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Etiology of Cardiac Enlargement

Enlargement of the heart is a condition which is seen in most types of pathological changes in the heart which cause decreased efficiency of the heart muscle or cause an increased load on the circulatory system. All of these conditions tend to diminish the volume of the circulation and as a result to diminish the oxygen-carrying capacity of the blood. It is primarily the metabolic activity of the organism which determines the minute volume of output and to counteract the impediments to the circulation which cause the lowered metabolism the organism is able to bring into play certain compensatory mechanisms. That these compensatory mechanisms can be very efficient in maintaining an adequate circulation is shown by the fact that the damage to the circulatory system does not lead to immediate and progressively decreasing efficiency of the oxygen-carrying capacity of the circulation ending in the syndrome of cardiac decompensation and eventual death from anoxia of the tissues of the body in all cases of severe damage. Mild degrees of damage to the heart, such as very slight valvular damage as a result of acute rheumatic fever, are consistent with a long active life and autopsy on such cases often shows no evidence of cardiac dilatation or hypertrophy. More severe circulatory impairment such as occurs in hypertension is not incompatible with arduous physical labor as long as a compensatory hypertrophy has occurred.

The process of circulatory compensation occurs in three general

ways as mentioned by Fishberg (20):

1. Through mechanisms tending to maintain the minute volume of circulation despite the valvular defect or other handicap. These involve not only increased work on the part of one or more chambers of the heart but often, in addition, coordinated adaptations of the vessels.

2. Through vasomotor mechanisms tending to deviate a higher portion of the decreased cardiac output to the active organs.

3. Through more efficient utilization of such volume of circulation as can be maintained. Examples of this are the more complete reduction of hemoglobin in the capillaries as a result of the slowing of blood flow and the increased oxygen-carrying capacity of the blood due to the polycythemia that develops in certain congenital and other forms of circulatory impairment.

Fishberg (20) mentions the fact that there are three mechanisms by which cardiac circulatory compensation can occur. These are acceleration of the heart rate, dilatation, and hypertrophy. Acceleration and dilatation are mechanisms which can occur fairly rapidly whereas hypertrophy occurs over a longer period of time after a considerable period of strain. This thesis is concerned only with the problem of dilatation and hypertrophy.

The relationship of dilatation and hypertrophy has only recently become more completely understood and even now it is a matter of controversy, but most writers seem to agree with Eyster and

his co-workers (17) in stating that dilatation precedes hypertrophy and is only the immediate temporary compensatory mechanism, whereas hypertrophy is the more permanent one. The fundamental biochemical changes which occur in hypertrophy are, as yet, little understood, but the mechanical changes leading to these biochemical changes are fairly well known and will be discussed in this paper.

Since dilatation precedes hypertrophy in compensation it should be discussed first. Whether dilatation always precedes hypertrophy or not is still a matter of controversy, but it always occurs in conditions in which fairly rapid compensation is needed.

The only characteristic of a dilated chamber of the heart is the increased capacity of its cavity. With concomitant hypertrophy the wall of the dilated chamber may be of normal thickness or of even greater thickness than normal. However, dilatation per se tends to thin the wall of the chamber and in some instances this thinning may be very marked; this thinning is most conspicuous in the auricles which may be almost paper-thin or where an aneurysm has formed in consequence of fibrous replacement of infarcted myocardium. The extent of dilatation may be enormous; when both sides of the heart are thus affected, the organ may extend from the left axilla almost to the right. The highest degree of dilatation is seen in the auricles. The capacity of the left auricle has been known to exceed a liter in rare cases of mitral stenosis. As the walls of the chambers are thinned out there is

an attenuation and elongation of the papillary muscles and chordae tendinae as well as flattening of the trabeculae of the ventricles and the muscular pectinatae of the auricular appendages; in extreme instances the latter may be barely discernible. An important accompaniment of some instances of well-marked cardiac dilatation is enlargement of the auriculo-ventricular orifices orifices, usually much more marked in the tricuspid than in the mitral valve. The rings leading to the pulmonary artery and aorta may also be dilated to a certain extent, but dilatation of these orifices is more often an accompaniment of dilatation of the arteries themselves just outside of the valves.

Kirch (301) by careful measurements of the various internal and external dimensions of the heart has found that dilatation does not involve the entire ventricle from the start but evolves in characteristic fashion. His studies were especially concerned with the inflow and outflow tracts of the ventricles. The inflow tract of the left ventricle extends from the mitral orifice to the apex, that of the right ventricle from the tricuspid valve to the apex. The corresponding outflow tracts extend from the apex of each ventricle to the aortic and pulmonary orifices respectively. Studying the left ventricle in hypertension and aortic valvular disease and the right ventricle in conditions with increased pulmonary resistance (mitral disease, emphysema), Kirch found that dilatation of a ventricle in these conditions always begins in the outflow tract which

is both elongated and broadened. Moreover, he found that dilatation starts in the terminal portion of the outflow tract, under the aortic ring in the left ventricle and in the pulmonary conus in the right. The dilatation then progresses against the direction of the blood stream down the outflow tract to the apex. Only subsequently is the inflow tract involved again in a direction contrary to that of blood flow, so that the dilatation finally reaches the auriculo-ventricular ring with the production of a relative incompetence. While Kirch thus found many instances in which the outflow tract (of the left ventricle in hypertension and aortic disease and of the right ventricle in mitral disease and emphysema) was dilated while the inflow tract was normal, he did not observe the reverse in over ten years of investigation.

In mitral valvular disease with pronounced regurgitation, the dilatation of the left ventricle may be especially marked immediately under the mitral valve, so that the chamber tends towards a spherical shape. The dilatation resulting from myocarditis or coronary sclerosis seems to involve all parts of the ventricle in question quite uniformly.

The scientists of a century ago regarded dilatation of the heart as a purely passive process, for which reason they termed it "passive aneurysm" in contradistinction to hypertrophy or "active aneurysm". They compared dilatation of a heart muscle to the

stretching of old rubber, solely a manifestation of impaired contractility, and in itself harmful to the function of the myocardium. Rosenbach (48, 49) seems to have been the first to point out on speculative grounds that cardiac dilatation at times serves a useful purpose to increase the capacity for work of the dilated chamber. Adequate basis for this conception has since been furnished by the studies of physiologists on the dynamics of the heart. The fundamental experiments are those of Frank (21) on the frog's heart and especially of Starling (53) on the heart-lung preparation.

The steps which occur in the production of dilatation have been well worked out by many workers in this field. Starling has done particularly outstanding work in this field. He reported that when either heightened arterial resistance or greater venous inflow increases the work of the heart, accommodation to the greater load involves dilatation of the heart.

The following steps occur when there is increased resistance within the aorta. The heart fails to empty during the first few beats as completely as before with the result that the residual blood in the left ventricle at the end of systole rises progressively with each of these beats. Inasmuch as the venous inflow during diastole remains constant, there is a corresponding increase in the volume of the ventricle at the end of diastole; i.e. of what might be termed the presystolic volume. However with a rising presystolic volume with each contraction the output rises with successive beats

until it equals the inflow and a state of equilibrium is reached. However in this compensatory mechanism the presystolic and systolic volumes of the heart have increased so that although the output is the same as at a lower arterial resistance it is effected from a higher level of dilatation.

By means of this dilatation the inadequacy of the circulation is compensated for but at the expense of cardiac reserve. In order to overcome the greater arterial resistance the heart has to beat at a greater stroke pressure and to do this dilatation has to occur for reasons which will be discussed later. As the ventricle becomes distended there is an increased residual of the blood remaining in the ventricle at the end of diastole since the venous return to the heart is substantially the same as in the normal heart. This results in a rise in intraventricular pressure and as a result in an increase in the pressure in the pulmonary veins and left auricle. Further increase in arterial pressure will result in further increase in venous pressure and the point is soon reached where pulmonary edema and the syndrome of decompensation occur. The process of dilatation causes the heart to do more work per beat according to Starling's law, and the increase in venous pressure is not so great as the increase in arterial pressure so that the heart acts as a buffer system between the arterial and venous systems. This buffer system however has only limited possibilities if it relies on dilatation alone, and this is the reason that further compensatory mechanisms must be brought

into play.

Starling found that as the arterial pressure is increased, a greater proportion of the output of the left ventricle passes through the coronary circulation. This is of advantage to the heart since it is doing more work than it normally does and therefore needs more blood. Fishberg (20) considers the possibility that increased coronary flow through greater wear and tear might play a significant part in the production of coronary arteriosclerosis in hypertension.

Starling found a similar picture when the arterial resistance was kept constant and the venous return to the heart increased. Here, also, the output of the first few beats of the heart falls progressively behind the inflow so that the presystolic volume is increased. But, as the volume of the heart at the end of diastole increases with each beat the output also rises until equilibrium with the increased venous inflow is reached. The volume of the heart at the end of systole is greater than with a low venous return according to Starling. Patterson, Piper, and Starling (43) conceived it theoretically possible for a heart of great physiological efficiency to discharge all of the surplus blood it receives and thus maintain the larger stroke volume with only diastolic but no systolic dilatation. According to Katz and Wiggers (63) the increased output following augmentation of venous return is accomplished by both greater velocity of ejection and

prolongation of stroke.

Starling has pointed out that in his experiments on the heart-lung preparation the isolated heart accommodates itself to either increased arterial resistance or greater venous return solely by increasing the energy of the individual contraction and not by increasing the rate. The rate was not altered at all by increasing the arterial resistance or the venous return but changing the temperature had an immediate effect in the rate. This would seem to indicate that the tachycardia associated with heart failure is an extrinsic adaptation dependent on the nervous control of the heart.

These experiments on the heart-lung preparation by Starling have been confirmed in the intact animal by Wiggers and Katz (63) and by Meek and Eyster (17).

On the basis of his observation that the accommodation to either increased arterial resistance or greater venous return is associated with dilatation, Starling enunciated his law of the heart. Patterson, Piper, and Starling (43) stated: "The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy set free in passing from the resting to the contracted state depends on the area of chemically active surfaces, i.e. on the length of the muscle fibers."

Contraction of a dilated heart is similar to the contraction of a weighted skeletal muscle in many respects and follows the same

laws. It is well known that skeletal muscle contracts more forcibly if it is loaded by a weight before it is excited (6). This can be determined by very simple experiments. The weight stretches the muscle fibers, increasing their length and exerting a certain tension upon them. If the muscle is made to contract isometrically the tension developed during the contraction is found to be proportional to the initial length of the muscle before excitation. The tension which the load exerts upon the fibers just prior to their contraction is called the initial tension. The tension developed when the muscle contracts isometrically is the developed tension which is a measure of the force of contraction. When a resting muscle is weighted, little change in initial tension actually occurs until it is extended beyond a length corresponding to that which it possesses when in its natural position in the body, its physiological length. Up to this point the developed tension increases with each increment in initial length. Yet, it is only when the muscle is stretched beyond its physiological length that any marked increase in intial tension occurs. The power of contraction of a skeletal muscle is therefore dependent upon initial length and not upon any stimulating effect exerted upon the muscle fibers by initial tension.

There has been some controversy as to whether the energy liberated by the cardiac muscle is, like skeletal muscle, dependent mainly upon initial length or upon initial tension. The experi-

ments of Starling indicate that initial length is the sole determining factor.

In Starling's experiments there was no way by which the length and tension of the cardiac muscle during its relaxation (diastole) or the tension developed during contraction (systole) could be measured directly as in skeletal muscle. Yet, the diastolic volume depends upon fiber length (initial length); the intraventricular pressure during diastole represents initial tension; and the pressure developed during systole is related to the tension set up by the contracting fibers, the developed tension. When, therefore, simultaneous records of diastolic volume and intraventricular pressures during diastole and systole are secured the diagram obtained is similar to that obtained by diagramming the initial length and tension of skeletal muscle contracting isometrically (6, P. 364). The venous pressure which stretches the cardiac muscle during diastole corresponds to the weight applied to the skeletal muscle. The opening of the semilunar valves against the aortic pressure represents the load against which the cardiac muscle has to contract. The diagram shows that the force of the ventricular contraction increases with the diastolic volume until the heart becomes over distended and a rise in diastolic pressure occurs. The force of contraction then falls off, the two curves approaching one another and finally meeting. From this data Starling formulated the Law of the Heart.

The experiments of Anrep and Segall (3) are also confirmatory of Starling's conclusion. These observers found that when the isolated frog's ventricle contracted isometrically the contractile force, up to a point (systolic pressure), increased proportionately with the filling of the ventricle (diastolic volume); the maximal tension developed when the ventricle was filled to two-thirds of its maximal capacity. Filling beyond this caused a rise in the initial (diastolic) tension accompanied by a reduction in the developed tension. Katz (29) was able to dissociate the effects of these two factors upon the development of tension by the turtle heart. When initial tension was varied but initial length kept constant, or the converse, or when both were varied in the same or in opposite directions, the results always indicated that initial length was the factor which determined the force of the contraction. Changes in the initial tension amounting to over 200 mm. of water were usually without effect upon the height of the intraventricular pressure provided the diastolic volume was kept constant.

When the heart compensates for greater venous return or arterial resistance by means of diastolic dilatation, it performs more mechanical work. In accord with this, Evans and Matsuoka (14) found that when the arterial resistance or the venous inflow is increased there is a rise in the oxygen consumption and carbon dioxide production of the heart.

It has also been shown by Starling and Visscher (60) that the oxygen consumption of the heart muscle is directly proportional to fiber length, which varies with diastolic volume. The ratio between oxygen consumption and diastolic volume remained constant, though diastolic volume varied widely. The work performed by a heart in good physiological condition also bears a linear relationship to diastolic volume and consequently to the oxygen consumption. On the other hand, when as a result of fatigue the condition of the heart deteriorated, its diastolic volume was much greater in proportion to the work performed than in the case of the well-conditioned heart. This means that the ill-nourished muscle fiber in order to gain energy for the performance of a given amount of work must be stretched to a greater extent. Nevertheless, whether the condition of the heart muscle was good or bad the relationship between oxygen consumption and diastolic volume was the same. This means, of course, that, since it dilates more, the poorly nourished heart uses more oxygen for the performance of a given piece of work than does a heart in good condition; or the proportion of the total energy expenditure which appears as mechanical work, the efficiency, is lowered when the heart muscle departs from its prime physiological state.

The increased metabolism of the heart with progressive dilatation is probably often of significance for the pathogenesis of cardiac failure. Thus, if the coronaries are sclerotic, the blood supply

may be inadequate for the greater metabolism accompanying dilatation due to hypertension or a valvular defect.

Just as the energy of contraction of skeletal muscle increases with initial elongation only up to a certain maximum, there is also an optimal dilatation for the heart as has already been shown. What determines the degree of dilatation above which the output of the heart decreases is not known. One factor probably is the greater tension on the muscle fibers. For if the pressure within the chamber remains constant, the tension on each individual fiber increases with the radius (20). The maximum tension which the muscle fibers can withstand without giving way is presumably a function of their physiological fitness, but this statement adds nothing to our knowledge.

Such sudden dilatation of the heart beyond the optimum, which would be followed by quick failure, is largely prevented by the pericardium. In health, the heart does not fill the pericardium, so that room is available for some dilatation. While the findings in pericardial effusion and in enlargement of the heart show that the pericardium can dilate enormously as a result of gradual pressure, it is practically inextensible to sudden stretching and thus will prevent very great immediate dilatation. The restraint of dilatation by the pericardium is brought out in the experiments of Van Liere (57, 58) who showed that the pericardium prevents excessive dilatation following vagal stimulation and that the cardiac dila-

tation due to severe anoxemia is greater in animals with the pericardium removed. Working with the heart-lung preparation, Kuno (34) found that if the pericardium is removed any increase in the work of the heart is dangerous to the organ, for hemorrhages into the myocardium or valvular incompetence may develop. On the other hand, he observed that with the pericardium intact the heart requires a higher venous pressure to perform a given amount of work than when the pericardium is opened; this is presumably because the heart dilates more readily in the absence of pericardial restraint. Gibbon and Churchill (22) also found that removal of a pericardium which interferes with the dilatation of a heart performing increased work materially lessens the degree of cardiac decompensation. Attempts have been made by Felix (19) and others to facilitate compensatory dilatation by opening the pericardium.

Acute dilatation of the ventricles is a condition which is still under dispute. Roberts (47) states that it is a dangerous condition of the heart and is most likely to be associated with rheumatic fever in early life (55, 35, 9) and as such may become extreme. It often occurs in dry or plastic pericarditis. Usually though dilatation in the early stages of rheumatic fever is only temporary. The lesion is in the interstitial tissue so we would not expect as high an incidence as in diphtheria. Sequeira (50) maintained that cardiac enlargement is accompanied by dilatation

of the fibrous pericardial sac which is a consequence of the softening of this structure due to inflammation. He agreed with Barnard (5) that the normal function of the pericardium is to prevent dilatation of the heart beyond a certain point; and insisted that not only may the pericardium be acutely dilated with effusion to a remarkable extent but that the plastic forms of pericarditis also softens it, thus diminishing its resisting power. The heart dilates and distends the yielding pericardium which while still inflamed adheres to the chest wall and diaphragm. Sequiera also regarded the movements of chorea when violent and of long duration as a factor in dilating the pericardium.

Dietlen (11) and Doner (12) as quoted by Palmer (42) reported that in diphtheria there are pathological changes consisting of fatty degeneration of muscle fibers and patches of interstitial myocarditis. In view of this fact it might be suspected that permanent changes might be left in the heart, but Jones and White (27) report that five years after attacks of severe diphtheria no evidence could be found in one hundred patients of sequelae in the heart by clinical signs. These findings have also been confirmed by other workers.

Acute dilatations with regression to normal size is a fairly normal occurrence in acute nephritis as such men as Levy (36) have tried to prove by means of X-rays. Palmer (42), however, in examining the plates made by these men claims that the evidence is

not convincing and that in only a small percentage of cases is the evidence conclusive enough to prove the presence of dilatation. Ellis (13) calls attention to the importance of congestive heart failure in acute nephritis and presumes that part of the heart enlargement may be on this basis. Alwens and Moog (2) and Assman (4) consider pericardial effusion as a cause of apparent enlargement on the X-ray.

Moritz (41), Hering (23) and others have tried to differentiate pathogenetically distinct varieties of dilatation. The main types recognized have been:

1. A purely compensatory dilatation of the healthy heart muscle in order to meet a greater heart load. This is the so-called physiological or active dilatation, termed by Moritz tonogenic dilatation, or dilatation due to increased tension. The conception has been that in this variety the heart is dilated only in diastole while the systolic volume is normal. However, the experiments on the heart-lung preparation indicate that the residual blood in the ventricle at the end of systole is increased even in a healthy heart when the arterial resistance is elevated.

2. Dilatation due to impaired contractility of the damaged myocardium. This is pathological or passive dilatation, the myogenic dilatation of Moritz.

3. Dilatation due to diminished diastolic tone of the heart. Hering conceives that this may result from either increased vagus

or decreased accelerator tone.

Clinically it is often impossible to differentiate the role played by myogenic and tonogenic factors in producing dilatation, such as in valvular lesions on hypertension with associated valvular changes. These are, however, dilatations which can be classified as purely myogenic or tonogenic (20). Examples of myogenic dilatation are encountered in arteriosclerotic myomalacia without hypertension, post-diptheritic heart disease, and rheumatic myocarditis with little valvular defect. Tonogenic dilatation occurs in nephritic or essential hypertension in the young, although even here, despite the fact that the coronary arteries are widely patent and histological examination reveals no lesions of the heart muscle, the question may be raised whether superadded myogenic factors are not also concerned.

From the point of view of the compensatory nature of the process, it does not seem that a distinction can be drawn between myogenic and tonogenic dilatation. For even when the dilatation results from damage to the heart muscle and not from increased load, the greater volume of the heart is accompanied by augmentation in the energy of systolic discharge. Evidence to this effect is furnished by the experiments with the heart-lung preparation of Socin (52), who injured the heart with chloroform, and those of Sulzer (56), who used alcohol for the same purpose. These investigations revealed that the dynamics of the hypodynamic heart is qualitatively identical with that of the healthy organ. Just as is true of the latter,

increased filling and greater arterial resistance are met by dilatation, as a result of which systolic energy is increased and the greater load mastered. But Socin found that in order to meet a given load it was necessary for the heart damaged by chloroform to undergo greater systolic dilatation and accumulate a larger systolic residue than was needed by the healthy heart. Furthermore, the damaged heart failed at a smaller load than did the healthy one. In other words, dilatation of the damaged heart fulfills the same function of increasing the energy of systolic contraction as does dilatation when the heart muscle is uninjured. Thus, it would seem that myogenic dilatation is to be viewed as essentially similar to the dilatation that the healthy heart undergoes in the face of an increased load; it is present because the injured heart muscle can meet the normal load only with a greater presystolic fiber length than the undamaged cardiac muscle requires (20).

Loss of tone of the heart muscle has often been attributed a role in the production of dilatation. When fluoroscopic examination reveals a dilated heart in which the differentiation of the individual segments of the borders is less clear than usual, which lies with a broad base on the diaphragm, and the amplitude of the pulsations is diminished, the tone of the heart is often considered to be low. Even at postmortem the flabbiness of the muscle often encountered in post-diphtheritic or other myocardial degenerations or inflammations is not uncommonly considered to indicate that the

tone of the heart was low during life.

It seems, however, that these interpretations are based on a loose concept of tone which is the maintenance of a sustained, most often relatively slight degree of contraction in smooth and skeletal muscle. In the case of cardiac muscle, Meek (39) defines tone as "a condition of sustained diastolic contraction, by virtue of which the muscle fibers resist distension more than they would because of their mere physical properties." Such diastolic tone has been demonstrated in the tortoise heart. However, Meek comes to the conclusion that there is as yet no adequate evidence of the existence of diastolic tones in the mammalian heart, although the possibility cannot be considered as disproved. Patterson, Piper, and Starling (43) found no evidence of tone as defined above either so they propose that the word tone be used to designate the physiological fitness of the muscle fiber as measured by its efficiency in carrying on the circulation without elongating. Fishberg (20) considers this definition as being the same as that for contractility and thus unwarranted in clinical medicine. He considers that dilatation of the heart results only from failure of the systolic accomplishment of the heart to equal the venous return.

Smith (51) in his studies on the relation between heart weight and body weight has shown that there is a close correlation between the two. In males the heart weight is approximately 0.43% of the

body weight and in females the ratio is 0.40%. The ratio is slightly higher in thin persons and slightly lower in obese ones. Smith states that the average weight of the heart of an adult male is 294 gm. which corresponds to the average heart weight of a man weighing 150 lbs. In women the average heart weight is 250 gm. which corresponds to a body weight of a little less than 140 lbs. The weight of the heart does not increase with increase in age regardless of the weight of the body if all other factors remain the same. However the weight of the heart does increase with an increase in the weight of the body.

Hirsch (25) had shown previously that there is a close parallelism between the heart weight and the general muscular development of the individual; fat but flabby individuals generally have relatively light hearts. This is the result that one would expect to see if the mass of the heart muscle is a function of the work it performs. Herxheimer (24) carried out roentgenographic studies on the hearts of athletes who took part in the Olympic games and found that the hearts of athletes, and particularly those who took part in the endurance contests, were enlarged. Likewise, Tung (57) and his associates have shown that 45 per cent of Chinese ricksha pullers, who perform very hard work, have enlargement of the heart sufficient to be demonstrated during life.

Experimentally Kuelbs showed that when the work of the heart

is increased by exercise, it hypertrophies. He studied two dogs of a litter on the same diet. One was kept quiet while the other was exercised vigorously over a period of months. He found as much as a 50 per cent enlargement in the weight of the heart of the dog that was exercised over the heart of the dog that was not. A carefully controlled experiment was made by Steinhaus, Hoyt, and Rice (54) who studied the effects of running and swimming on the organ weights of growing dogs. These authors stated in their conclusions: "Exercise produced a true work hypertrophy in the heart which, under the condition of our experiments, was more marked in swimmers than in runners. The cardiac hypertrophy involves both ventricles with just a little excess in favor of the left heart. There is no indication of a comparable hypertrophy of the skeletal musculature of the limbs nor of the limb bones".

The most convincing evidence that increased work of the heart can cause hypertrophy is encountered at the necropsy table (65). Individuals with hypertension and disease of the aortic valve are found to have thickened left ventricles. The occurrence in such cases of right ventricular hypertrophy also can be ascribed to overwork as a result of the increase in pulmonary vascular pressure which accompanies congestion of the lungs. Mitral stenosis is usually accompanied by right ventricular hypertrophy and when the valvular lesion is of marked degree the left ventricle may be atrophic.

Certain clinical facts indicate that increased work per beat is more important than increased work per minute in causing cardiac hypertrophy. Thus, enlargement of the heart is usually less in patients with thyrotoxicosis than in those with complete heart block. That increase in metabolic rate can, however, cause cardiac enlargement is suggested by the observations of Boas and Landauer (8) who found that the frizzle fowl, which has a high metabolic rate, displayed cardiac hypertrophy.

Certain authors can find no evidence of hypertrophy as a result of increased work. Eyster (15, 17) was unable to find such evidence in either men or animals. He was unable to find hypertrophy in the hearts of athletes as measured by radiographic methods nor could he find it in the overactive hearts of neurocirculatory asthenia or hyperthyroidism. Dogs doing daily work in the treadmill and white rats running in revolving cages showed no evidence of cardiac enlargement as compared to controls.

One of the first studies on cardiac enlargement in athletes was made by Michel (40) on the undergraduates of the University of Cambridge. He used 1200 rowing men, 410 football players, and a few runners. Each individual was examined twice a day in morning and evening. A finding in practically all of the men studied was a gradual increase in the size of the heart as shown by a progressive recession of the left heart border away from the midsternal line by percussion.

Certain authors have taken issue with the theory of work hypertrophy of the heart and advanced theories of their own, mostly based on theories of changed nutrition or damaged myocardum. Albrecht (1) was the first to advance such a theory. He proposed his theory of a "pathological nutritive stimulus" of cardiac hypertrophy and dissented on theoretical grounds from the theory of work hypertrophy. Lewis and Drury (37) suggested that the enlargement found in aortic insufficiency and arteriovenous aneurysm might be due to deficient circulation dependent on the lower diastolic pressure which accompanies these conditions. However, the work of the heart is increased in both these conditions. Porter (45) reports that enlargement of the heart is seen in severe anemia but this can also be explained on the basis of work hypertrophy because the cardiac output is increased in severe anemia. Christian (10) was of the opinion that hypertrophy was a result of disease of the heart muscle. He did not think that there was sufficient evidence that physical work of any type could lead to hypertrophy and said hypertrophy was a potential evil which resulted from myocardial disease and that once it was started it continued in a vicious circle leading to greater and greater decrease in efficiency.

Harrison (65) tries to reconcile these two viewpoints. He thinks that the evidence in favor of work hypertrophy is too strong to be disregarded and thinks that one must accept the idea that ordinarily cardiac hypertrophy is due to overwork. He agrees with the experi-

ments of Kuelbs and others that exercise in itself, if severe enough, may lead to hypertrophy in young animals, but this is rarely the case in adult individuals. Such persons probably do not develop hypertrophy unless the work of the heart is increased continuously, for during sleep the physico-chemical processes which tend to produce hypertrophy may possibly be reversed. Such a conception would account for the fact that athletes and laborers do not often have hypertrophied hearts, whereas persons with valvular lesions do. Furthermore, if it is granted that hypertrophy of the individual cardiac muscle fiber is due to increased work of that fiber, then it would seem to make little difference whether such a greater strain is thrown on it because of a general strain on the heart as a whole, or because of disease of other fibers with consequent inability to carry their share of the load. Such a conception would therefore account for most of the cases of cardiac hypertrophy, because in nearly all of them there is either some obvious condition, such as a valve lesion or hypertension, causing overwork, or there is extensive disease of the muscle, and frequently both factors are present. There remain, however, a few cases which in life reveal no increased strain on the heart and at autopsy show no disease of the muscle. It seems likely that some of these cases have had hypertension in the past, although they may not have had it while under a physician's observation. In favor of such an assumption is the fact that one does occasionally see

patients who live for years with an elevated blood pressure and then for some unknown reason exhibit a normal blood pressure at a later stage of their disease (20).

It was formerly taught that hypertrophy was a compensatory and desirable process, whereas dilatation was a pathological manifestation and hence wholly undesirable. Experimental studies made in the last two or three decades seem to refute this idea entirely. The chief investigations were those made by Eyster and his co-workers (15, 16, 17). These investigations seem to indicate that dilatation precedes and probably causes hypertrophy. In experimental lesions of the aorta with hypertrophy Eyster had noticed that microscopically soon after production of the lesion the muscle showed a hydropic degeneration typical of reaction to injury which had disappeared by the time hypertrophy was complete leaving a picture of simple hypertrophy of an increase in size of individual fibers without any increase in fibrous tissue. The period of dilatation was not associated with a rise in venous pressure in the right auricle. If of a mechanical nature, the effect is, therefore, confined to a chamber affected directly by the lesion. In following this chain of reasoning through, Eyster came to the conclusion that the passing off of the dilatation is not due to any compensatory reaction in the circulation outside the heart and appeared to be the result of a cardiac muscle reaction of some nature. In production of a

regurgitation they found that there was a period of dilatation which lasted for 3-6 days. Following this the dilatation gradually receded and hypertrophy took its place (17). In order to prove that the hypertrophy was not on the basis of work but as a result of injury caused by stretching of the fibers they performed the experiment of putting rubber bands around the aortas of several dogs (15). At the end of 3-6 days these bands were removed in part of the dogs at a period before any evidence could be found for hypertrophy. The results showed that there was a hypertrophy of the hearts of the dogs in whom the bands were removed comparable to that found in the animals in which the bands were left in place. As a further proof Eyster (16) tried massive blood transfusions, increasing the blood volume by 75% to 100% in each dog. The results duplicated the previous work. Further transfusion given after the hypertrophy had become well established repeated the picture with a preliminary dilatation of the already hypertrophied muscle and in increase in the hypertrophy.

Increase in the mass of the heart disproportionate to the development of the skeletal musculature occurs in two general conditions (20):

1. When the work of a cardiac chamber is increased in an absolute sense. Examples are hypertension, valvular defects, and some forms of adhesive mediastino-pericarditis. The hypertrophy is confined strictly to the chambers which perform the increased

work. It used to be believed that when a chamber hypertrophied from increased work there might develop a hypertrophy of another chamber on the basis of hypertrophy of common muscle fibers or increased blood supply to both chambers, but this hypothesis has never been proved. It has been pretty well established that hypertrophy of the right chamber in hypertension does not occur until the left ventricle has become insufficient and pressure in the pulmonary circuit has been raised.

2. Hypertrophy may develop when the functional capacity of the myocardium is impaired, even though the work it is called upon to perform is not elevated. Nevertheless, although the absolute work of the heart is not augmented, there is a relative increase in the sense that the actual work performed approaches more closely to the maximum of which the heart is capable. Hypertrophy of this type is seen in some cases of rheumatic myocarditis with little endocardial or pericardial involvement.

Often increases in cardiac work and myocardial damage are combined in producing hypertrophy. Such is the case in valvular defects with accompanying rheumatic myocarditis and in hypertension with coronary artery disease.

Cardiac enlargement due almost entirely to hypertrophy is known as concentric hypertrophy, whereas when there is combined hypertrophy and dilatation it is known as eccentric hypertrophy. The distinction is not considered to be as important now as it

used to be. P. D. White (62) divides the etiology of enlargement of the heart into two factors, extrinsic and intrinsic. The intrinsic factors include valvular disease, myocardial infarction, and the true myocarditis of rheumatic fever. The extrinsic factors include hypertension, chronic thyrotoxicosis, and severe anemia.

The most common factors of heart strain which lead to enlargement of the heart are essential hypertension and valvular disease of rheumatic or syphilitic origin. Less common causes are true myocarditis (especially in rheumatic fever), cardiac infarction from severe coronary disease, thyrotoxicosis, chronic pulmonary disease, and congenital defects. Rare causes are arteriovenous aneurysms, severe anemia, beri beri, hypothyroidism, (myxedema), thoracic and spinal deformities, chronic pericarditis with external adhesions, and cardiac neoplasms. A few cases are of unknown cause. A few possible factors not yet clearly recognized as causes of cardiac enlargement are as follows: a severe infection, rheumatic or otherwise, may cause so much myocardial damage that the heart dilates and does not recover sufficiently to return to its normal size, whether the valves are damaged or not; excessively severe or prolonged physical strain, as in athletic sports, may rarely in the case of a sensitive heart produce some permanent cardiac enlargement; prolonged and excessive tachycardia in certain arrhythmias (especially auricular flutter and fibril-

lation) may be to blame in a minority of patients so afflicted but particularly in infants; a rare case of congenital idiopathic cardiac hypertrophy of lesser degree may survive to adolescence or adult life; a combination of two or more of these factors is most probable of all.

Cabot (66) has reported on the percentage of cases in certain cases coming to post-mortem out of 622 cases as follows:

Hypertension in 12 cases out of 12 (100%)
Leucemia in 7 cases out of 7 (100%)
Pernicious anemia in 12 dases out of 13 (92%)
Syphilitic valvular disease in 17 cases out of 20 (85%)
Nephritis (probably hypertensive) in 67 out of 78 (85%)
Rheumatic valvular disease in 69 out of 86 (80%)
Chronic exophthalmic goiter in 4 out of 6 (66%)
Chronic pericarditis in 16 out of 28 (57%)
General arteriosclerosis in 248 out of 513 (46%)
Myocarditis in 4 out of 10 (40%)
Acute endocarditis in 19 cases out of 54 (35%)
Chronic nondeforming endocarditis in 17 out of 56 (30%)
Hypoplastic aorta in 5 out of 15 (33%)
Acute pericarditis in 11 out of 80 (14%)

Cabot (66) also gave the average heart weight associated with the various lesions:

Syphilitic aortic regurgitation	613 gm.
Aortic stenosis (rheumatic)	580 gm.
All valve lesions except above	512 gm.
Chronic pericarditis	500 gm.
Arteriosclerosis and nephritis	487 gm.
Nephritis alone	453 gm.
Arteriosclerosis alone	429 gm.
Mitral stenosis	426 gm.
Hypertrophy and dilatation without other lesions	384 gm.

White (62) has classified the causes of cardiac enlargement

as follows:

A. Factors responsible for enlargement of the left ventricle.

1. Hypertrophy with little or no gross dilatation is caused by uncomplicated chronic hypertension most often and occasionally by aortic stenosis.

2. Dilatation with little or no hypertrophy is caused by serious acute myocarditis as in some cases of rheumatic fever and diphtheria, acute myocardial infarction or large size, acute high grade anemia, and severe trauma.

3. Hypertrophy and dilatation are caused by aortic regurgitation, mitral regurgitation, chronic high grade anemia, chronic adhesive pericarditis rarely, and most often by left ventricular failure which is complicating chronic hypertension, aortic stenosis, or myocardial infarction from acute coronary occlusion.

B. Factors responsible for enlargement of the right ventricle.

1. Hypertrophy alone is caused by failure of the left ventricle without failure of the right ventricle occasionally in mitral stenosis, and rarely in extensive pulmonary fibrosis, pulmonary endarteritis obliterans, or congenital pulmonary stenosis.

2. Dilatation is caused by serious acute myocarditis of

rheumatic or diphtheritic origin, acute high grade anemia, severe trauma, and acute massive obstruction in the pulmonary circulation from pulmonary embolism.

3. Hypertrophy and dilatation both occur in right ventricular failure complicating left ventricular failure most commonly, mitral stenosis occasionally, pulmonary stenosis occasionally, chronic cor pulmonale occasionally, tricuspid valve disease, chronic high grade anemia, chronic severe thyrotoxicosis, congenital idiopathic hypertrophy, and pulmonary regurgitation.

White thinks that several factors act simultaneously on both ventricles to cause acute dilatation and chronic dilatation and hypertrophy, but uncomplicated hypertrophy of either ventricle is independent of the other; when hypertrophy of the right ventricle follows hypertrophy of the left ventricle there is always an essential element of dilatation of the left ventricle as part of the sequence.

Enlargement of the left auricle is chiefly the result of dilatation and occurs most markedly with mitral valve disease but also often with failure of the left ventricle. Similar enlargement of the right auricle is chiefly due to dilatation and results from tricuspid valve disease or much more commonly from failure of the right ventricle.

The question of cardiac hypertrophy in relation to arterio-

sclerosis has been studied recently in animals and humans. Early work in the hemodynamics of arteriosclerosis were made by Fahr and his associates (18). They concluded as follows: "Provided that the diastolic diameter of the rigid artery is the same as that of the less rigid artery and the resistance of the larger arterial system is about 10-15% of the whole vascular resistance: 1. The energy consumption of the heart is not increased but is slightly decreased when the coefficient of volume elasticity of large arteries is greatly increased. 2. The extrinsic work of the left ventricle is not increased when the coefficient of volume elasticity is greatly increased, rather the extrinsic work is slightly decreased in severe arteriosclerosis of the large arteries because the mathematical mean pressure during systole remains nearly the same and the minimum volume decreases a little. 3. The flow through the coronary vessels decreases 20-25% after severe increase in the rigidity of the large arteries because the mathematical mean pressure falls about this much during diastole, the period during which most of the flow takes place in the coronary arteries. Under certain circumstances it may fall so far that the inherent contractile property of the heart is impaired."

Kahn (28) and others have made a study of the clinical relation between arteriosclerosis and hypertrophy. They found a definite relationship which suggests that sclerosis of the coronary arteries may play a part in the genesis of cardiac hypertrophy in patients with prolonged hypertension. Hurwitz and Friedberg (26) studied the

relationship of heart size to cholesterol content in experimental atheromatosis of the rabbit. They found that demonstrable sclerosis of the coronary arteries with resultant myocardial fibrosis was produced in rabbits by the feeding of diets high in cholesterol. A comparison of heart weights in these compared to control series showed a distinct increase in size and weight of the heart with an increase in the percentage of total body weight by the heart. There was also a definite increase in the cholesterol content of the heart which was not sufficient to account for the increase in size. According to the studies of Fahr this increase could not be due to sclerosis of the aorta or other large arteries.

One type of cardiac enlargement which is not a true hypertrophy or dilatation is that which occurs in Von Gierke's glycogen storage disease. Lindsay (38) has discussed this disease and reviewed the literature. The disease is defined as a disturbance of glycogen metabolism which appears in early infancy and is characterized by an abnormal deposit of glycogen in the liver, kidney, heart and other organs, which become so enlarged with glycogen that they assume an enormous size. The peculiarity of this stored glycogen is that it becomes fixed and cannot be mobilized to any extent by natural means. The etiology is quite obscure. A study of the amylase in the liver and blood has not had too uniform results. Although amylase is present it seems to be unable to

liberate glucose from the glycogen. An interesting observation on autopsy is that liver glycogen fails to disappear within a few hours after death as should normally occur. Bischoff (7) and Putschar (46) first reported examples of the cardiomegalic form of the disease. The heart may be five or six times normal size. The true nature of the disease is seldom recognized before death and often they are considered to be cases of congenital idiopathic hypertrophy.

Congenital idiopathic hypertrophy of the heart is a condition which in its true form is being seen less often all the time as we become more familiar with other causes for cardiac hypertrophy.

Kugel and Stoloff (33) have reviewed the literature and summarized the findings on this subject. According to definition the term congenital idiopathic hypertrophy of the heart presupposes that the enlargement of this organ is due to pure hypertrophy of the muscle bundles with no recognized etiology. In view of the fact that they found evidence of myocardial disease in all their own cases, they reviewed the literature and classified all cases into three categories.

1. So called congenital idiopathic hypertrophy of the heart (true form). In this group no etiologic agent was discovered and a thorough microscopic examination showed pure hypertrophy of the myocardium with no demonstrable pathologic lesions. It is probable that with increasing knowledge of the various etiologic factors

causing dilatation and hypertrophy of the hearts in children, this group may entirely disappear.

2. Secondary form of hypertrophy (pseudo - idiopathic group). On microscopic examination this group showed myocardial damage such as degeneration, fibrosis, and round-cell infiltration. Cases with anemias, congenital anomalies, intrapulmonic disease, a primary vascular disease, which have been wrongly called idiopathic hypertrophy, have been analyzed under this group for the sake of a complete review.

3. So called idiopathic hypertrophy of the heart (questionable group). In this group a complete examination was not recorded, and hence no classification could be made. The cause of the dilatation and hypertrophy is still obscure. Many theories have been advanced but none proved. Some believe that there is a "congenital weakness" of the germ plasm or a familial tendency.

Other authors feel that this group bears relationship to so-called status thymicolymphaticus. A relationship between the presence of enlarged lymph nodes and the enlargement of the heart has been hypothesized by many writers, particularly in the German literature. Several of these writers have noted a relationship between myocardial round cell infiltration and thymicolymphaticus and called the former a manifestation of the latter. However, others in compiling statistics on autopsies on children find no

constant relationship between myocardial round cell infiltration and status thymicolymphaticus and conclude that this is only a chance finding. Vischer (60) has done much work along this line in disproving these theories.

A few writers have suggested the possibility of a relationship between hypertension in the parent and idiopathic hypertrophy of the heart in the child. Several cases have been brought forward in support of this theory although the evidence seems inconclusive.

Infection is a factor which should be taken into account. Usually the antecedent history is indefinite. In some cases, however, there is a history of severe pertussis or poliomyelitis. Toxins from infection have been implicated by a few writers. Rheumatic fever is excluded by careful pathologic examination.

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