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Mechanism of cardiac dilation and hypertrophy

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The Mechanism
Of Cardiac Dilatation and Hypertrophy

By

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I Introduction

Why did I choose to write on cardiac dilatation and hypertrophy as the subject of this thesis? The actual composition of a paper is in many ways less disconcerting and time consuming than the choice of a topic itself. I endeavored to make a choice which would result (selfishly) in the maximal benefit to me, and at the same time a choice of a contemporary controversial topic. The cardiovascular system has always been a source of intrigue to me, and were I to choose a subspeciality of internal medicine, cardiology would be my first choice. As to why cardiac dilatation and hypertrophy specifically- these two cardiac mechanisms are the commonest and the most important evidences of cardiac disease, yet the basis of their conception is as yet in an unsettled state. Despite this fact, the research pertinent to cardiac enlargement today is indeed minimal, certainly not adequate; and of the research which has taken place, chiefly since the time of Starling and his coworkers, a comprehensive and analytical review and criticism are wanting. Therefore, I have chosen this topic (in no particular order) :

First, because of the benefit I hoped to derive from it;

Second, because of an intense interest in the

cardiovascular system.

Third, because the problem of dilatation and hypertrophy is surrounded by ambiguity and conflict.

Fourth, because, I found no evidence of a critical survey on this topic.

The method in which this paper has been divided is arbitrary; its intent is clarity of thought without disunion of thought. Each and every category is integrally interrealted despite the divisions of this paper.

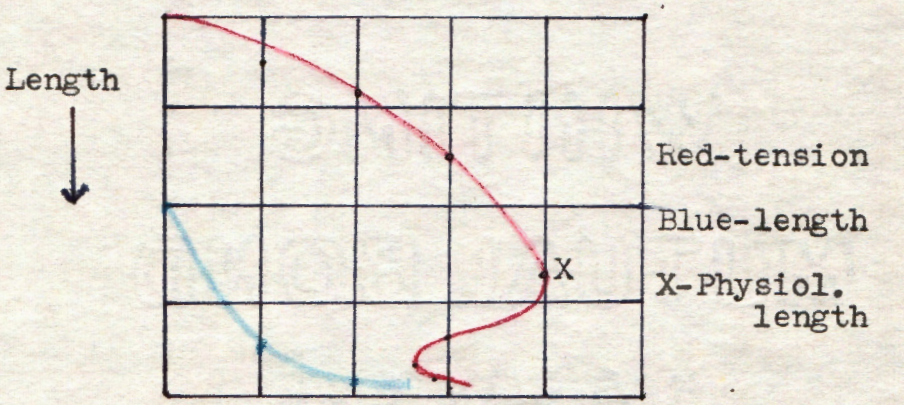
II Basic Physiology

The experimentation leading to the present day knowledge of cardiac enlargement had its roots in the works of Starling and his coworkers. For a complete comprehension of their works and the works of subsequent investigators, certain concepts must be understood.

Dilatation consists of a stretching of the individual fibers of the heart wall. Hypertrophy consists of the increase in size of the individual muscle fibers, and, it is thought, not an increase in their number, although isolated examples of active proliferation of the heart have been reported in children and infants (MacMahon, 1937).

We know that muscle contracts more forcibly if it is loaded by weight before excitation. The weight stretches the fibers and exerts a tension upon them. If the muscle contracts isometrically, the developed tension is found to be proportional to the length of the muscle before excitation. The latter is called the initial length of the muscle. The tension exerted by the load on the fibers just prior to contraction is called the initial tension. The tension developed when the muscle contracts is referred to as the developed tension. The length of a muscle correspond-

ing to that which it possesses in its natural position in the body is spoken of as the physiological length. When we weight a resting muscle (skeletal), there is little change in initial tension until the muscle is stretched beyond its physiological length. However, up to this point, the developed tension actually increases with each increment of initial length, but beyond it the developed tension diminishes with increasing initial length. Yet, only when the muscle is stretched beyond its physiological length is there any marked increase in initial tension. We may therefore conclude that the power of contraction of skeletal muscle is dependent upon initial length and not upon a stimulating effect of initial tension on the muscle fibers (Best and Taylor, 1944). In diagram "A" below, these relationships for skeletal muscle are clearly seen.

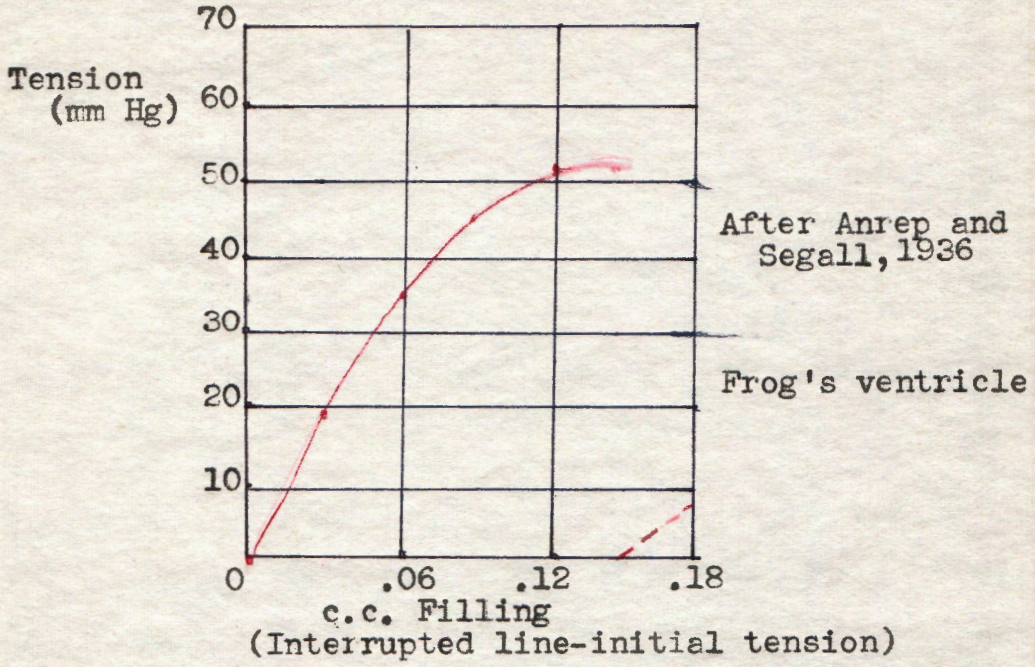


(After Starling, 1914)

Diagram "A"

The relation of initial length and developed tension in skeletal muscle may also be applied to heart muscle. When simultaneous records of diastolic volume and intraventricular pressures(initial length and developed tensions) are obtained and charted, a graph closely simulating Diagram "A" is the final result. These early experiments of Starling(1914) serve as the basis for his Law of the Heart, namely, that the energy set free at each contraction of the heart is a simple function of the length of the fibers composing its muscular walls. The greater energy liberation associated with the increased initial length has been attributed to the increased chemically active surface resulting from dilatation. Anrep and Segall(1936) have also confirmed these early conclusions; these investigators found that when the isolated frog's ventricle contracted isometrically, the contractile force up to a point increased proportionately with the filling of the ventricle; the maximal tension developed when the ventricle was filled to two-thirds of its maximal capacity. Filling beyond this two-thirds caused a rise in the initial tension and a reduction in the developed tension. In other words, the process of dilatation would seem to be compensatory until the physiological length is reached. These relationships, including

initial tension, are shown below in diagram "B".



Katz(1934), working with the turtle heart, showed that when he dissociated the effects of these two factors upon developed tension, that is, when the initial tension was varied but initial length kept constant or the converse or when both were varied in the same or opposite directions, the result always indicated that initial length was the factor which determined the force of contraction. Thus, the relation between initial length, initial tension, and developed tension seems well established.

In all of the above experiments, whether the condition of the heart was good or bad, the relationship

between oxygen consumption and diastolic volume was the same; this means that for a given piece of work the poorly nourished heart uses more oxygen since it dilates more than does a heart in good condition, or the proportion of total energy expenditure which appears as mechanical work is lower when the heart muscle departs from its prime physiological state. This constant ratio of oxygen consumption to diastolic volume was clearly shown by Starling and Visscher in 1927.

The reserve of the heart depends on or resides in the extensibility of the muscle fibers, within the physiological limits. We may define the cardiac reserve as the difference between the energy at rest and the maximal energy that the heart is capable of exerting. It is apparent that the nearer the fiber during diastole approaches its physiological length, the greater will be the encroachment on the heart reserve.

Henderson and Barringer (1913) have shown that the cardiac output and venous pressure parallel each other up to a venous pressure of about 50mm. of water, but above this level each further rise in venous pressure is accompanied by a smaller rise in cardiac output. Their experiments, performed on dogs, have not been

III Dilatation

Pathology

Dilatation is the stretching of the heart wall due to the weakening or atonic state of the muscle or response to physical demand for increased output of blood per beat. If the process is acute, it may go back to normal; if it is chronic, there may be permanent stretching; however, the usual course is for dilatation to persist or progress.

Grossly, the dilated heart is enlarged and usually of globular form. In secondary forms, the muscle is soft, flabby, and dark red. In primary forms, the muscle shows various forms of degenerations, anemia, or necrosis. The ventricles show a particular feature of dilatation in the flattening of the columnae carnae and papillary muscles.

Microscopically, the muscle fibers are narrowed because of attenuation. There may be no notable degenerative changes in the muscle or there may be cloudy swelling, fatty degeneration, or necrosis. The principle effects of dilatation are fall in the mean systolic pressure and in pulse pressure associated with passive hyperemia of the viscera, with all the changes incident to passive hyperemia, both functional and

morphological.. The passive hyperemia has as its important anatomical sequelae not only stagnation of the blood in the vessels but also edema, pigmentation, haemorrhage, parenchymatous degeneration, catarrhal in flammation, and fibrosis (Karsner, 1943). Thesemay all give symptoms and signs referable to the region.

Dilatation is said to be myogenic when the myocardium itself is the site of the anemia or some degenerative pathological process. Dilatation is said to be tonogenic when it is secondary to increased work on a normal myocardium. The dilatation of a hypertrophied heart may apparently be tonogenic when the limit of hypertrophy is reached, for in certain cases, no extrinsic myocardial disease is found to explain the dilatation. The dilatation usually effects the chamber which has the greatest load; in myogenic dilatation, when all four are usually affected, the right atrium is the most severely affected. In some instances, the dilatation may be tonogenic and myogenic so that all chambers are involved but one in particular.

Anatomy

A fact of great interest is that dilatation does not from the start involve the whole ventricle, but evolves in characteristic fashion. This knowledge is

largely due to the careful measurements, internal and external dimensions, carried out by Kirch (1921). His studies were concerned chiefly with the inflow and outflow tracts of the ventricles. The inflow tract of the left ventricle extends from the mitral orifice to the apex; the outflow tracts extend from the apices to the pulmonary and aortic orifices. Studying the left ventricle in hypertension and aortic valve disease and the right ventricle in conditions of increased pulmonic resistance (mitral disease and emphysema), Kirch found that the dilatation of a ventricle in these conditions always begins in the outflow tract which is both elongated and broadened, and he also found that the dilatation began in the terminal portion of the outflow tract under the pulmonary conus and aortic rings. The dilatation then progresses against the direction of blood flow to the apex; then the inflow tracts are involved so that the dilatation finally reaches the auriculo-ventricular rings. In over ten years investigation, he found many instances when the outflow tract was involved and the inflow tract normal, but never the reverse. The dilatation from coronary disease or myocarditis seems to involve all parts of theventricle equally.

Kirch also found that in tonogenous dilatation the principle change was elongation of the outflow and then the inflow tracts, while in myogenous, broadening predominates over elongation. He observed elongation of over 20% above normal with only minimal broadening in the apical region; since tonogenous dilatation is usually the basis on which the heart dilates in arterial hypertension, these observations furnish an explanation for the well known fact that in compensated hypertension of any years standing, roentgenology reveals little or no increase in the transverse diameter of the heart, but an often marked elongation of the left ventricle down into the shadow of the diaphragm. However, when failure results in such a case as a result of coronary atherosclerosis, the resulting myogenous dilatation is marked by a broadening of the organ. Kirch also believes that this tonogenous dilatation is the predominant reason why the heart immediately after exercise does not reveal the enlargement that would be expected. The independent behavior of the inflow and outflow tracts as regards dilatation and hypertrophy is evidently an expression of functional difference between the two portions of the ventricle.

The extent of dilatation may be enormous; the highest degree of dilatation is seen in the auricles.

With the thinning of the walls of the dilated chamber goes an attenuation and elongation of the papillary muscles and chorda tendinae as well as flattening of the trabeculae of the ventricles and the pectinate muscles of the auricular appendages; in extreme instances these latter muscles may be hardly discernible. An important accompaniment of well marked dilatation maybe enlargement of the auriculo-ventricular orifices, usually more marked in the tricuspid than the mitral valve. While the arterial rings may be involved too, these are much more closely related to the condition of the aorta and pulmonary artery. With high grade dilatation and hypertrophy of the left ventricle, the interventricular septum protrudes into the right ventricle, giving the latter a crescentic appearance in cross section and a diminished capacity; as will be shown later, it is this protrusion which is responsible for involvement of the right side of the heart in some cases of hypertension. A dilated chamber may compress any of the surrounding structures depending upon the direction of enlargement-lungs, bronchi, diaphragm, esophagus, and so forth.

The Mechanism of Dilatation

The conditions leading to cardiac dilatation may be divided into two categories, although there are a few exponents for the third category to bementioned below. In the first category we have that dilatation which results from anincreased load on a healthy cardiac muscle; this is called physiologic, active, or tonogenic dilatation(Moritz, 1908). We would include under this heading the increased work known to result from hypertension and valvular disorders. The experiments of Starling (1914) on his heart-lung preparation have gone unquestioned in this respect. In his experiments with a well controlled closed system, the elevation of arterial pressure and production of valvular lesions with resultant tonogenic dilatation corroborate the impressions noted at autopsy. Thus, the conlusions arrived at from research and postmortem examination are compatible with the material mentioned under Basic Physiology and to be reemphasized in this thesis, that is, a greater load on a healthy muscle increases the energy ouput, encroaching upon the maximal energy, decreasing the cardiac reserve, producing dilatation, with a resultant increased in developed tension paralleling the degree of dilatation, and serving as a temporary compensatory mechanism.

In the second category of conditions leading to cardiac dilatation is that dilatation due to impaired contractility of a damaged myocardium, which may have only a normal amount of work placed upon it. This dilatation is called pathological, passive or myogenic dilatation (Moritz, 1908). In this case, too, the cardiac reserve is decreased, but not due to increased load on a healthy muscle, but due to same load on a diseased muscle; this then would result in a broadening of the cardiac silhouette, as opposed to primary elongation with dilatation in a healthy muscle. Included in this category are such myocardial inflammations as dipheritic and rheumatic, as well as coronary disease.

In the third category is that type of dilatation which is though to result from decreased diastolic tone dependent on aberrations of the nervous control (Hering, 1921). This theory has never been amply proven or confirmed and at the most would only account for a very small percentage of the total cases of cardiac dilatation.

Common to the main categories above is a decrease in the cardiac reserve, whether it be tonogenic or myogenic in nature; if this basic idea is kept in mind, the processes of dilatation and hypertrophy will be considerably clarified. The diagrams which follow with their

accompanying explanations should go far towards removing the ambiguity concerning dilatation and hypertrophy.

Diagram C

Normal Person

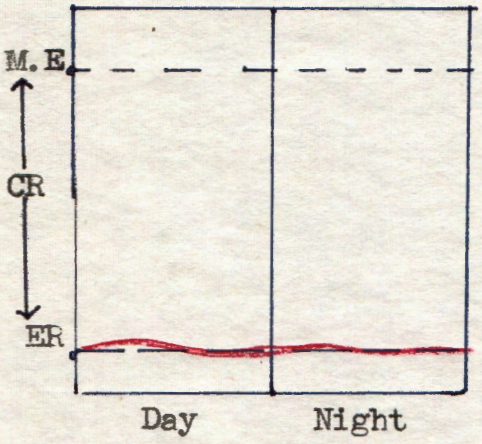


Diagram D

Normal Person with strenuous exercise

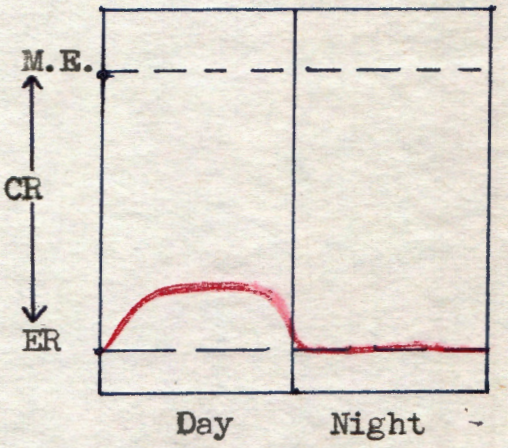


Diagram E

Tonogenic etiology

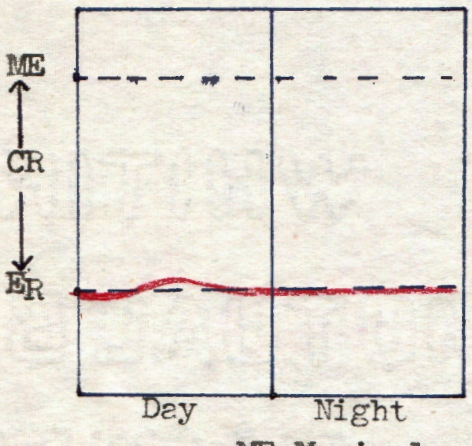
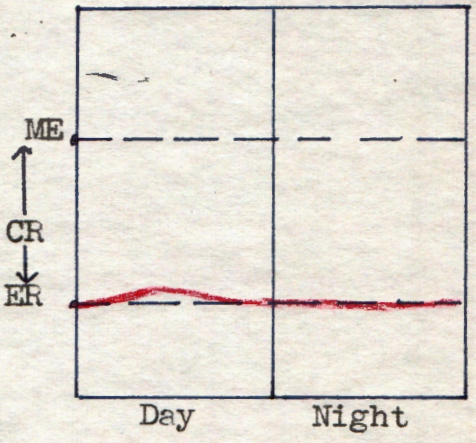


Diagram F

Myogenic dilatation



Key

ME-Maximal energy
CR-Cardiac reserve
ER- Energy at rest
Red line- cardiac energy(kinetic)

(Original diagrams by R. B. Kalmansohn)

The vertical divisions of energy in the above diagrams

are not correct absolutely or relatively, but they do serve the purpose for which they were intended. Diagram "C" depicts a normal individual with normal daily physical activities. It can be seen that there is little deviation from the base line of energy at rest, that when deviation does take place, it takes place chiefly during the day. As a result, the cardiac reserve is maximal for that person.

Diagram "D" depicts a normal person(from a cardiovascular standpoint) subject to strenuous exercise. It will be seen that there is a reduction in the cardiac reserve during the day, when physical activity is at its maximum, but that this cardiac reserve is almost completely restored to normal during the period of inactivity or sleep.

Diagram "E" depicts a person with a normal myocardium, but an excess load on that myocardium. As a result, the cardiac reserve is decreased, due to an increased energy utilization at physical rest, though the maximal energy that that heart is able to attain is still the same. It is important to note the difference in this graph as opposed to graph "C". Whereas in "C", there is a return to a normal energy utilization at night and an opportunity to reverse the physicochemical processes responsible for dilatation,

in "D" no such opportunity exists, forthe factors responsible for the increased cardiac load, hypertension and valvular disease, persisted constantly.

Diagram "F" depicts an individual with an abnormal myocardium. The cardiac reserve in this case is diminished becauseofthe damage to the myocardium resulting in a diminution in the energy that the heart is capable of attaining, or a diminution in the maximal energy. The cardiac reserve is also decreased because working inefficiently as it must it requires a greater energy expenditure for the same amount of work. It can be seen that in both tonogenic and myogenic dilatation, there is a decrease in the cardiac reserve, although the mechanisms responsible for this decrease are dissimilar. From the above diagrams, we may conclude that dilatation is brought about by a decrease in the cardiac reserve, that this is only temporary unless the basic mechanism is continually exerting its effect.

We thus see that there are two major categories of physiological and pathological phenomena which may lead to dilatation. It was not necessary to attempt to prove these in this paper, as th e evidence in their favor is overwhelming and their validity is recognized by all authorities in the field. However, what was

within the scope of this paper was an attempt to evaluate these two categories and determine the common denominator of the two; in other words, what one mechanism common to the two could help explain the transition from a normal to a dilated heart. As stated above, upon the basis of known physiology, a decrease in cardiac reserve would appear to be the element common to both. A diagrammatic clarification has been attempted.

The physiological groundwork for the discussion of dilatationas a compensatory mechanism has already been set forth under Basic Physiology and a more comprehensive analysis will follow in Part V, where the compensatory nature of dilatation will be correlated with the other cardiac compensatory mechanisms. From the point of view of compensation, we cannot draw a distinction between tonogenic and myogenic dilatation, as dilatation in the pathological muscle is accompanied by an increased systolic contraction. Socin(1914) injured the myocardium with chloroform and Sulzer (1924) used alcohol for the same purpose; they found that although the degree of compensation was less than with tonogenic dilatation, the dilatation served the same purpose here that it did in the healthy muscle. A century ago the clinician regarded dilatation as a passive aneurysm in contrast to hypertrophy as an active aneurysm; they thought it analagous to the stretching of an old rubber, a manifestation of impaired contractility, and deleterious to the function of the myocardium. Rosenbach (1879 was the first to oppose this view; he felt that the dilated ventricle was a compensatory process increasing the capacity for work; he spoke of this as hyperdiastole. The other

physiologists have since confirmed this theory. The basic experiments are those of Starling (1914) on the mammalian heart lung preparation. Starling's law of the heart and the research leading to its statement have now become classics in cardiology. To amplify what has already been said under Basic Physiology, Starling found that elevated arterial pressure or greater venous inflow increases the work of the heart, the accomodation to the greater load involving dilatation. The steps in these experiments have been as follows: when the resistance of the aorta has been increased, the heart fails to empty during the first beats as completely as before; the result is that the residual blood in the left ventricle at the end of systole rises progressively with each of these beats; inas much as the venous inflow during diastole remains the same, the presystolic volume increases. However, the output also rises until it equals the inflow. Thus a readjustment has taken place with the following new conditions: 1 systolic and presystolic volumes of the heart are greater; 2 pressure in the pulmonary veins and left auricle is increased due to greater resistance in the left ventricle;3 a greater percentage of the outflow of the left ventricle passes thru the coronary circulation-this is a useful adaptation but may

be important in the genesis of coronary atherosclerosis in hypertension. The same line of reasoning was proven for increases in venous pressure; so that the heart accomodates to increased arterial resistance or venous return by increasing the energy of individual contractions, not by increasing the rate. As stated previously, Starling felt that it is the greater length of the fibers that resulted in the greater energy liberated in the following systole. On the other hand, Straub (1919) felt that the presystolic tension and not the fiber length is the important mechanism; he also felt that contrary to Patterson, Piper and Starling changes in intraventricular pressure could never be dissociated from changes in systolic discharge; he concluded that initial length cannot be regarded as the only constant factor in determining systolic discharge.

Gesell (1925) also feels that both an increase in initial length and tension of the fibers are of importance in increasing the strength of ventricular contraction. However, in view of the experiments of Starling and his coworkers and repeated by countless investigators, we are safe in concluding that developed tension depends chiefly upon initial length, that, therefore, when the cardiac reserve is decreased, the diastolic volume of the heart increases, that is the heart dilates,

and acts as a compensatory mechanism as the resultant increase in developed tension is proportional to the degree of dilatation until the physiological length is reached. It is noteworthy that Wiggers and Katz and Gesell at no time attempt to evaluate the respective influences of initial tension and initial length on developed tension-they only claim that both of these factors influence the degree of developed tension. Starling and his coworkers in reality don't disagree with this viewpoint; they merely went further and attempted to show that though they both may exert their effect, initial tension is by far the most instrumental in the determination of developed tension. There is no evidence to the contrary.

In considering the role of dilatation in cardiac compensation, it is well to note the role of the pericardium in acute dilatation. The pericardium acts as a safety valve against sudden failure due to acute dilatation. While the pericardium can dilate enormously as a result of gradual pressure, it is practically inextensible to sudden stretching and thus prevents a quick failure. This has been shown in the experiments of Van Liere (1927,1930). Kuno (1915) has found with the heart lung preparation that with the removal of the pericardium, an increase in work is dangerous to the

organ and haemorrhage into the myocardium occurs, also that a higher venous pressure is necessary before a given amount of work is performed. Animals with pericardium removed show a greater cardiac dilatation in severe degrees of anoxemia, especially in monkeys. The protective action of the pericardium as regards the prevention of acute cardiac dilatation probably never comes into play in the normal animal, except possibly in instances of extreme stress on the heart.

A practical example of the compensatory nature of dilatation is given by Tinsley Harrison(1936). He states: "When a boxer flexes his arm thus extending his triceps for a short distance, he can strike his opponent with a certain degree of force; if he flexes the biceps more thus extending his triceps more, the force of contraction is greater; the immediate response to increase in work, therefore, is dilatation." Now Starling (1914) has translated the above example in skeletal muscle to the conditions existing in the heart. According to Starling, " if a man starts to run, his muscular movements pump more blood into the heart, so increasing venous filling, while the central nervous system by contracting the arteries of the abdomen, increases peripheral resistance, raises arterial pressure

and forces all available blood through the active muscles. As a result the heart is overfilled during diastole and impeded from emptying during systole; its volume both in systole and diastole enlarges progressively until by lengthening of the fibers so much more of the active surfaces are brought into play within the fibers that the energy of contraction becomes sufficient to drive on into the aorta during each systole the largely increased volume of blood enetring the heart. In these circumstances the heart is dilated; but in a healthy individual, this is only temporary; a rise of blood pressure produces a more abundant flow of blood through vessels supplying the wall of the heart and this increased supply of oxygen and foodstuffs improves the physiological condition of each muscle fiber, so that at each contraction it is able to concentrate a larger number of active molecules on each unit of active surface; the tone, that is the ffitness of the heart, is therefore improved and the heart gradually returns to normal volume, even though doing increased work. It is only when the heart is fatigued or diseased that this secondary improvement fails to appear; then, the dilatation may become permanent." In thus explaining how dilatation acts as a compensation, Starling also shows how exercise produces only a temporary

dilatation: the erroneous conclusion should not be drawn from the above quotation that tonogenic dilatation is not permanent, for Starling himself has shown the contrary to be true, so that even in healthy muscle if the extra load is of sufficient duration even good tone is not enough to restore the muscle to normal. Patterson, Piper, and Starling (1914) used the term tone (as used above) to mean physical fitness of the muscle fibers, this being the outcome of their nutritive condition and being manifested by their ability to develop energy. Tone, therefore, means greater force of contraction during systole and not lessened relaxation during diastole. It follows that for any given increase in the length of the fibers, the contractile power of a well nourished heart will increase more than that of a heart whose nutrition is impaired, and that if the contractile power of the two hearts be the same, the ill-nourished one must dilate more: this explains the dilatation of the heart during coronary insufficiency when the poorly nourished heart must dilate to perform the work of a normal heart.

In summary, Starling's law of the heart, although it may be subject to certain modifications, goes far towards elucidating the compensatory nature of dilatation: as a result of additional strain on healthy

muscle or same strain on pathological muscle, the heart fibers dilate; this dilatation serves as a compensatory mechanism increasing the force of systolic discharge; at the same time, however, the cardiac reserve is more encroached upon, and this may lead to a vicious cycle ending in cardiac failure. The dilatation may be only temporary if the duration of the underlying factor is not long and if the tone of the muscle fibers is good. We, therefore, may eliminate a great deal of confusion in regard to cardiac dilatation if we will just remember that dilatation takes place as a result of a decreased cardiac reserve and serves as a compensatory mechanism, and that the duration of the dilatation depends upon the duration of the underlying factor as well as the heart tone.

IV Hypertrophy

Pathology

Hypertrophy is an increase in the size of the individual muscle fibers. The chief criterion for hypertrophy is increase in weight; the thickness of the walls cannot be depended upon for diagnosis, because dilatation may thin the walls of the hypertrophic heart to a measurement less than normal, and stoppage in systole may result in a wall thicker than normal. Arbitrarily, a heart of over 600 grams is spoken of as cor bovinum, usually caused by aortic regurgitation.

Grossly, the muscle of a hypertrophied heart is firm and of more reddish tinge than normal. Fibrosis, a common accompaniment, increases firmness and degenerations decrease firmness. The papillary muscles and columnae carnae are likely to be round and large. The endocardium and valves especially of the left side are somewhat thickened and opaque because of fibrosis. The coronary arteries grow somewhat in length and increase some in diameter in consonance with the growth of the heart. Two forms of hypertrophy are described: concentric and eccentric; in the former, the walls are thickened and chambers reduced in size; due to postmortem rigor; the latter

shows increased weight and increased size of the chambers. The enlargement of the chambers may well be a part of the hypertrophy in the sense that the factors that induce the hypertrophy cause a certain amount of dilatation. Nevertheless, great hypertrophy may exist without any increase in the transverse diameter of the heart in the living patient by x-ray study.

Microscopically, the fibers increase in width and length. They approach uniformity of length and width; e- this increase affects chiefly those fibers that were originally of smaller size. The nuclei are characterized by an increase in transverse diameter and squaring of the ends. Shipley and Wearn (1937) found that as the fibers grow the capillary supply per unit of volume does not keep pace and is relatively reduced, thus limiting the progress of the hypertrophy and ulti ately leading to cardiac failure. Roberts and Wearn (1941) have lent further credence to this theory in showing that there is an apparent failure of the blood supply to keep up with the hypertrophy, as there is only one capillary per muscle fiber regardless of the size of the muscle fiber. MacMahon (1937) has reported finding in infants and children active proliferation of the heart with mitoses evident after severe injury; ap - parently this only takes place in the younger age

group, as hyperplasia has never been demonstrated in adults.

It is thought that hypertrophy never actually decreases the cavity of a chamber, except indirectly as impinging on the interventricular septum of the right ventricle by the left ventricle. According to Fishberg (1927), we cannot consider the male heart hypertrophied until it exceeds 400 grams or the female until it exceeds 350 grams. Since the time of Laennec, it has been said that the heart of a normal person should be equal to the fist of the cadaver at autopsy; today we know this to be too rough of an estimation as the factors of body weight and basic habitus must be considered. Aschoff and Tawara (1906) have found that the fibers of the conduction system do not participate in the cardiac hypertrophy.

Mechanisms of Hypertrophy

Corvisart (1812) was the first to emphasize that the mass of the myocardium was the function of the work it performs, with the work being considered as the reaction to the functional fitness of the myocardium. It has often been shown that in animals the relative heart size shows a direct correlation with the physical activity of the particular species(Herrmann, 1926). Parrot (1921) has observed the biggest hearts in those birds that fly the most and sing the most. The human investigations have been conducted chiefly by Muller

and Hirsch. Muller (1883) has shown that the heart weight tends to increase with the body weight, although not in direct proportion, so as the heart weight increases, the ratio of heart weight to body weight decreases. Although Muller's findings were pertinent, Hirsch (1899) completed the picture by showing a fairly accurate correlation between heart weight and skeletal musculature.

Increase in the mass of the muscle disproportionate to the skeletal musculature occurs under two general conditions. First, hypertrophy may occur when the work of the cardiac chamber is increased in an absolute sense. It was formerly thought that when strain was placed on a heart, the chamber exposed to the greatest strain hypertrophied, and the others also underwent sympathetic hypertrophy; today, however, we must discard this theory for there is voluminous evidence by postmortem examinations to prove that the site of the greatest strain suffered the greatest hypertrophy; for example, in hypertension, the left ventricle may hypertrophy but the right ventricle does not undergo hypertrophy unless decompensation ensues. This modern viewpoint was first corroborated by Chanutin and Barksdale (1933). There are four general conditions which

will lead to hypertrophy of a healthy muscle: an increase of the heart as a result of increased physical exertion, protracted, and with increase in stroke volume; increase to resistance of expulsion of blood (hypertension and valvular disease); when in addition to expelling the blood, the heart mustdrag with it other structures in systole, for example, Pick's disease; when the volume of blood expelled per stroke is increased, as in valvular insufficiency, Grave's disease, and anemia. Because of the association of each of the above factors with hypertrophy, and the artificial production of hypertrophy with the above etiological factors (Starling, 1914; Eyster, Meeks, and Hodges 1927; Fishberg, 1931; and others), we may assume that their relation to hypertrophy is well established. In each of the above factors the work of the heart has been increased, that is there is work hypertrophy; conflicting viewpointswill be presented in the following pages as regards work hypertrophy, although as mentioned above this now seems well established.

The second general condition conducive to hypertrophy is an impairment of the functional capacity of the muscle thought the work the heart is called upon to perform is the same. In this case there is a rel-

ative increase in the work of the heart in the sense that the work performed more nearly approaches the maximum that the heart is capable of performing at that time. Arteriosclerotic heart disease and rheumatic myocarditis are the notable examples in this category. In many cases an increase in work is combined with the impairment of function to produce the hypertrophy, for example rheumatic myocarditis with valvular lesions.

In each of the above two categories, there is a decrease in the cardiac reserve. Also, it would seem that hypertrophy seems to be on the basis of preexisting dilatation; there is little evidence to the contrary. Rosenbach (1878) showed that an artificially produced aortic regurgitation results in dilatation and then hypertrophy. Eyster, Meeks, and Hodges(1927) showed that hypertrophy always exists on the basis of antecedent dilatation. Further, in the case of acute glomerulonephritis of a few months duration with hypertension, hypertrophy is invariably found with the dilatation. However, there are certain hearts at autopsy that show only hypertrophy; it would be logical to suppose that the dilatation had proceeded to a very small degree before hypertrophy took place-Fishberg's observations (1931) in glomerulonephritis and aortic regurgitation seem to confirm this.

Following is a bipartisan discussion of work hypertrophy with the negative viewpoint presented first. The importance of the principles underlying work hypertrophy cannot be overemphasized in a discussion of the mechanisms of hypertrophy.

According to Best and Taylor (1943), increased work is not the only or even the major factor in the production of hypertrophy; the extra burden thrown upon theheart by the valvular lesion is often not sufficient to encroach upon the reserve power of the heart to any extent, and the grade of hypertrophy is often out of proportion to the amount of work that the heart is called upon to perform. Arterial hypertension, if it is developed gradually, may cause little hypertrophy though the work of the heart is increased 40%. Lewis (1914) states that in a large proportion of cases of mitral stenosis there is as great hypertrophy of the left ventricle as of the right, and in aortic disease the right as well as the left ventricle may be increased in bulk; he also states that hypertrophy occurs in coronary disease where there is no evidence of increased work. As mentioned above, Eyster and associates have thrown some light on this problem; they have artificially produced aortic stenosis and regurgitation

with resulting dilatation, reaching a height on the sixth day; if the causes of the lesions are then removed, the dilatation disappears and the diastolic volume of the heart returns to normal, but gradually hypertrophy occurs reaching a height at the eighteenth day, apparently a reaction of injury brought about by the sudden dilatation. In coronary disease, the fibers are forced to lengthen unduly in order to liberate the energy required; so increase in fiber length apparently leads to overgrowth; this mechanism is unknown, but Starling and Visscher (1927) suggest elevation of the metabolism of the muscle as a possible explanation.

To bring out one of the most conflicting viewpoints, one may quote Christian (1928): " To say that the heart fails by reason of fatigue following sustained overwork is no real explanation, for very often we have no evidence of overwork to cause the fatigue or to cause the hypertrophy preceding the fatigue. Are we really sure that the heart can undergo a work hypertrophy? there is no satisfactory evidence that physical work of any kind leads to work hypertrophy, while there are numerous observations on long distance runners and the like which point to the nonoccurrence of a work hypertrophy of the heart. We seem forced to conclude that

hypertrophy with incident dilatation is a potential evil, that in some way as soon as the heart becomes much enlarged, it is placed ata disadvantage and fails to do work placed upon it with its previous efficiency, that once started it is a vicious cycle, less efficient work causing further hypertrophy, leading to still further decrease in the efficiency."

Many investigatorys have pointed out that one occasionally sees a heart weighing 500 grams or more and showing extensive fibrosis without valvular disease or pericardial adhesions in a patient whose blood pressure was followed in life for long periods of time and was never elevated.

To summ arize the arguments against work hypertrophy: 1 Cases have been reported of hypertrophy without antecedent valvular disease or hypertension.

2 There is an absence of hypertrophy in athletes or those subject to great physical work.

3 There are many cases of hypertrophy in chambers not subject to the greatest strain.

T. Harrison (1936) takes issue with the viewpoint that the chamber subject to the greatest work is not necessarily the chamber that shows the greatest hypertrophy. From his experience with postmortem examina-

tions, he has noted that those patients who have a pronounced hypertension or aortic insufficiency but die of causes other than heart disease, usually present at autopsy moderate to severe hypertrophy and some dilatation of the left ventricle only, the right ventricle showing little or no enlargement; similarly, in mitral stenosis without regurgitation, the right ventricle is dilated and hypertrophied, the left ventricle may even be atrophic. If, however, there is mitral stenosis with regurgitation, there may be enlargement of the left ventricle too. Instances such as these indicate that unilateral hypertrophy and dilatation not only may occur but usually do occur. However, in isolated cases of hypertension signs of right ventricular failure appear before the left; this is thought to be due to the pushing of the septum to the right and causing pressure in the right ventricle, or because the circular fibers traverse both ventricles and might on occasion involve both chambers, therefore. From this discussion we may conclude that dilatation, hypertrophy and failure involve primarily only one ventricle to any extent, but finally they affect the other ventricle, probably to a minimal extent in the beginning. However, once the process in the originally disordered chamber has progressed sufficiently to produce fatigue with its

consequent rise in pressure back of the filling chamber, then the second ventricle becomes subject to an increased load and from this point on it may fail as well. Thus in the early stages, we are likely to have failure of one side of the heart only, whereas in the later stages, the heart does fail as a whole; the great wealth of information and logic are in favor of this viewpoint. In the cases cited by Best and Taylor and Lewis of mitral stenosis causing dilatation and hypertrophy of both ventricles equally, some regurgitation was probably present; in the case of hypertension causing hypertrophy of both ventricles, the above explanation probably holds. These cases are in the vast minority however; all of this gives considerable credence to the theory that work is important in the production of cardiac enlargement, thru the mechanism of decreased cardiac reserve.

Now we must agree with Best and Taylor that increased work is not the only cause of hypertrophy; we brought that out clearly in the beginning of this discussion; however, we cannot agree with the statement that it is of little importance in subsequent hypertrophy.

Knubs (1906) reported an increase of 50% in the weight of the heart of young dogs who were exercised

as compared to the organs of control animals who were kept quiet. Steinhaus, Hoyt, and Rice (1932) studied the effects of running and swimming on the organ weights of growing dogs and concluded that exercise produced a true work hypertrophy, affecting both sides of the heart, but more on the left, with no comparable condition existing in the skeletal musculature. E. Koch (1921) noted hypertrophy of the left ventricle of dogs and cats in whom experimental hypertension had been produced by cutting the aortic and carotid sinus nerves. T. Harrison has concluded on the basis of the above experiments and chiefly on the basis of his postmortem findings that work does cause hypertrophy. Some men have stated that hyoertrophy is the result of disease of the myocardium; there is no real conflict here, particularly if we make the general statement that decreased cardiac reserve of a protracted nature tends toward hypertrophy; so we may again reiterate normal work on a diseased myocardium or continual excess work on normal myocardium causes decreased cardiac reserve and predisposes to dilatation and hypertrophy.

Now it is true that hypertrophy and dilatation are potential evils in the long range point of view, but

they occur in hearts whose reserve is decreased and act as compensatory measures, which though they may ultimately lead to failure because of the underlying etiology, prolong the date of failure longer than if they had not occurred. It would appear from the work of Kulbs and others that exercise in itself if severe enough may lead to hypertrophy in young animals, but this, we must admit is rarely the case in adult humans. Such persons probably do not develop hypertrophy because the work of the heart is not increased continuously; during sleep the physicochemical processes, whatever they may be, which tend to produce hypertrophy may possibly be reversed (See diagrams C-F). Such a conception would account for the fact according to Harrison (1936) that laborers and athletes do not often have hypertrophied hearts, while those with valvular disease do. Mitchell at Cambridge (1909) showed that the heart size of undergraduates underwent a gradual increase after a few years of physical training; however, this paralleled the increase in skeletal musculature, so that the ratio of heart weight to body weight shows no change or a very moderate one. During recent years the view has gained ground and is now widely held that in the healthy person the diastolic volume of the

heart does not become larger during exercise, and the necesary corollary to this view is that the output per beat is not increased during exercise. This opinion rests upon evidence that at first sight appears unimpeachable, namely that by means of orthodiograph or Roentgen rays before and after exercise direct measeurements are made. These experiments with minor variations were performed by Moritz in 1902, Hoffman in 1902, and de la Camp in 1903 and 1904. They found that in normal persons exercise carried to the point of exhaustion produced no dilatation of the heart and sometimes its volume was actually diminished; with the object of minimizing the interval between cessation of exercise and observation of the size of the heart, Nicolai and Zuntz in 1914 arranged the apparatus so that the picture could be taken almost during the exercise; they showed an average increase in the transverse diameter of the heart of 4 millimeters and a definite decrease within three seconds after cessation of exercise; this has been confirmed by Krogh and Lindhard (1913, 1914) who actually took the pictures at the height of the exercise and not even in a rest period near the height of exercise.

It may be concluded that although the orthodiograph records have demonstrated the rapidity with which the

heart decreases in size after exercise and have served incidentally to show the fallacy of percussion and palpation to show the absolute size of the heart, these records, with the possible exception of those by Nicolai and Zuntz, throw little light on the condition of the heart during exercise, and do not in the least controvert the evidence of Krogh and Lindhard that the output of the heart may be doubled or more than doubled during exercise, that the heart does dilate and since hypertrophy is the next step after dilatation we may assume that were this increased work to be present day and night, hypertrophy would supervene. Inall of these cases of work hypertrophy, if it is granted that hypertrophy of the individual muscle fibers is due to increased work on the fiber, then it would seem to make little difference whether the greater strain is thrown upon it as a result of general strain on the heart as a whole or because of disease of the other fibers with consequent inability to carry their share of the load.

In summary of the relation of physical work to hypertrophy, we may conclude:

1 This relation cannot be used as an argument against work hypertrophy as this work is not continual, day and night, as in hypertension, for example.

2 However, when x-rays are taken at the time of exercise, there is consistent evidence of dilatation. Therefore, if the exercise were to be continuous, we may reasonably assume that hypertrophy would result, as dilatation is the precursor of hypertrophy.

3 Men subject to increased exercise and who have been followed for years actually showed some increase in muscle thickness, though this is proportional to the increase in skeletal musculature.

So, in summarizing the arguments for work hypertrophy: 1 The chamber subject to the greatest strain does show the greatest hypertrophy; any deviation from this depends on common circular fibers or encroachment on the interventricular septum or failure to diagnose certain valvular diseases.

2 The relation of exercise to hypertrophy is an unfair comparison, because of its intermittent nature; however, even if we use this as an example, the presence of the precursor of hypertrophy, that is dilatation, can usually be demonstrated by good technique.

The presence of work hypertrophy is based, therefore, on incontrovertible evidence.

Hypertrophy as a Compensatory Mechanism

This section too will be further elaborated on in part VI, where its correlation with the other compensatory mechanisms will be discussed.

Very little quantitative data is available on the functional value of cardiac hypertrophy. Artfficially produced experimental lesions have proved that a higher pressure was attained after cardiac hypertrophy than after the defect. We know that when skeletal muscle increases in cross section, it becomes more powerful and there is every reason to believe that hypertrophy of heart muscle is an analogous process; hypertrophy of a chamber of the heart results in a more powerful systole from a given diastolic filling of the heart than was the case before the hypertrophy. We have also seen that hypertrophy seems to be a sequel to dilatation so we may assume that hypertrophy is an adaptation to the altered conditions resulting from dilatation. Fishberg (1937) has attempted to explain the role of hypertrophy on a more scientific basis; he has reasoned that since the volume of a sphere is proportional to the cube of the radius, as the sphere increases in size, equal increments of volume correspond to smaller and smaller increases in radius, so that the larger a cardiac chamber, the less its radius must be dimin-

ished to expel the same amount of blood, so the fibers of the dilated heart contract a shorter distance in maintaining the stroke volume than those of the normal organ; but the strength of the contraction must be correspondingly greater because the tension on the muscle fibers increases in direct proportion to the radius. Dilatation thus leads to the necessity of a shorter and more powerful contraction of the muscle fibers; hypertrophy seems to be the adaptation to these altered conditions. Although this theory of Fishberg explains fairly well the purpose served by hypertrophy, it does nothing towards elucidatingthe cause for the hypertrophy or the mechanism by which it is brought about. Hypertrophy is a disadvantage in that the greater thickness impedes the metabolic exchanges between the muscle fibers and the capillaries and predisposes to inadequate nutrition and cardiac failure. Hasenfeld and Romberg (1897) attempted to show by their experiments that hypertrophy interfered with the ability of the heart to increase its diastolic dilatation, which would diminish it s reserve force (although this may be a disadvantage at a future date, it is offset by the fact that the very act of hypertrophy is a compensatory device for a heart whose reserve has been diminished). For the compensation to

be complete in hypertrophy, the reserve force would have to be as great as it was before the presence of the circulatory defect for which the hypertrophy compensates; exercise tolerance tests reveal that this is rarely true.

We may summarize the section on hypertrophy in the following manner:

1 Hypertrophy is characterized by an increase in thickness of the fibers without an increase in the number of cells.

2 Hypertrophy is associated with a diminished cardiac reserve-increased work on a healthy myocardium or same work on diseased myocardium.

3 Hypertrophy predominates in chronic processes, whereas dilatation predominates in acute affairs.

4 Hypertrophy is invariably associated with a pre-existing dilatation.

5 Hypertrophy occurs in a heart which is not functioning to its optimum as a compensatory mechanism, at the same time prolonging the life of the individual while leading to his or her ultimate death by decreasing the maximal potential cardiac energy or cardiac reserve.

Cardiac Compensatory Mechanisms

Comparison and Correlation

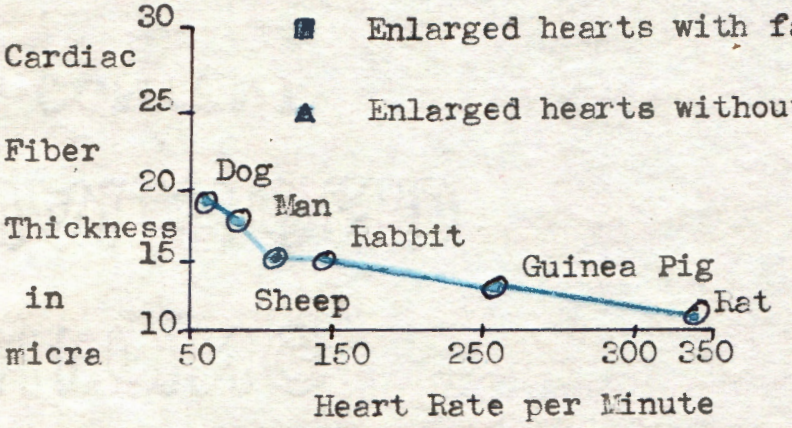
Patients with congestive heart failure often exhibit an increase in heart rate brought about by the Bainbridge reflex, that is, elevated venous pressure causes acceleration of the heart in the presence of normal nervous pathways. The advantage of such a mechanism is that it enables the heart to pump a given amount of blood per minute with lesser degree of dilatation, and thus to lower the venous pressure. This beneficial effect is more than offset by the harmful effects, as the greater the rate of the heart becomes, the more energy must be wasted in opening the semilunar valves, energy which is never used for the accomplishment of mechanical work, that is propelling blood. So, it can be seen that a given amount of work can be more efficiently accomplished at slower rates; this has been confirmed by Evans and Matsuoka (1915) and Starling and Visscher (1927) who found that for a given minute volume and peripheral resistance, the oxygen consumed by the heart per unit of time was greater at rapid than at slow rates. The harmful effects of fast rates can be seen clinically with healthy individuals with hearts that are apparently normal in every respect, but

develop congestive heart failure after long bouts of paroxysmal auricular tachycardia; following the restoration of normal rates, there is a rapid disappearance of the congestive failure; such cases prove quite definitely that rates of over 150 or 200 for a few hours will cause cardiac fatigue in a healthy heart muscle. There seems to be two factors which are instrumental in this fatigue: 1 Increased oxygen consumption necessitated by the faster rate, not only because the heart is actually busier, but also because so much anergy is wasted on opening the semilunars; 2 Diminution of blood to the left ventricle; the coronary flow to this chamber is intermittent and takes place mainly during diastole, for during systole the pressure in the left ventricle is greater than in the aorta and effectively prevents coronary flow and capillary diffusion of blood. Now we know that the duration of systole is relatively independent of the rate, so a decrease in the duration of the cardiac cycle inevitable at fast rates, takes place at the expense of the duration of diastole, so not only is more oxygen needed at faster rates, but there is an actual diminution in the effective blood flow to the heart.

The factors mentioned above, though they are important in explaining the detrimental effects of

tachycardia, leave much to be desired. Small animals such as the rat and the guinea pig live out natural spans of life with heart rates of 200 to 300 or more; it is obvious that if the heart muscle is not to become fatigued, the duration of diastole must be sufficiently long to allow the heart to recover completely between beats, and it is therefore evident that in animals that normally haverapid hearts the recovery process can take place more quickly or completely between beats than in animals who are unable to tolerate these rapid rates. Themost important factor in the recovery phase is oxygenation. Harrison, Ashman, and Larsen (1931) made observations on the relationship between the heart rates and the thickness of the cardiac muscle fibers in various animals; electrocardiographs were taken of the unanesthetized animals, trained to remain quiet while the records were taken; the TS interval was taken as the duration of diastole. From the animals of the various species block of tissues were taken and average cardiac muscle thickness ascertained; the same was done with humans with normal hearts, enlarged hearts with congestive failure, and enlarged hearts without congestive failure. The results appear in Diagram G

below. The heart rates of various animals are plotted against the average thickness of their muscle fibers. It can be seen that these two variables in the normal human are in agreement with those in animals whereas the fiber thickness in enlarged human hearts is much greater in proportion to the pulse rate than in normal man or animals.



(Harrison, Ashman, Larsen; 1931)

These observations seem to indicate that there is a disproportion between heart rate and fiber thickness in humans with large hearts, and if it may be assumed that the heart rates of normal animals were optimal, then we may conclude that in the enlarged human heart the optimal rate would fall considerably below the normal individual's rate; or by the graph, the

the optimal rate would probably fall between 30 and 45 for the enlarged hearts.

According to A.V. Hill (1929), the rate of diffusion of oxygen thru tissue varies directly as the square of the distance diffused. Since the recovery time of the heart is more nearly related to the duration of diastole than to the duration of the entire cycle, the fiber thickness may be properly charted against the duration of diastole. When this is done, all points tend to follow a straight line, that is as the rates of the animals increase, the thickness of the fibers decreases; or as the thickness increases, the duration of diastole increases in direct proportion. So it seems likely that in the human heart, too, the time required for oxygen to diffuse varies as the square of the distance thru which it diffuses. The average length of diastole in normal hearts was .56 seconds, which we may assume is optimal. Now as A.V. Hill has calculated and as has been corroborated by Harrison et al (1936), the duration of diastole varies as the square of the oxygen diffusion distance for optimal conditions; if we assume that systole is .3 seconds in duration , then according to the above statement, duration of diastole for normal person is to the muscle thickness squared of the normal person as the

duration of diastole for the enlarged heart is to the square of the muscle fiber of the large heart; when these values are substituted, we find that the optimal diastole for large hearts with mean fiber thickness of 24.5 micra would be 1.26 seconds, as opposed to the .42 that is usually found, and that the optimal rates for these enlarged hearts would be 38(this is for the patient with enlarged heart without congestive failure). For thepatient with enlargement and failure, the duration of diastole would be 2.3 seconds instead of .43 and the optimal rate would be 23. These calculations tell us of the optimal duration of diastole and a rough estimate of the best rate for hearts of given enlargement. Therefore, we can see that the consideration of any given compensatory mechanism in itself is fallacious; hypertrophy is a compensatory device, but as indicated above unless the rate decreases with the hypertrophy, the ability of hypertrophy to alleviate the cardiac condition and the ability of the heart to compensate is indeed minimal, and hypertrophy with accelerated heart rate is not compensatory at all.

It is probably safe to assume that clinical manifestations of fatigue will develop in the normal adult human heart if it beats indefinitely at more than

150 beats per minute; at such rates the duration of systole is slightly diminished (.2 seconds) and the duration of diastole is .2 seconds; using the above ratio again, if normal heart of 16.2 micra thickness(fiber) fatigues with a .2 second diastole, then an enlarged heart of 24.5 micra fiber thickness will fatigue at a .45 second diastole or rate of 80; also an enlarged heart with congestive failure wil fatigue at .76 second diastole corresponding to a rate of 57 beats per minute. On theoretical grounds, therefore, we could assume that the patient with moderate thickness or hypertrophy would develop decompensation if not at rest, while more advanced hypertrophy would cause decompensation even at rest. Now, Krogh (1929) has done some rather elaborate computation on this aspect of cardiac nutrition and has arrived at the same results. His calculations have involved the assumption that normally the amount of fluid between capillary and muscle fiber is negligible, and whereas this may be the case in the normal individual, it is probably not true in hearts of congestive failure where edema is present-so actually the recovery rate should be longer and the rate slower than the computed optimums; also the calculations have been based upon the premise that diffusion takes place at the onset of diastole-this, too,

is probably not entirely true as at the end of systole the capillaries are completely empty and a certain time will elapse before they will again be filled.

The obvious conclusion of the above experimentation and computation is that a fast heart is a chemically inefficient heart, that in hypertrophied muscle fibers the heart rate should be slower than normal if the proper nutritional and metabolic status is to be maintained.

Slight to moderate degrees of hypertrophy are often seen at autopsy in individuals who were symptom free in life, while marked hypertrophy is never found without a history of protracted decompensation. This is explained by the fact that a slight increase in the fiber thickness is accompanied by a relatively great increment in the fiber strength with a negligible rise in the tension necessary to supply oxygen; but as the hypertrophy proceeds, the oxygen tension requirements increase more rapidly, so that at the 60 micra fiber thickness, the oxygen requirement is greater than in air; the average muscle fiber is 15 micra and it appears that up until 25 micra, hypertrophy is beneficial; beyond this point the mechanical advantage is far offset by the netabolic disadvantage.

The application of the above calculations to biological phenomena, though they may not be statistically correct is sound from the standpoint of the general conclusions to be drawn. We have explained how a powerful looking hypertrophic muscle may not carry on an efficient circulation. Hypertrophy is a compensatory mechanism which carries with it the disadvantage that even when slight it predisposes to fatigue due to insufficient oxygenation of the thicker fibers at rates which could be tolerated by a normal heart, and which if they be extreme may lead to failure even at slower than normal heart rates.

From the above, we may conclude that the bradycardia is beneficial to patients with enlarged hearts; this is borne out by clinical experience, for according to Harrison (1936), patients are much less likely to manifest congestive heart failure at rates of 50 or 60 than at rates of 70 or 80; the prognosis is better with complete heart block than with incomplete heart block. So any benefit to be derived from a fast heart in a cardiac patient is far outweighed by the disadvantage. Dilatation, the second compensatory mechanism, offers a chemical advantage because of the greater surface and consequent increased opportunity for chemical interchange between the blood and fibers; also, according to Starling's law, the developed tension increases

and accomodates to the greater load, but the latter is accomplished by a great expenditure of energy because of the greater distance the fibers must now contract; by some unknown means, this disproportion between length and diameter of muscle fibers leads to hypertrophy, so the original relation of length to diameter is restored. There is, therefore, a mechanical advantage from hypertrophy in that we get a more powerful contraction without as great an expenditure of energy; however, conditions are not the same as in the normal heart because whereas the mass of the tissue to be nourished has increased as the square of the radius of the fiber, the surfaces of the fibers through which the nutritive processes must take place has only increased as the first power of the radius; so that, hypertrophy while gaining a mechanical advantage suffers a chemical disadvantage and thus dilates further under conditions of strain and ultimately leads to heart failure.

Before summarizing this aspect of the paper, reference to the following diagrams may further elucidate the interrelationship between these cardiac compensatory mechanisms.

Diagram H

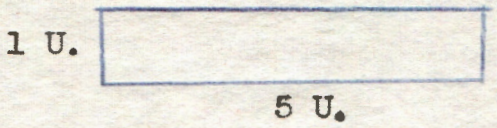


Diagram I

Diagram J

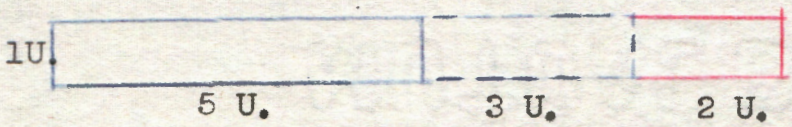


Diagram K

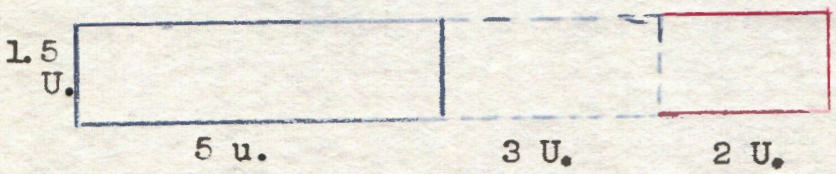
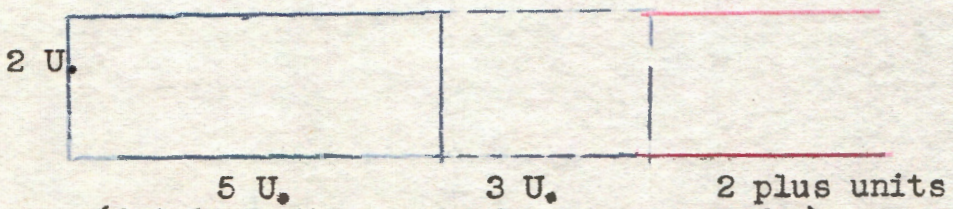


Diagram L



(Original diagrams by R. B. Kalmansohn)

In the above diagrams, I have arbitrarily taken one unit as a cardiac fiber width and five units as cardiac fiber length. Diagram H represents the fiber of an average individual with a normal heart; here the cardiac reserve is at its maximum. Now as the cardiac reserve decreases, either on a tonogenic or myogenic basis, the fiber lengthens and as it does so the developed tension increases according to Starling's Law. The heart has thus accomodated to the altered conditions, but at the expense of the cardiac reserve, as each dilatation brings the heart closer to its maximum reserve. Diagram I represents the new condition of the fiber with a lengthening to eight units, which we shall arbitrarily say is the physiological length.

As we have already proven, lengthening beyond this physiological length results in a decreased developed tension, because the disadvantages of dilatation, mechanical in nature, then become dominant. Now if the cardiac reserve is more diminished and dilatation to the physiological length is not adequate, the fiber stretches beyond the physiological length as shown in Diagram J, where the red box indicates dilatation greater than the physiological length. Now each increases in length is accompanied by a decrease in developed

tension. Thus dilatation is no longer compensatory.

Now, the second compensatory mechanism comes into play-hypertrophy. This results in an increase in the fiber width, as shown in Diagram K. At this new width the developed tension present at eight units length or at the physiological length will again be restored; in other words, the physiological length only holds true for agiven width, so that at this new width we will say the physiological length is ten units.

However, any further depletion of cardiac reserve will result in further hypertrophy and dilatation in an already hypertrophied and dilated muscle fiber which has approached the maximal energy it is capable of exerting with each compensatory mechanism, and now because of the mechanical and chemical disadvantages inherent in these compensatory devices, the limit of compensation is reached and the heart fails. It must be emphasized that each compensatory mechanism laid the groundwork for ultimate failure because of its inherent weaknesses. This end stage is shown in Diagram L, where the hypertrophy is no longer compensatory and where the dilatation is beyond the physiological length, even for a hypertrophied fiber.

In summary of Section V, we may say that the heart has three lines of defense in the event of depletion of cardiac reserve; these are accelerated heart rate, dilatation and hypertrophy. They each possess advantages and disadvantages one of which usually outweighs the other. As compensatory mechanisms, the y may prolong the life of the individual; however, they never restore the metabolic and mechanical relationships present in the normal individual.

1 Tachycardia: Advantage-this mechanism reduces the venous pressure. Disadvantage- there is a waste of energy in opening the semilunars, and the coronary flow is decreased as diastole is decreased.

2 Dilatation: Advantage: the developed tension is increased; there is an increased surface for nutritional diffusion. Disadvantage: there is a great amount of energy for performance of given amount of work as increased area is involved in the contraction.

3 Hypertrophy: Advantage- less energy is required to perform a given amount of work as there is a more powerful contraction of a shorter fiber.

Disadvantage-there is a relative decrease in the nutritional diffusing surface; the blood supply does not parallel the hypertrophy; usually accompanied by tachycardia with shorter diastole.

VI Summary

This paper has dealt with the mechanisms of cardiac dilatation and hypertrophy, including the physiological basis of our present knowledge, the conditions leading to these mechanisms, their role in compensation, and their interdependency.

Starling's Law(1914) has probably been the most noteworthy physiological contribution to this topic. The constant relationship between oxygen consumption and diastolic volume has helped to explain the inherent weakness of a large heart.

Dilatation has been defined as a stretching of the heart wall. The gross and microscopic pathological pictures have been presented along with an explanation of tonogenic and myogenic dilatation. Kirch's theory of initial involvement of the outflow tracts has been included; the characteristic elongation found with tonogenous dilatation and widening found with myogenous dilatation have explained those cases of protracted hypertension without evidence of widening of the cardiac silhouette.

The mechanisms of dilatation have been related to a tonogenous and myogenous basis, and possibly a decrease in diastolic tone, the important alteration in

the heart being a decrease in cardiac reserve. There are included graphs showing the relation of cardiac reserve in normal persons, normal persons with strenuous exercise, persons with tonogenic etiology and with myogenic etiology. For the production of dilatation there must be a decrease in the cardiac reserve, and this decrease must be continual if the dilatation is to be permanent.

The role of the pericardium in acute dilatation has been evaluated. The term heart tone has been defined, and its importance in increasing systolic contraction has been emphasized.

Hypertrophy has been defined as an increase in the size of the muscle fibers. The pathological picture in hypertrophy has been presented. It has been shown that hypertrophy results from an absolute increase in the amount of work or an impairment of the myocardium-in either case, there is a decrease in the cardiac reserve.

An extensive discussion of work hypertrophy has been included with arguments pro and con and a fair analysis of the arguments. I t has been shown that exercise is not fair criterion of work hypertrophy, that the chamber subject to the greatest strain actually suffers the greatest hypertrophy.

As a compensatory mechanism, hypertrophy results in a more powerful systole; according to Fishberg's calculations, based on sound reasoning, a large increase in volume is accompanied by a small increase in radius, so comparatively the dilated fiber contracts less to accomplish the same amount of work, which necessitates a stronger contraction , this being furnished by subsequent hypertrophy. Hypertrophy, however, has a relatively decreased surface for nutrition and has a poor relation of capillary to muscle fiber.

We have seen that it is folly to dissociate the compensatory mechanisms from each other or from the patient as a whole. Tachycardia is associated with a decrease in venous pressure, but decreased coronary flow and waste of energy in opening the semilunars; hypertrophy is associated with increased force of systolic discharge, but a chemical disadvantage as well as a poor vascularization. It has been shown that the optimal rates for moderately enlarged hearts with and without failure, respectively, are 23 and 38 beats per minute, and that fatigue will ensue at 58 and 80 beats per minute.; therefore, although hypertrophy may be compensatory per se, if it associated with tachycardia it may lose its compensatory properties.

In general, we may say that dilatation is a cardiac compensatory mechanism until it has reached the physiological length; similarly, we may say that hypertrophy is a compensatory mechanism until the relative surface of diffusion is too small, which in man approximates a width of 25 micra for the individual cardiac fiber; also we may say that tachycardia is really never compensatory in that the disadvantages outweight the advantages.

We have visualized by diagrams the sequence of dilatation to the physiological length and beyond, compensation with hypertrophy, and terminal dilatation and hypertrophy.

The following information pertinent to these mechanisms is as yet unknown:

1 The exact means that a decreased cardiac reserve results in dilatation;

2 The means by which hypertrophy is engrafted upon dilatation.

3 The usefullness of tachycardia.

4 The exact role of heart tone with compensation.

VII Conclusions

1 Dilatation may be tonogenic or myogenic depending on whether there is increased work on normal muscle or same work on weakened muscle.

2 Hypertrophy, too, following dilatation, may be tonogenic or myogenic in nature.

3 The physiological condition which must be met before either of these two processes supervene is a decrease in the cardiac reserve.

4 The presence of dilatation and hypertrophy with a bradycardia would produce maximal compensation.

5 Dilatation compensates by increasing the area of contact and diffusion; hypertrophy compensates by increasing the power of contraction; tachycarida is not really compensatory.

6 Dilatation and hypertrophy have inherent defects which delimit their usefulness and predispose to cardiac failure.

7 Many questions relative to dilatation and hypertrophy remain unanswered.

So we are forced to conclude that if the cardiac reserve is diminished to any degree for a sufficient length of time to ellicit the production of permanent

dilatation and hypertrophy, although there may be temporary compensation, the detrimental aspect inherent in these mechanisms will inevitably lead to cardiac exhaustion and failure.

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