cardiac performance and myosin ATPase activity and contractility are dependent on at least four principal variables: (1) degree of hemodynamic stress, (2) duration of such stress, (3) nature of the inciting stimulus, and (4) the species, age, and health of the animal studied. Newborn hearts, exercised hearts, hearts subjected to mild stenosis, and hyperthyroidism afford useful experimental models for physiological hypertrophy.

Since all metabolic and mechanical indices of cardiac performance are elevated in experimental hyperthyroidism, this disorder may serve as a prototype of physiological cardiac hypertrophy. In experimental hyperthyroidism, left ventricular weight is increased considerably (Goodkind et al., 1974). In addition, hemodynamic variables are augmented and myocardial contractility is increased (Goodkind et al., 1974). Biochemically, there is increased cardiac Ca\(^{2+}\) ATPase activity in the sarcoplasmic reticulum (Limas, 1978) with enhanced Ca\(^{2+}\)-stimulated myosin ATPase activity in the contractile proteins (Banerjee and Morkin, 1977). Present evidence indicates that the increased thyroxine-induced myosin ATPase activity underlies the augmented contractile state (Banerjee and Morkin, 1977). These alterations, which occur in myosin ATPase activity in the hyperthyroid state, appear to be due to structural changes in myosin (Banerjee and Morkin, 1977; Flink and Morkin, 1977).

**Degree and Duration of Ventricular Wall Stress**

The degree of hemodynamic stress is one of the principal determinants stimulating alterations in myosin ATPase activity (Wikman-Coffelt et al., 1975a) and modulating contractile performance in the hypertrophy process. Thus, depending on the degree of pulmonary banding in dogs, there occurred in the pressure-overloaded ventricle a transitory increase (Wikman-Coffelt et al., 1975b), a sustained increase (Stewart et al., 1978), or a diminished myosin ATPase activity (Wikman-Coffelt et al., 1976). We have designated the varying degrees of pulmonic stenosis as mild, moderate, and severe, respectively. Thus, with pulmonary artery banding causing a 50–100% rise in right ventricular peak systolic pressure, right ventricular free wall weight increased 30% (Wikman-Coffelt et al., 1975a). A moderate elevation of right ventricular peak-systolic pressure of 150% resulted in an increase of rightventricular free wall weight of 100% (Stewart et al., 1978), whereas a severe right ventricular peak systolic pressure rise of 200% caused an increase in free wall muscle mass of 50% (Wikman-Coffelt et al., 1975a). The study of severe pulmonic stenosis indicates that factors other than wall stress determine the degree of hypertrophy. Consistent with the effects of the duration of increased wall stress on hypertrophy, the hemodynamically nonstressed ventricle does not increase in muscle mass until 3–4 months after moderate pulmonic artery banding in dogs (Laks et al., 1974; Wikman-Coffelt and Mason, 1977). In accordance, the ATPase activity of myosin and hemodynamic variables are related and both vary concordantly, depending on the duration of increased wall stress.

In studies of newborn lambs, both ventricles possess equal K\(^+\)-activated myosin ATPase activity (Wikman-Coffelt et al., in press). However, parturition is associated with physiological hypertrophy of the left ventricle in which both contractility and K\(^+\)-stimulated myosin ATPase activity increase to
reach adult values by 16 weeks postnatally (Wikman-Coffelt et al., in press).

From the observations discussed within this section on the extent of ventricular wall stress, it is clear that the degree and duration of hemodynamic overload contribute importantly to the magnitude of the hypertrophy process. Furthermore, the degree of ventricular wall stress largely determines whether the hypertrophy process is physiological or pathological.

**Reversibility of the Hypertrophy Process**

Reversibility of cardiac hypertrophy occurs at various stages following hemodynamic overload. Thus, rapid regression of hypertrophy takes place with relief of excessive pressure or volume load on the heart. Experimental and clinical data show complete regression of hypertrophy after treatment of hemodynamic overload, repair of ventricular septal defect, and operative correction of aortic regurgitation (Hall et al., 1953; Beznak et al., 1969; Gault et al., 1970; Cutiletta et al., 1975; Carey et al., 1978). Complete or partial regression depends on the degree of hypertrophy, as well as on the age and health of the animal.

There is nearly complete regression of the increased heart weight in various types of experimental hypertrophy (Cutiletta et al., 1975). Furthermore, the protein and RNA content of the hypertrophied rat heart returned to normal values within 2–4 days after relief of aortic stenosis (Cutiletta et al., 1975), and complete reversal of depressed myosin ATPase activity occurred after removal of pulmonic stenosis (Carey et al., 1978).

Although ventricular hypertrophy regresses after correction of experimental and clinical hemodynamic overload, contractility often remains depressed (Gault et al., 1970). In general, connective tissue does not appear to regress as readily as myocardial mass (Cutiletta et al., 1975). Recovery of depressed right ventricular contractile state has been reported despite persistent experimentally induced pressure overload of the chamber in cats (Williams and Potter, 1974).

Differences in the extent of reversibility of changes in contractility appear dependent on the inciting stimulus, duration of wall stress, and the age, health, and species. Cardiac hypertrophy is partially reversible in patients who have decreased velocity of contractile element shortening associated with volume overload (Gault et al., 1970). In hypertrophied left ventricles of dogs subjected to brief pressure overload, there may be some reversibility of depressed contractile state (Sasayama et al., 1975).

Present evidence indicates that hypertrophy is both induced and reversible. These phenomena may be incited by cAMP changes mediated by norepinephrine or pressure per se, perhaps via fiber stretch. The pressure stimulus may act directly on the myocardial nucleus (Schreiber et al., 1978) or may act indirectly by the following sequence of events: Ca\textsuperscript{2+} from the sarcoplasmic reticulum may increase cAMP and protein phosphorylation. This immediate elevation in cAMP and protein phosphorylation may increase protein synthesis, whereas decreases in cAMP may cause decreased protein synthesis. Thus, the nucleotide, cAMP, which has been shown to control the synthesis of selective proteins in several types of tissues, may be an important regulating factor in the hypertrophy process (Wicks, 1974); however, this mechanism remains hypothetical.

**Nature of the Inciting Stimulus**

It is necessary, in the hypertrophy process, to consider not only the degree and duration of wall stress but also the abruptness and type of intervention. For example, suddenly (vs. gradually) applied severe pressure overload may well produce disparate hypertrophic responses (Skelton and Sonnenblick, 1974). Thus, it is reasoned that, because abrupt increases in wall stress may afford some degree of short-term compensatory hemodynamic benefits by increasing contractile units, the hypertrophy mechanism so immediately induced does not provide an optimal myocardial response (Wollenberger et al., 1966). In this regard, if the hypertrophy process is rapid and abrupt, there may result an asynchronous synthesis of contractile proteins and abnormal genesis of subcellular elements, e.g., mitochondrial-to-myofibrillar content, as well as defective capillaries and abnormal quantities of connective tissue.

The importance of the abruptness with which a work overload is applied has been emphasized in studies showing the unfavorable synthesis ratio of mitochondrial-to-myofibrillar proteins induced by sudden experimental creation of marked aortic stenosis (Wollenberger et al., 1966). It has been proposed that gradual increments in the severity of wall stress may produce different hypertrophy patterns, in contrast to those obtained by abrupt intervention, especially relative to connective tissue synthesis (Bartosova et al., 1969; Bishop and Melse, 1976). Furthermore, cardiomegaly induced by isoproterenol causes excessive oxygen consumption leading to myocardial hypoxia, creating a selective augmented synthesis of connective tissue (Bartosova et al., 1969), whereas cardiac hypertrophy induced by thyroxine may not be accompanied by increases in collagen (Bartosova et al., 1969). On the other hand, pressure overload, like catecholamine-induced hypertrophy, appears to cause a considerable increase in collagenous stroma (Ljungqvist and Unge, 1973). In other comparative studies of the inciting stimulus, cardiac hypertrophy induced by exercise appears to elicit neoformation of coronary vessels, whereas hypertrophy induced by aortic stenosis is accompanied by only negligible
myocardial vascular changes (Kossman, 1965).

Concerning the induction of cardiac hypertrophy by increased stimulation with endogenous hormones, it has been shown that chronic infusion of subhypertensive doses of norepinephrine results in left ventricular hypertrophy (Laks, 1977). Importantly, circulating norepinephrine increases within 30 minutes after the creation of aortic stenosis in rabbits (Calderara et al., 1971). In related studies, epinephrine content has been shown to be decreased in pulmonic stenosis in cats (Coulson et al., 1977). Profound depletion of cardiac norepinephrine occurs with the development of heart failure (Wollenberger and Schultz, 1962). The cardiac catecholamine depletion in the right ventricles of cats with pulmonic stenosis has been shown to be irreversible after relief of pulmonary banding (Coulson et al., 1977).

In addition, differences in contractile state dependent on the nature of the inciting stimulus have been demonstrated for the hypertrophy process in experimental pulmonic stenosis in rats, hereditary cardiomyopathy in the Syrian hamster, and chronic administration of thyroid hormone in cats (Skelton et al., 1965). Since it is apparent that different immediate-inciting stimuli of cardiac hypertrophy produce disparate alterations in myocardial metabolic and mechanical function, it is important for unification to designate hypertrophy as either physiological or pathological. All inducers of hypertrophy appear to initiate the process by a common mechanical-biochemical coupling mechanism; the work overload causes an increased pressure on the myocardial cells and stretch of muscle fibers and, perhaps mediated by norepinephrine release, causes an augmentation of RNA transcription and protein synthesis. Then, depending on the severity of the workload, secondary factors such as increased tissue PCO₂ could determine whether the heart adjusts to the new work demand by developing the characteristics of either physiological or pathological hypertrophy.

Species, Age, and Health of the Animal

In contrast to larger animals (dog, sheep, human) (Henderson 1970; Wikman-Coffelt et al., 1975a, 1975b, 1975c, 1976; Malhotra et al., 1977), pressure overload induced in small animals (rat, guinea pig, cat, rabbit) is more likely to decrease myosin ATPase activity and contractility (Bing et al., 1971; Draper et al., 1971; Hamrell and Alpert, 1977; Carey et al., 1978). It is reasoned that both the high metabolic rate and the rapid cardiac rate manifested in smaller animals signify that their hearts normally function at greater baseline wall stress (Higuchi et al., 1978a), thus, myosin ATPase activity is normally high (Higuchi et al., 1978a; Delcayre and Swynghedauw, 1975). Therefore, when the smaller animals are subjected to work overload, the course of the hypertrophy process in their hearts is likely to respond differently to hemodynamic stress compared to the hearts of larger animals, particularly when the inciting wall stress is severe in magnitude. For example, excessive increases in cardiac metabolism may lead to tissue acidity and thus result in diminished myosin ATPase activity and a depressed velocity of muscle shortening (Wikman-Coffelt and Mason, 1977). Thus, in severe aortic stenosis in dogs in which there were decreases in both contractility and myosin ATPase activity, tissue acidity was documented by elevated myocardial PCO₂ (Wikman-Coffelt et al., 1978). Furthermore, the course of the cardiac hypertrophy process also appears to respond differently to exercise in various animal species (Tomanek, 1970; Williams and Potter, 1976). As an example of disparities in the response of various species to pressure overload, when the dog (Wikman-Coffelt et al., 1975a) and cat (Carey et al., 1978) were subjected to the same degree and duration of pulmonic stenosis, physiological hypertrophy occurred in the dog (Wikman-Coffelt et al., 1975a) whereas pathological hypertrophy occurred in the cat (Carey et al., 1978). Thus, in dogs with pulmonic stenosis, average cardiac cellular diameter increased 44% without alteration of contractility (physiological hypertrophy); whereas, in cats with the same type, duration, and degree of pressure overload-induced hypertrophy, the fiber diameter increased 50% with depressed contractility (pathological hypertrophy) (Spann et al., 1967; Fisher and Kaveler, 1970).

Relative to age, comparison of aortic stenosis between young and old dogs revealed that the ratio of mitochondrial to myofibrillar mass was lower in adult, relative to young, animals (Wollenberger and Schultz, 1962; Wollenberger et al., 1966). In other studies in guinea pigs and rats, it has been shown that both contractility (Draper et al., 1971) and myosin ATPase activity (Cheski and Rackstein, 1977) were decreased in older, compared to younger, animals. In contrast to experimental animals, cardiac myosin ATPase activity has been shown not to be altered with age in nonhypertrophied hearts of humans (Malhotra et al., 1977). These data indicate that not all animals respond similarly to the same degree and duration of different inciting stimuli of cardiac hypertrophy and that there exists a disparate tolerance to stress-induced hypertrophy according to animal species, age, and health.

This review has been concerned with a general review of the hypertrophy process and its evolution into either physiological or pathological hypertrophy. The constellation of factors which determine the course of the hypertrophy process are essentially a combination of four major determinants: the degree of ventricular wall stress, the duration of such stress, and the nature of the inciting stimulus, as well as the species, age, and health of the animal. The indices, myosin ATPase activity and velocity of muscle shortening, used to distinguish the two types of hypertrophy (Scheuer and Bhan, 1979), have been studied more extensively than other cri-
teria at this time. Future studies may, however, reveal new parameters which will further correlate with the known data, making it easier to understand the evolution of physiological vs. pathological hypertrophy. The evolution of hypertrophy, the parameters affecting its development into either physiological or pathological hypertrophy, and the indices used to distinguish the two types of hypertrophy are presented in this review as initial developments in unification of this complicated subject.

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