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# Vibration As A Cause Of Arterial Dilation

Derek Richard Boughner

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VIBRATION AS A CAUSE  
OF  
ARTERIAL DILATATION


by

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A thesis submitted in partial fulfillment  
of the requirements for the degree of  
DOCTOR OF PHILOSOPHY

FACULTY OF GRADUATE STUDIES  
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ABSTRACT

Arteries dilate distal to a stenosis because of altered elastic properties of the vessel wall. Vibration, induced by intravascular turbulence, may produce these changes.

Such vibration can occur without a stenosis, due to a high flow rate alone. The flow murmur from the pulmonary arteries of patients with atrial septal defect (A.S.D.) should produce similar dilatation. The elastic properties of 25 human pulmonary arteries (mean age 9.7 years) were measured *in vivo*. Radiopaque dye injections were recorded and vessel radii measured at maximum systolic and minimum diastolic pressures. Two points, which lay on the initial slope of the elastic diagram, were calculated and a line through them to zero wall tension gave resting radius ( $R_0$ ). Plotting wall tension versus strain ( $R/R_0$ ), the pulmonary artery elastance at normal pressures was calculated for normals ( $2.15 \times 10^4$  dynes/cm), for poststenotic dilatation ( $1.00 \times 10^4$  dynes/cm) and for A.S.D. ( $0.89 \times 10^4$  dynes/cm). Pulmonary arteries in A.S.D. and pulmonary stenosis showed similar distensibility ( $p > 0.1$ ) which was significantly greater than normal ( $p < 0.01$ ). A case of Marfan's syndrome also showed an increased distensibility.

Vibration, heard as a murmur, may cause this dilatation. Twenty-four human external iliac arteries mounted and distended at 100 mm Hg pressure were exposed to individual low frequency vibrations found in murmurs. Young arteries, 16-44 years, dilated to the lowest

frequencies (< 100 Hz); arteries age 45-60 years dilated to the middle frequency range (100-200 Hz); arteries 61-77 years dilated to the high frequencies (> 200 Hz). One 68 year old common carotid artery also dilated when exposed to vibration above 200 Hz. The elastic diagrams, after vibration, showed a decrease in the initial slope with no change in the final slope. This corresponds to post-stenotic dilatation *in vivo* and is likely due to disruption of inter-lamellar elastin nets.

A frequency analysis of seven murmurs of aortic stenosis, recorded from patients 33-64 years, showed the frequencies used experimentally are associated with aortic dilatation *in vivo*. One patient with few frequency components predicted to produce dilatation in his age group had little poststenotic dilatation while the other six had dilatation and corresponding frequency components for their age group.

Therefore intravascular turbulence, whether due to a stenosis or other causes, produces vibration of an artery and results in dilatation by altering the elastic properties of the wall. Frequencies that produce such dilatation *in vitro* are found *in vivo* in murmurs accompanied by poststenotic dilatation. Age alters the frequency required to produce these changes.

CHAPTER I



## INTRODUCTION

Poststenotic dilatation results from altered arterial wall elastic properties in the area of turbulence distal to a stenosis (143,144,145,146). Although Roach<sup>(143,144,146)</sup> suggested that turbulence produced these changes she did not show how they occurred, nor did she consider whether turbulence from other sources could have the same results.

This thesis will attempt to show that intravascular turbulence from any source can produce similar vessel changes and that, under certain conditions, these changes can be measured *in vivo*. It will also attempt to demonstrate that wall vibration, such as that induced by turbulence, can, in fact, produce the "structural fatigue" postulated by numerous authors<sup>(66,80,125,144,146,158)</sup> and that some frequencies are more effective than others in producing these changes. Finally, I will attempt to show that the frequency spectrum of murmurs is variable and can only be accurately assessed by recordings from within the vessel. The thorax attenuates many frequencies<sup>(50, 181)</sup> and recordings from the chest surface give an inaccurate indication of the true frequency content of the murmur.

Although I have attributed the source of a murmur to intravascular turbulence, this is not the only theory available for sound production by a stenosis. In all, four theories have been proposed.

Hugh and Fox<sup>(83)</sup> feel there is insufficient energy in turbulence to produce sound and have suggested that cavitation or bubble formation occurs in the blood within a stenosis. Collapse



of these bubbles distal to a stenosis then could provide the energy for vibration. They calculated that the increase in the kinetic energy of blood sufficiently decreases the potential energy to a level within the stenosis where dissolved gases come out of solution. This would require a negative pressure of about eight atmospheres (73,145), unless the blood is supersaturated with a gas. Harvey<sup>(73)</sup>, therefore, doubts that turbulence could produce bubble formation in the body. In addition cavitation should produce sounds of about 3000 Hz<sup>(145)</sup> which is a much higher frequency than is found in murmurs<sup>(32,115,174)</sup>.

Bruns<sup>(20)</sup> proposed that murmurs could be explained by the 'Aeolian harp theory'. He suggested that vortices are shed from the obstruction and move downstream. This presupposes the presence of a rigid edge followed by channel widening to give vortex shedding. The resulting murmur would have a single frequency equal to the frequency of shedding (e.g., "dove coo" murmur of calcific aortic stenosis). This mechanism cannot explain the broad band of frequencies contained in an ordinary murmur<sup>(32,115,174)</sup>, nor can it explain murmurs produced by incompetent valves.

Kjellberg *et al*<sup>(91)</sup> suggested that the sound originates from a jet of blood striking the vessel wall distal to a stenosis. This would require an asymmetric stenosis or a bend in the vessel to place the arterial wall in front of this high velocity stream. Areas of localized pathology ("jet lesions") have occasionally been found to support this theory. However, poststenotic dilatation is a diffuse process and not localized to such lesions which actually

seem to be associated more with dissecting aneurysms<sup>(122)</sup>.

Finally, the most popular theory is the one which I accept. Turbulence develops distal to a stenosis. This breakdown of streamline flow results in random motion of the fluid as demonstrated in glass models by Burton and others<sup>(26,86)</sup> who claim it is associated with murmur production<sup>(29)</sup>. McDonald<sup>(111,112)</sup> has noted that sound occurs when eddies occur, and that the two are probably causally related. Meisner and Rushmer<sup>(124,125)</sup> demonstrated that distensible plastic tubes vibrate if turbulent flow is present within them, and Foreman and Durie<sup>(52)</sup> examined the frequency distribution of turbulent flow beyond models of stenosed dog iliac arteries. Yellin<sup>(180)</sup> concluded that turbulent pressure fluctuations were 'transduced' into sounds and that most of the energy to vibrate the wall, in models, originated at the point of maximum fluid vibration. Roach<sup>(144,145)</sup> observed that areas of intravascular turbulence and the presence of palpable arterial wall vibrations corresponded in stenosed dog femoral arteries. Vibrations such as these are transmitted along the vessel wall<sup>(6,47,49)</sup> and from there pass along tissue planes to the body surface<sup>(46,159)</sup>.

Reynolds<sup>(139)</sup>, in 1883, was one of the first to study the formation of turbulence in flowing fluids. He demonstrated that for any fluid moving in a long straight tube, turbulence would appear suddenly at a critical point which depended on the four variables he incorporated into the following equation:

$$\text{Re} = \frac{v \times \rho}{\eta} \times d$$

Where Re = Reynolds number  
 v = mean fluid velocity  
 ρ = fluid density  
 η = fluid viscosity  
 d = diameter of the tube

He found that when Re = 2000 any fluid in a long straight tube became turbulent. Coulter and Pappenheimer<sup>(37)</sup> later showed that the apparent Reynolds number for blood in glass tubing was  $1940 \pm 160$ . This minimum value of Re when fluid becomes turbulent has since become known as the critical Reynolds number.

From Reynolds' equation we can see why turbulence will develop beyond a stenosis (Fig. 1). Originally as the fluid enters the stenosed area its velocity is immediately increased. Since the tube diameter decreases, however, the 'Re' value is relatively unchanged and no turbulence should appear within the stenosis. When the blood passes beyond the stenosis its high velocity is maintained due to its momentum and, since the tube diameter has returned to normal, the Reynolds number exceeds 2000 in this area and turbulence develops.

With this understanding of the formation of turbulence we can see that an arterial stenosis is not a prerequisite. A sufficient change in any of the variables contained in Reynolds' equation can result in the appearance of turbulent flow in a vessel. Thus, if the viscosity of blood decreases, as it does in severe anemia, the Reynolds number will be increased. The presence of loud systolic ejection murmurs in such patients is a common finding<sup>(84)</sup> and can be explained either on this basis alone or in combination with the associated increase in stroke volume. These murmurs are usually

### Figure 1

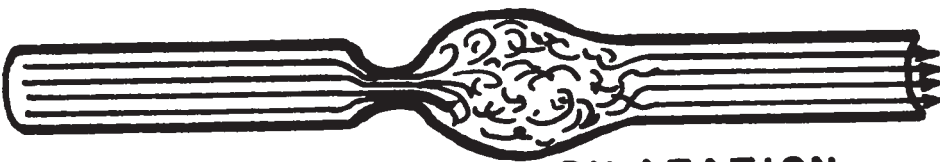
Reynolds' equation defines the point at which any flowing fluid becomes turbulent in a long straight tube. The Reynolds number (Re) depends directly on the tube diameter (d) and on the fluid velocity (v) and density ( $\rho$ ). It varies inversely as the fluid viscosity ( $\eta$ ). Turbulence develops at the critical Reynolds number,  $Re = 2000$ .

The increased fluid velocity produced by a narrowing of the tubular lumen results in turbulence downstream from the stenosis. This area of turbulence produces vibration of the tubular wall (= a murmur) and is usually accompanied by dilatation of the area when such turbulence occurs in the vascular system.

$$Re = \frac{V \times \rho}{\eta} \times D$$



**STENOSIS = TURBULENCE**



**TURBULENCE = DILATATION  
+  
A MURMUR**

short-lived, disappearing with treatment of the anemia<sup>(176)</sup>, and no vascular dilatation has been shown to accompany them. Patients with an atrial septal defect also develop vascular murmurs in the absence of stenosis<sup>(54)</sup>. In this congenital disorder, blood is shunted from the left to right atrium through a defect in the atrial septum (Figs. 2 and 3). This increased volume is then ejected from the right ventricle into the pulmonary artery and a systolic murmur is heard over this vessel.

Turbulence probably occurs in these vessels even with relatively small shunts. Considering a normal pulmonary artery diameter of about 2.0 cm and a normal cardiac output of 5 liters/min, giving an average systolic blood velocity of 25 cm/sec<sup>(30)</sup>, the Reynolds number for flow is then 1250 in this vessel. A 2:1 shunt (pulmonary:systemic flow) would, therefore, produce the critical Reynolds number of 2000. This size of shunt is quite common with an atrial septal defect<sup>(55)</sup>, but many patients do have smaller shunts which are also accompanied by a murmur. This suggests that the Reynolds number for a branching system of tubes may be less than that calculated for long straight tubes, a possibility previously suggested by Meisner and Rushmer<sup>(124)</sup> and by Stehbens<sup>(163)</sup>.

In patients with atrial septal defects the pulmonary murmur is present for years, usually until surgical correction is performed. The earliest reports of patients with this congenital defect stressed the presence of a dilated main pulmonary artery and branches<sup>(153,164)</sup> yet no adequate explanation for this finding has been offered. Since it has been suggested that not just a stenosis but turbulence

Figure 2

Schematic diagram of atrial septal defect. Blood returning from the lungs to the left atrium crosses back into the right atrium through the defect. The increased right ventricular output produces increased pulmonary artery flow and turbulence results.

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Schematic diagram of atrial septal defect. Blood returning from the lungs to the left atrium crosses back into the right atrium through the defect. The increased right ventricular output produces increased pulmonary artery flow and turbulence results.



ATRIAL SEPTAL DEFECT

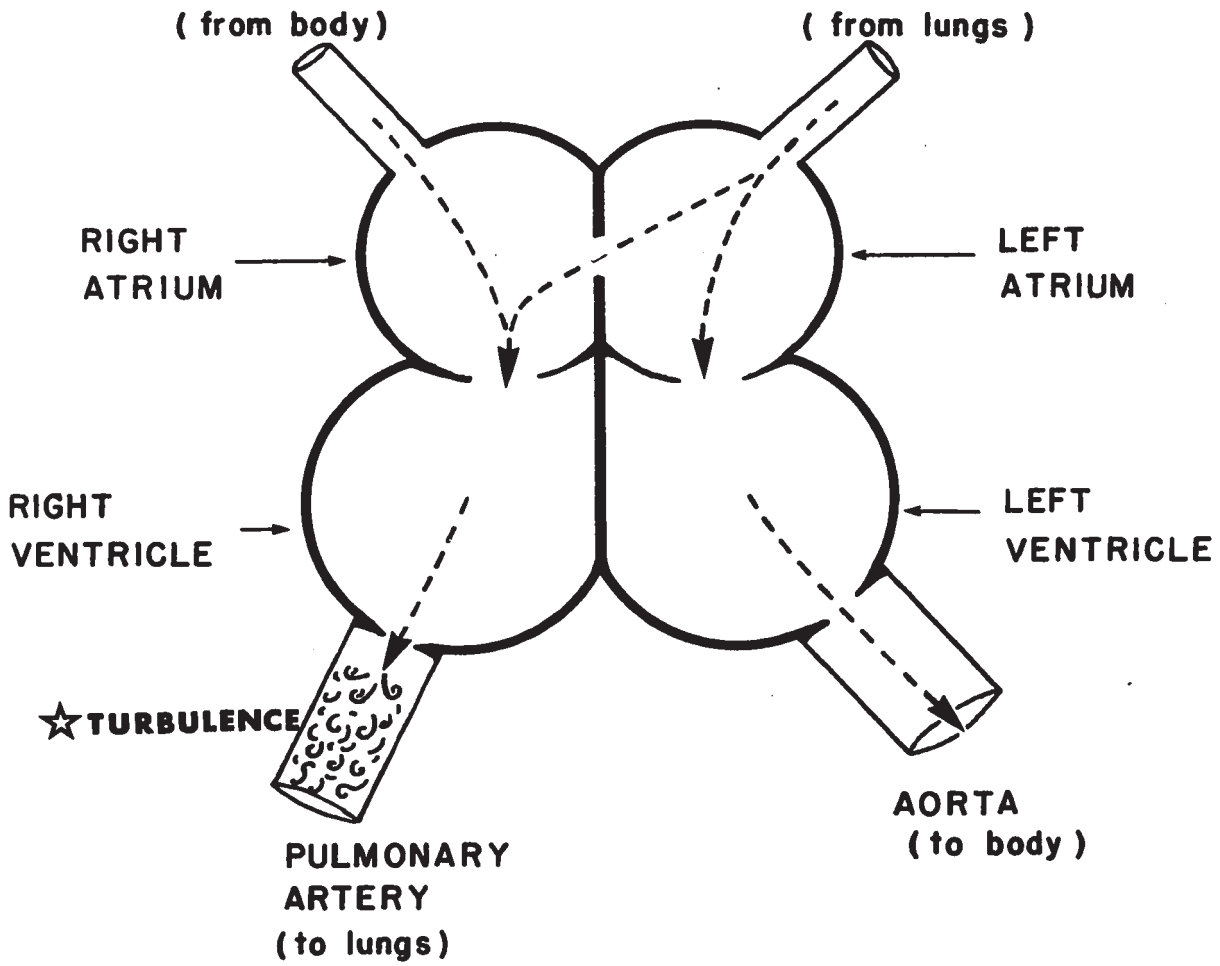


Figure 3

Photograph of a heart demonstrating a large atrial septal defect. The right atrium and right ventricle are opened with the communication between the left and right atria being evident.

[from Taussig, Harvey and Follis (164)]



ATRIAL SEPTAL DEFECT  
[INTERIOR OF RIGHT ATRIUM AND  
VENTRICLE EXPOSED]

from Taussig et al, 1938.



ATRIAL SEPTAL DEFECT  
[INTERIOR OF RIGHT ATRIUM AND  
VENTRICLE EXPOSED]

and a murmur are the prerequisites for arterial dilatation<sup>(145)</sup> it is, therefore, necessary to demonstrate that the same alteration in the physical properties of these pulmonary vessels occurs as is found distal to a stenosis.

The changes in the elastic properties of arteries that result in poststenotic dilatation have been demonstrated<sup>(143,144,145, 146)</sup> yet the cause of these changes remains unknown. Roach<sup>(143,144)</sup> has suggested that it may be the vibration of the vessel wall caused by the murmur which produces the alterations. To support this concept she attached segments of human external iliac arteries to a cocktail mixer and subjected them to random vibration. Examination of the vessel after such activity revealed changes similar to those seen in poststenotic dilatation. Unfortunately this method allows no control of the frequency of the vibration to which the vessel wall is being subjected.

Murmurs contain a variety of frequencies ranging from 30 Hz to occasional frequencies above 600 Hz<sup>(116,119,175)</sup>. By subjecting a vessel to individual frequencies from this range it should be possible to determine whether any of these vibrations are capable of inducing the typical alterations in the elastic properties of an arterial wall that are seen with poststenotic dilatation.

Although it is generally accepted that murmurs contain the frequencies mentioned above, the actual frequencies with which the arterial and cardiac walls are vibrating is not clear. The problem lies in the fact that the frequency analysis of human cardiac murmurs has been carried out only from recordings taken on the chest

surface<sup>(32,107,115,175)</sup>. Several reports<sup>(50,117,181)</sup> indicate that this frequency band is altered by the natural frequency of the thorax, i.e., the tissues through which the murmur is conducted attenuate some frequencies and amplify others. If, as we propose, arteries are to be exposed to various frequencies *in vitro*, we must demonstrate that these really are the frequencies to which they are exposed *in vivo*. Also, no report is available correlating the presence or absence of vascular dilatation and the frequency content of murmurs. It is, therefore, necessary to show that the frequencies used in our *in vitro* experiments actually do occur with poststenotic dilatation *in vivo*.

In summary, murmurs usually are associated with vascular dilatation distal to a stenosis. When they occur in the absence of a stenosis, as in patients with atrial septal defects, they may be accompanied by similar dilatation due to alterations of the vessel wall elastic properties. If the vibration of the wall is directly responsible for the dilatation, then individual frequencies contained in murmurs should produce similar changes in an artery. Finally, these frequencies must be demonstrated to occur in association with *in vivo* poststenotic dilatation.

## CHAPTER II

HISTORICAL REVIEWHistorical Review (i)Turbulence without Stenosis

In 1934 Roesler<sup>(153)</sup> collected and summarized all previously reported cases of atrial septal defect (A.S.D.). At that time 62 cases of this congenital disorder were available in the literature and in his summary, among other findings, he noted the presence of (i) a murmur along the left sternal border in a high proportion of cases and, (ii) characteristic X-ray findings consisting of a dilated pulmonary artery and its branches plus "hilar dance" (an abnormally great pulsation of the hilar vessels). Although pointing out the common occurrence of the systolic murmur he did not emphasize its importance in the diagnosis. Taussig<sup>(164)</sup> also noted the presence of the murmur over the second and third left interspace and remarked on its variability from patient to patient and time to time in the same patient. This contrasted greatly with the murmurs of other congenital defects which tended to be of constant and relatively predictable intensity.

In a more recent series of 133 children with atrial septal defects<sup>(169)</sup>, 91% had a systolic murmur over the pulmonary area and 26% of these had a palpable thrill over the same area. Similarly, in a group of 62 patients over the age of 40, 85% had a murmur over this area<sup>(55)</sup>. The reason for the somewhat decreased incidence of murmurs in the older age group appeared to be related to the higher incidence of pulmonary hypertension (13%) producing a balanced or predominantly



right to left shunt.

For years the source of the systolic murmur was undetermined, and as late as 1957 Wagner and Graham<sup>(169)</sup> suggested that it might be caused by flow across the interatrial septum. Actually this flow occurs mainly during late systole and early diastole with further augmentation during atrial contraction<sup>(93,104,109)</sup>. At about the same time Leatham<sup>(101)</sup>, showing somewhat more insight, suggested that the systolic murmur was "caused by the ejection of blood into the pulmonary artery". He stated that it seemed to be "related to the increased flow into the pulmonary artery rather than to dilatation of this vessel", and added that with "pulmonary hypertension and.... relatively normal flow, the murmur tended to be diminished or even absent". With the advent of phonocardiography the murmur was shown to originate in the pulmonary vessels<sup>(179)</sup> and generally was attributed to a "relative stenosis" of the pulmonary valve<sup>(54,93)</sup>. This is not strictly true for, as illustrated in the introduction, turbulence arises within the pulmonary trunk due to the increased flow through the vessels themselves, not just across the pulmonary valve. When the flow velocity and vessel diameter combine to exceed the critical Reynolds number the flow becomes turbulent and a murmur is heard.

More important than the murmur, to the early investigators, was the presence of characteristic changes on chest X-ray and fluoroscopy. According to Campbell<sup>(33)</sup>, Assman in 1928 first emphasized the presence of right sided cardiac enlargement, a prominent pulmonary conus and increased hilar shadows in patients with atrial septal defects. It was later shown that right ventricular enlargement was

unnecessary in making the diagnosis and was often not present. The size of the aorta was usually difficult to assess and often normal in size<sup>(12)</sup>.

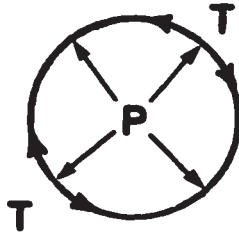
Thus the most common and helpful findings in patients with A.S.D. are the enlargement of the main pulmonary artery and bilateral pulmonary plethora<sup>(12,77,78,103,128,160)</sup>. Baltaxe and Amplatz<sup>(10)</sup> showed these signs to be present in 97.7% of 596 cases with proven atrial septal defects. In addition Taussig<sup>(164)</sup>, Wagner<sup>(169)</sup> and Campbell<sup>(33)</sup> emphasized the frequent occurrence of "hilar dance" on fluoroscopy. This term describes the radiologist's subjective impression of abnormally increased pulsation of the hilar vessels. Donzelot *et al*<sup>(39)</sup> recorded the hilar vessel wall movements by an electrokymogram (EKG), a device which measures the excursion of a moving shadow on the fluoroscope. The EKG tracing of the left pulmonary artery verified the radiologist's opinion that, in 15 patients with A.S.D., a larger than normal "amplitude" excursion of the pulmonary artery walls was a common finding.

Several theories have been advanced to explain the enlarged pulmonary vessels seen with A.S.D. These theories include (i) congenital enlargement of the pulmonary artery perhaps accentuated by increased volume flow<sup>(164)</sup>, (ii) increased volume flow from the right ventricle to the pulmonary artery<sup>(33,39,78)</sup>, and (iii) post-natal growth of the pulmonary artery due to the stimulation of wall receptors by the increased flow<sup>(10)</sup>. None of these suggestions, however, can adequately explain all of the changes seen in these vessels.

The Law of Laplace (Tension = Pressure x Radius), as modified for arteries<sup>(25,27,28)</sup>, suggests that only two factors govern the radius of any vessel (i) the intraluminal pressure and (ii) the elastic properties of the wall (Fig. 4). The pulmonary arteries in patients with atrial septal defects have a normal pressure in most cases<sup>(55,87,169)</sup>. Pulmonary hypertension is uncommon in children with this defect<sup>(169)</sup> and is only slightly more common in similar patients over the age of 40<sup>(55)</sup>. Good and Dry<sup>(60)</sup> stated that the X-ray findings of enlarged pulmonary vessels always were associated with an elevated pulmonary vascular pressure. However, Keats *et al*<sup>(87)</sup> and Doyle *et al*<sup>(41)</sup> showed that no accurate comparison could be made between the pulmonary artery size and the pulmonary artery pressure in a variety of congenital heart disorders including atrial septal defect, ventricular septal defect (V.S.D.) and patent ductus arteriosus (P.D.A.). Barber *et al*<sup>(11)</sup> examined 62 cases of atrial septal defect, 21 of whom were catheterized and showed an average shunt of 2.5 to 1. They concluded that the X-ray examination of the pulmonary vessels and right ventricle may not distinguish atrial septal defect from V.S.D. or P.D.A. Similarly, Zaver and Nadar<sup>(183)</sup>, on studying 298 cases of A.S.D., stated that the chest X-ray could not be used to define the presence or absence of pulmonary vascular disease or give any hint as to the size of the right to left shunt. Abrams<sup>(3)</sup> showed the mean size of peripheral pulmonary arteries to be smaller than normal with pulmonary hypertension but larger than normal with increased flow. Simon<sup>(160)</sup> felt that the size of the pulmonary artery trunk was so unreliable in determining the size of a left to right shunt that it should be ignored.

Figure 4

This illustrates how the Law of Laplace is applied to a cylindrical blood vessel. The intraluminal pressure ( $\rho$ ) in dynes/cm<sup>2</sup> produces distension of the vessel to a certain radius (R) in cm. The wall develops a circumferential tension (T) in dynes/cm which counteracts the distending force.



Law of Laplace :

$$\text{Wall Tension} = \text{Intraluminal Pressure} \times \text{Radius}$$

$$T = P \times R$$

The persistent discrepancy between pulmonary vessel diameter and intraluminal pressure leads us to suggest that the elastic properties of the vessel wall may be altered. Such a suggestion has not been made previously. A finding which further suggests this possibility is "hilar dance". No adequate explanation has even been offered for this clinical finding and it may also be related to an alteration of the pulmonary artery elastic properties.

Historical Review (ii)Poststenotic Dilatation

Chevers<sup>(35)</sup> in 1842 may have been the first to describe poststenotic dilatation when he noted that distal to a stenotic aortic valve the aorta had "widened to as great an extent as its contractile fibers (would) allow".

Little further interest was shown in this finding until 1916 when Halstead<sup>(66)</sup> and Reid<sup>(135)</sup> noted that subclavian artery dilatation frequently occurred distal to an area of compression by a cervical rib. Following a number of animal experiments in which they partially occluded dog aortas with metal bands, they concluded that a vascular narrowing often resulted in a circumscribed distal dilatation and that the disturbed flow and the altered pressure in this area might be the important factors. Little further work was done until 1954 when Holman and others<sup>(80,81,158)</sup> reported model experiments with rubber tubing. By partially occluding the tubular lumens they noted the gradual development of temporary, then permanent, dilatation distal to the stenosis when water was pumped through them. Dye injections showed turbulence within the dilated area and they also noted the presence of a noise and palpable vibration over this region. Extending this work to *in vivo* studies, Holman loosely ligated dog thoracic aortas and observed the development of poststenotic dilatation as the vessels grew. Similarly Aars<sup>(1,2)</sup> produced dilatation in the ascending aorta of rabbits by narrowing the lumen with a tapered nylon ring just above the valve. He observed that dilatation of the remainder of the ascending aorta plus the whole of the arch and a few

centimeters of the descending aorta occurred within a few days.

Poststenotic dilatation has been reported in many major arteries of the body. It is very frequently observed distal to a stenosed aortic valve<sup>(35,54,85)</sup> or a stenosed pulmonic valve<sup>(16,22,40,89)</sup> and occasionally beyond muscular subaortic stenosis<sup>(171)</sup>. It is also well reported distal to coarctation of both the aorta<sup>(91,136,182)</sup> and pulmonary artery<sup>(7,56,140)</sup> and is usually seen with renal<sup>(17,90,110,148)</sup> and carotid artery stenosis<sup>(67)</sup>. It can also occur beyond a narrowing produced by an external compression such as the compression of the subclavian artery by a cervical rib<sup>(66)</sup>.

Despite the length of time that this lesion has been known, and the multitude of reports describing its existence, the basic etiology of poststenotic dilatation remains unexplained. Since the transmural pressure and the elastic properties of the vessel wall determine a vessel's radius<sup>(25,27)</sup>, these two aspects have been examined by several investigators.

The intraluminal pressure distal to a stenosis has been shown to be normal or below normal by several authors. Robiscek<sup>(151)</sup> measured pressures beyond stenoses in glass and rubber tubes as well as beyond pulmonary valve stenosis and aortic coarctation. In all cases he found the luminal pressure to be decreased beyond a stenosis. Similar results were reported by May *et al*<sup>(123)</sup>. In somewhat more sophisticated studies, De Vries and van den Berg<sup>(168)</sup> also demonstrated the pressure to be below normal in the poststenotic areas of models as well as *in vitro* and *in vivo* preparations of arteries. Therefore, increased intraluminal pressure can be excluded as a cause of the



dilatation.

Thus alteration in the vessel wall may explain the enlargement. The general structure of the arterial wall has been known for some time but only recently has the functional histology of the arterial media been described. Wolinsky and Glagov<sup>(59,177)</sup> fixed segments of rabbit aorta at various distending pressures from 0-200 mm Hg. They observed that at pressures up to 60-80 mm Hg the elastin lamellae gradually straighten (unfold) and become thinner (Fig. 5). The interlamellar spaces decrease. The number of elastin lamellae differs in the aorta of different species and for man is 58<sup>(178)</sup>. Lying between, and attached to, the elastin lamellae are many fine elastin fibrillar nets, visible only on electron microscopy. At low pressures these nets are arranged almost perpendicular to the axis of the vessel but with increasing wall tension they quickly become oriented circumferentially and serve to distribute the tension. When the intraluminal pressure exceeds 60 mm Hg, the collagen fibers, which lie in the interlamellar spaces, begin to become oriented circumferentially. Prior to this they are arranged in a random fashion and do not appear to be involved in the production of wall tension. By 120 mm Hg pressure all collagen fibers lie parallel and are circumferentially oriented and provide the main resistance to pressures. At and above this level little further change occurs in the thickness of the wall.

Such histologic findings correspond extremely well with earlier work by Roach and Burton on the elastic properties of the arterial wall<sup>(141)</sup>. As early as 1880 Roy<sup>(154)</sup> demonstrated that the tension-length curve for arteries was nonlinear; i.e., did not obey

Figure 5

Cross sections of the wall of the rabbit aorta fixed at various intraluminal pressures and stained with Weigert's stain show the gradual histologic changes that occur with increasing pressure. The elastin lamellae gradually unfold and straighten. Their thickness decreases and the interlamellar spaces become less.

At pressures above 100 mm Hg little further change in the total wall thickness or vessel radius occurs. The collagen fibrils are all oriented circumferentially and apparently resisting the stress.

[from Wolinsky and Glagov (177)]

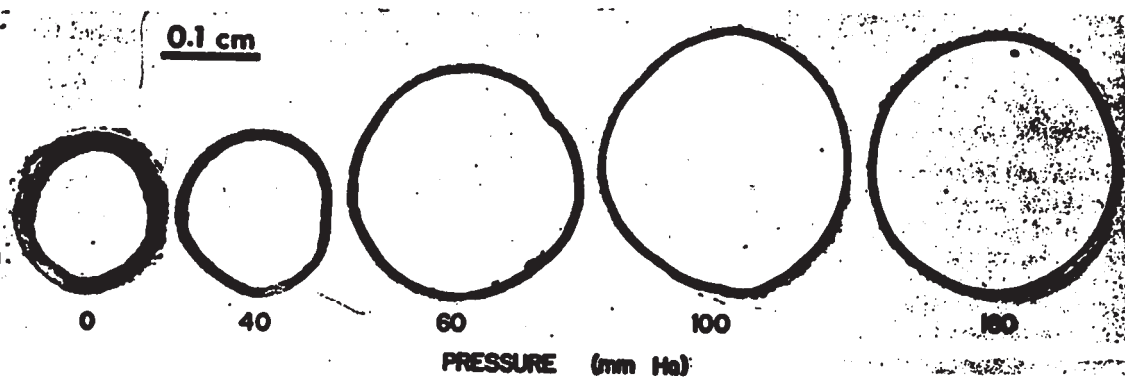
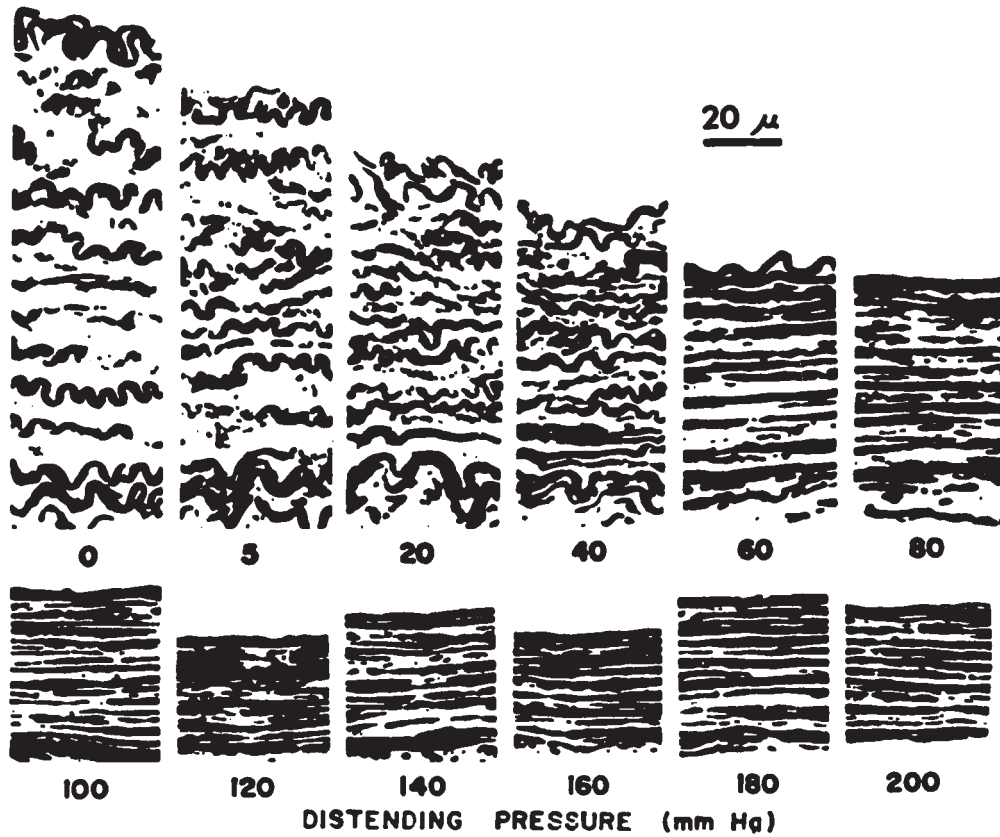


FIGURE 2

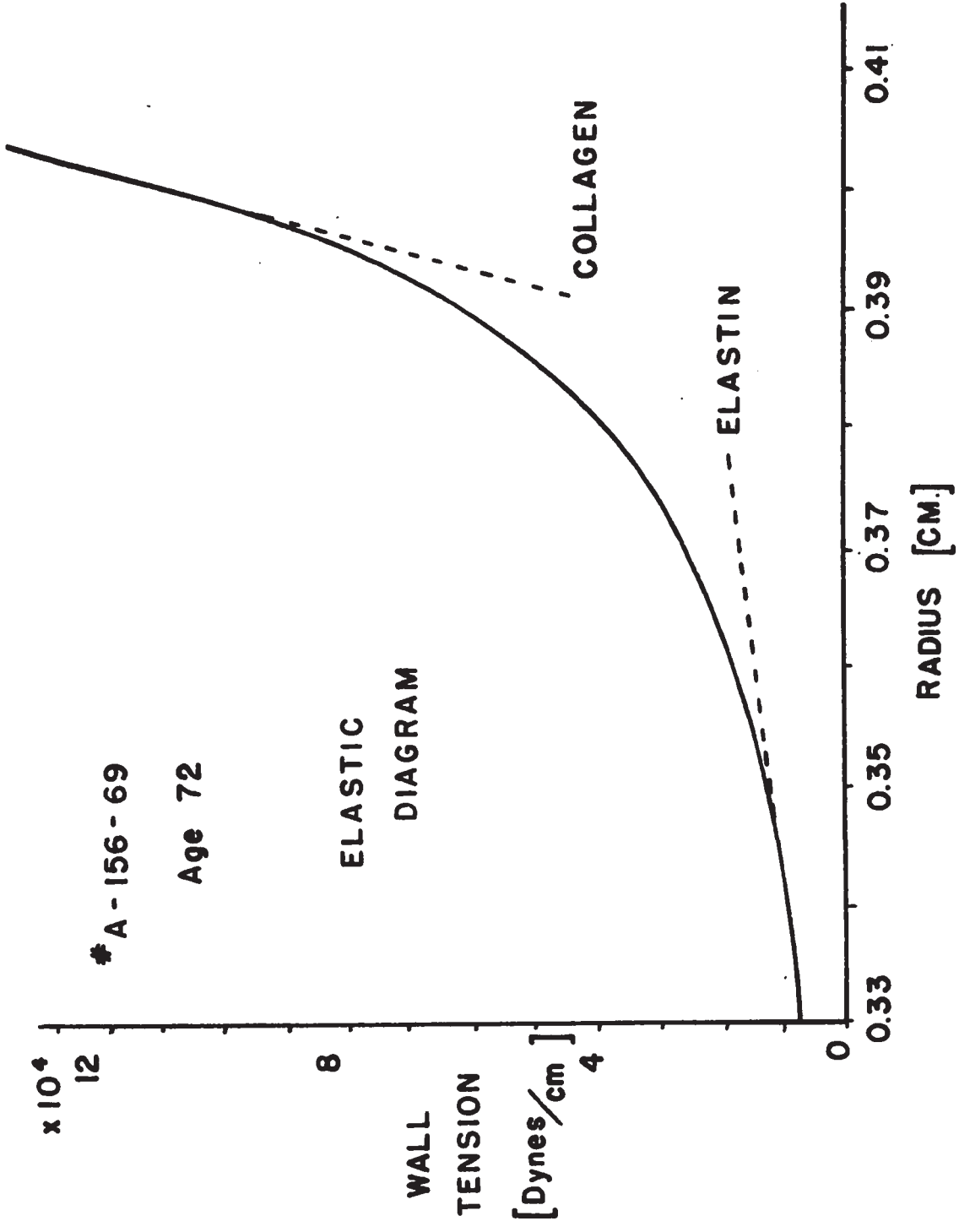
*Cross sections of rabbit aortas fixed at various distending pressures. Differences in radius and wall thickness among the vessels fixed at 0, 40, and 60 mm Hg distending pressures are obvious; differences in radius and wall thickness between the vessels fixed at 100 and 160 mm Hg are barely discernible.*

Hooke's law. By hanging weights on a circumferential strip of artery he showed that blood vessels resist stretch more strongly the more they are stretched (Fig. 6). Lawton<sup>(98)</sup> confirmed and expanded upon these findings in 1955. Roach and Burton<sup>(141)</sup> felt that the elastic diagram produced appeared to be a two-component curve resulting from the heterogeneous makeup of the wall. After digesting the collagenous fibers with formic acid for three hours the remaining vessel showed a linear elastic diagram of low slope that represented the action of the remaining arterial wall elastin network. Digestion of the arterial wall with crude trypsin, which contains an elastase, resulted in an elastic diagram which turned upward quickly and reached a final slope very similar to the final slope for the unaltered vessel. This represented the action of collagen. On this basis it was concluded that the initial slope of the arterial wall elastic diagram represents the tension produced by the elastin network of the wall while the final slope represents the collagen (Fig. 6). The inflection of the curve represents an area of crossover when increasing numbers of collagen fibers are gradually being stressed. Thus, physical properties and histologic findings have been shown to correspond for the normal arterial wall.

As mentioned above, distal to a stenosis we would expect changes to be present in the arterial wall which account for the post-stenotic dilatation. Various opinions have been expressed regarding the presence of histologic changes in this area. Clagett *et al*<sup>(36)</sup> reported few medial changes in a series of 124 cases of aortic coarctation. Ten patients did show medial changes but these were associated with aneurysm formation. Dunnill<sup>(42)</sup> reported an increased

Figure 6

The elastic diagram for a human external iliac artery is illustrated. The curve is nonlinear and contains two components. The initial low slope (rapid increase in radius with increasing wall tension) represents the elastic modulus of the elastin network. The final high slope (small increase in radius with increasing wall tension) represents the modulus of elasticity of the collagen content of the wall.



number of elastic laminae proximal to eight of nine coarctations and distal in only two. Robiscek<sup>(150,151)</sup>, however, found a decrease in the elastic fibers distal to a stenosed pulmonary valve but similar changes were reported to occur in idiopathic pulmonary dilatation<sup>(22)</sup>. Roach<sup>(144)</sup> observed no difference between the proximal and distal segments of artificially stenosed dog femoral arteries despite the presence of poststenotic dilatation.

The variety of interpretations placed on the histologic findings may be due to the fact that none of the arteries examined were fixed under physiologic pressures. As shown by Wolinsky and Glagov<sup>(59,177)</sup> the functional histology can be much better appreciated by this method, and consistent abnormalities of structure would more likely be visible under these conditions<sup>(23)</sup>. However, it is also possible that the critical changes are not gross enough to be visualized by light microscopy but require examination with the electron microscope. This would be true if the elastin nets described by Wolinsky and Glagov<sup>(177)</sup> are important.

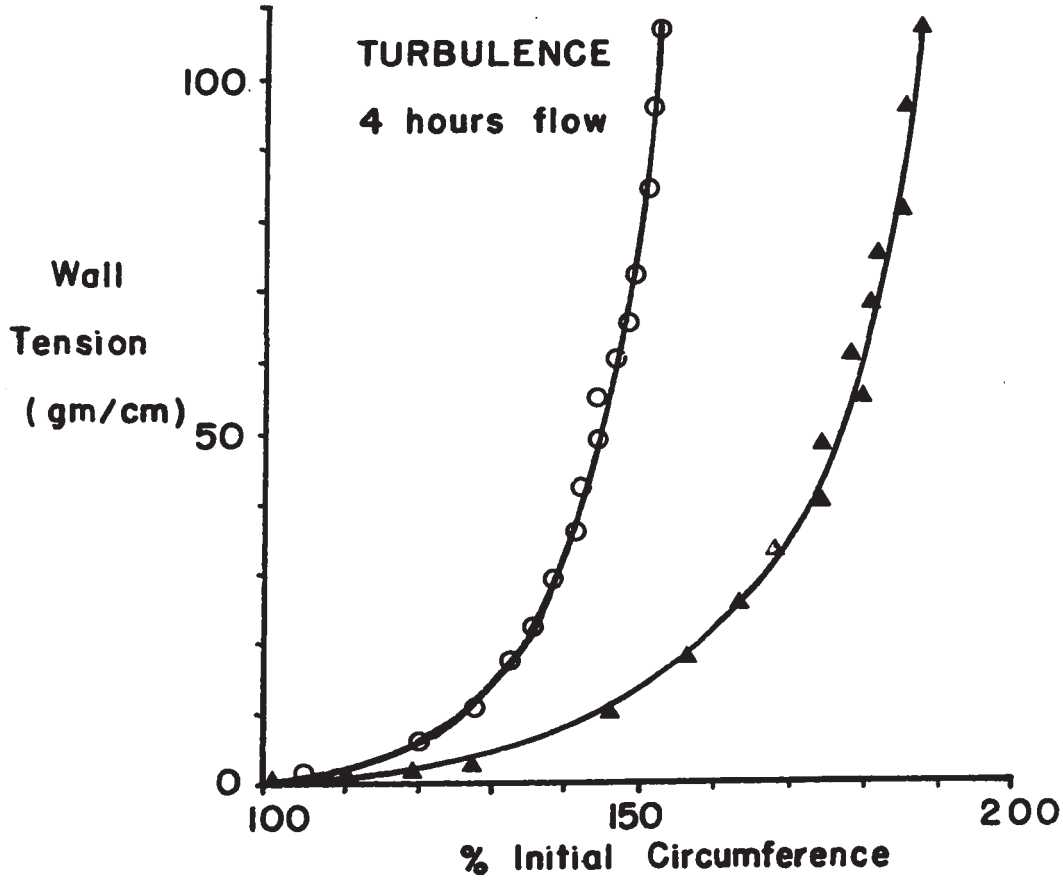
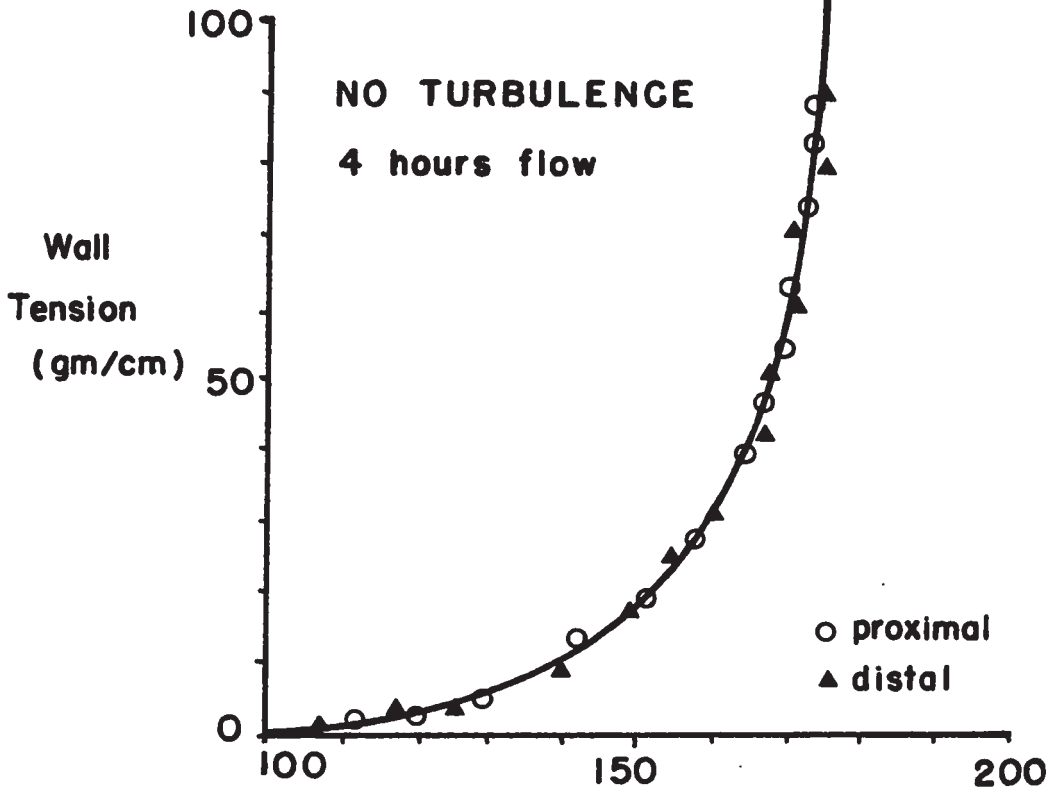
The physical properties of arteries exhibiting poststenotic dilatation have been examined and have given more definite results. Roach<sup>(143,144,146)</sup> demonstrated that the elastic properties of arteries distal to a stenosis are altered when compared with the proximal segment. Experimentally, stenoses were produced in canine femoral arteries by nylon taffeta bands. When poststenotic dilatation developed the dogs were sacrificed and the elastic properties of the vessels examined both above and below the stenosis. The elastic diagram for the distal segment was shifted to the right (Fig. 7) when compared with

Figure 7

The elastic diagram for two human external iliac arteries of the same age group (4th decade) mounted and perfused *in vitro*. The top graph illustrates the absence of any change with 4 hours of laminar flow. The lower graph illustrates the change in the elastic diagram that occurs distal to a stenosis with 4 hours of turbulent flow in the area. The initial slope decreases and the final slope remains unchanged producing a greater than normal radius for any given wall tension.

[from Roach (144)]





the proximal segment. The final slope remained unchanged. The artery assumed a greater than normal radius for any given pressure or wall tension. The maximum dilatation in dog femoral and carotid arteries was shown to be attained in about 10 days and to persist unchanged for up to 10 months<sup>(145)</sup>. This change was also shown to be reversible, *in vivo*. On relieving the obstruction in 14 dog femoral arteries the poststenotic dilatation disappeared within 12-48 hours<sup>(147)</sup>. Studies with isolated perfused human external iliac arteries<sup>(144,146)</sup> revealed that poststenotic dilatation could be produced *in vitro* as well, and that the changes in the elastic properties correspond to those demonstrated *in vivo*. The rate of dilatation was much more rapid in the isolated vessels, probably because of the steady flow used to perfuse the isolated, stenosed arteries. Foreman and Hutchison, however, could not confirm the finding of dilatation beyond an artificial stenosis *in vitro*<sup>(53)</sup>.

The studies of Roach led to a further observation<sup>(144)</sup>. Three degrees of stenosis were produced in the carotid and femoral arteries of dogs (i) minimal stenosis with no thrill or bruit, (ii) moderate stenosis with a thrill and bruit present, and (iii) severe stenosis with decreased or absent distal pulsations and no thrill or bruit. Only the group with moderate stenosis produced an audible murmur and palpable thrill and only this group showed poststenotic dilatation. Visible eddies and turbulence were often observed within the lumen of these vessels. From these findings Roach suggested that the vibration of the wall, as evidenced by the presence of a murmur and palpable thrill, might be directly responsible for the development of poststenotic dilatation. Such a suggestion has also been made by several other authors<sup>(66,81,125)</sup>.

The vibrations associated with a murmur apparently range in frequency from about 30 Hz to a few as high as 600-800 Hz. However, the majority of frequencies fall between 75 and 200 Hz (32,115,174) when observed and recorded from the chest wall. A number of authors have examined the effects of sonic vibrations on the properties of various tissues but the frequencies used mainly lie well above the frequencies found in murmurs. Gersten<sup>(57)</sup> demonstrated that ultrasound with a frequency of 1 megahertz decreased the elastic modulus of collagen in a strip of rat Achilles tendon. The alterations he produced decreased with depth and occurred without visible histologic change on light microscopy. He also showed that collagen fibers reacted differentially to mechanical vibrations depending on whether the vibrations were directed parallel or perpendicular to their surface and Fisher<sup>(51)</sup> found some tissues to be more sensitive to ultrasound than others. These observations demonstrate that vibration can alter structural proteins and the frequencies required to affect collagen lie well above any produced *in vivo*. A somewhat lower frequency, 10 kilohertz, has been shown to increase ATPase activity in muscle fibers<sup>(129)</sup> but again this frequency is far above the vibrations contained in murmurs. Sarvazyan *et al*<sup>(156)</sup> showed the speed of sound to be slow in gels and felt that the effects of audible sound on protoplasmic structures could be significant. Roach exposed human external iliac arteries to random low frequency vibrations<sup>(144)</sup> by attaching these vessels to the end of a cocktail mixer. After such exposure the elastic properties of the vessel walls were altered in a similar manner to that observed with poststenotic dilatation.

Unfortunately such experiments allowed no control over the frequency of the vibrations.

In model experiments carried out by Bruns<sup>(20)</sup> a vibrating blade (96 Hz) was placed within a fluid filled rubber tube and after 120 hours moderate dilatation of the tubing appeared. This then can be compared to the model experiments of Holman and others<sup>(80,81,158)</sup> which showed the development of dilatation distal to a stenosis in rubber tubing as mentioned earlier.

These studies indicate that vibration can alter biological tissue. No vessel has ever been exposed to specific low frequencies contained in murmurs. It seems reasonable to speculate that such frequencies might be responsible for the altered elastic properties seen with poststenotic dilatation.

In summary, vessels dilate in areas where intravascular turbulence causes vibration of the wall. The dilatation is due to alteration of the wall's elastic properties such that a greater radius is attained for any given wall tension. Since some biological tissue can be altered by vibrations of various frequencies, it is therefore possible that the low frequency vibrations produced by turbulence may be responsible for the altered arterial elastic diagram. It was, therefore, decided to expose human external iliac arteries to various specific low frequencies and measure their elastic properties before and after vibration. These vessels were chosen since they have been used previously for *in vitro* work on poststenotic dilatation.

Historical Review (iii)Frequency Content of Murmurs

Distal to a stenosis, over an area of poststenotic dilatation, a murmur and palpable thrill are present<sup>(144)</sup>. The murmur is generated when events occurring within the vessel (probably turbulence) are converted into sound<sup>(180)</sup>. This vibration can be felt as well as heard, suggesting that at least part, if not all, of its frequency content lies between 200 and 400 Hz, the most sensitive range for tactile discrimination<sup>(133)</sup>.

Although it is traditional for cardiologists to comment on the pitch of a murmur, Rushmer *et al*<sup>(155)</sup> have shown that "even the most expert cardiologist cannot distinguish the various sources of murmurs.....on the basis of frequency patterns or content". He suggested that the frequency content must be non-specific and that timing, intensity and localization are the most important distinguishing features for a murmur. The successful use of "white noise" in sound simulators for teaching cardiac auscultation<sup>(134)</sup> supports this viewpoint. The general statement that a murmur is high or low pitched may have little basis in reality.

Early attempts to determine the frequency content of heart sounds and murmurs recorded from the chest surface were made by Lewis<sup>(107)</sup>, in 1913, using an "electrophonograph" which exposed photographic film. In animal experiments he recorded the heart sounds of dogs. By destroying the aortic cusp in these animals he produced an early diastolic murmur with frequency components of 100-200 Hz. In humans he recorded and analyzed the murmurs of mitral regurgitation

(112 Hz and 140 Hz), aortic stenosis and aortic insufficiency (about 80 Hz). A musical aortic diastolic murmur had frequency components of 138 Hz and 180 Hz.

Cabot and Dodge in 1925<sup>(32)</sup> and Williams and Dodge in 1926<sup>(174)</sup>, using an "electrical stethoscope" and the then recently invented band pass filter, analysed another series of 39 murmurs. They found that the energy of murmurs generally lay below 660 Hz and they divided them into three groups (i) very low pitched murmurs, less than 120 Hz, (ii) low pitched murmurs with components up to 400 Hz, and (iii) high pitched murmurs with all components from 120-660 Hz. A few musical murmurs had components from 400-1000 Hz.

Little further work was done on the frequency content of murmurs until 1954 when McKusick introduced spectral phonocardiography<sup>(114)</sup>. By this method the murmurs were passed through a number of narrow range, band pass filters connected in parallel. The sound was then displayed on a frequency versus time graph with the intensity of each frequency being shown as variations in the grey scale.

From this work he concluded that the heart sounds lay generally below 200 Hz<sup>(115,119)</sup> but no conclusions were reached regarding murmurs and the exact or estimated frequency content of different types of murmurs was not commented upon. This omission was likely due to difficulties, referred to by Winer<sup>(175)</sup>, in interpreting this grey scale display method. On examination of the published records it is apparent that the frequency content of murmurs ranges about 30 Hz to an occasional peak of 1000 Hz seen with a "musical" murmur<sup>(115,116)</sup>. The majority of frequencies appear to lie between

70 and 250 Hz with considerable variation being apparent.

Contour plotting<sup>(175)</sup> is a more recent and more clearly readable technique of frequency analysis. This "three dimensional" approach gives a good display of the frequency content of individual murmurs. Unfortunately, only a few papers have been published using this method and from these we again obtain only a general impression of the frequencies contained in most murmurs. Van Vollenhoven *et al*<sup>(167)</sup> attempted to distinguish between aortic insufficiency and mitral stenosis by the frequency content of these two murmurs. Their success was limited and the frequency contents were not clearly spelled out in their report.

All of these methods have given a general estimate of the frequency content of murmurs as recorded from the chest surface. However, since a relatively large quantity of tissue lies between the vessel or chamber in which the murmur originates and the receiver, it seems possible that the frequency spectrum may be altered by its passage to the surface.

The thorax (a general term representing the tissues other than the heart and great vessels) apparently has a "resonant frequency" which lies within the range of the frequency content of murmurs. McKusick<sup>(117)</sup>, using sound spectrography, percussed the chest and reported resonance at about 140 Hz. Zalter *et al*<sup>(181)</sup> produced sounds within dog hearts. He compared the frequencies from the heart and vessel surface with those recorded on the chest surface and reported that the chest attenuated frequencies below 100 Hz moderately and above 300 Hz considerably. Frequencies from 150-200 Hz were conducted

best and he noted sharp resonant peaks on the chest wall at 180 Hz and 130 Hz in 2 dogs. Feruglio<sup>(50)</sup>, using a specially designed vibro-catheter, produced vibration of various frequencies from 24-10,000 Hz within the right ventricle and main pulmonary arteries of humans. He noted again that the thorax attenuated frequencies below 100 Hz and above 350 Hz while frequencies between 150-200 Hz showed relatively little attenuation. He claimed the latter to be the "natural frequency" of the thorax. In addition, normal respirations produced little change in the transmission characteristics, but full inspiration produced a 50% increase in the attenuation and full expiration a 15% decrease in attenuation of a 350 Hz signal. Externally recorded murmurs, when reproduced within the heart or a vessel, showed only small changes in frequency content when re-recorded on the chest surface. This seems analagous to passing a filtered signal back again through the same filter.

It is apparent, therefore, that an analysis of the frequency content of a murmur recorded from the chest wall will not give a true picture of the frequency spectrum of the vibrations occurring in the vessel wall. As outlined in the Introduction, the most likely cause of a murmur is intravascular turbulence. Such turbulence, in model studies, has most of its energy in the lower frequency range between 20 and 500 Hz<sup>(52,180)</sup>. These fluctuating pressures, associated with the turbulent kinetic energy, are converted into vibrations by the vessel wall<sup>(29,111,112,180)</sup> or into electrical energy by vibrating a piezoelectric crystal<sup>(106,180)</sup>, i.e., a phonocatheter. Wallace *et al* (170) reported the frequency analysis by sound spectrography of the



output from a phonocatheter. They took one sample each from a variety of murmurs and no conclusion as to the frequency spectra, other than upper and lower limits, was made. For a murmur of aortic stenosis recorded in the aorta, the turbulent pressure fluctuations had an upper limit of 500 Hz corresponding to that seen in the model studies outlined above<sup>(52,180)</sup>.

How the vessel responds to the turbulent pressure fluctuations within it is not entirely clear. Meisner and Rushmer<sup>(125)</sup> showed that, for distensible plastic tubes, the same frequencies appeared on the surface as were measured in the turbulent fluid within them. There was no evidence of resonance. Foreman and Hutchison<sup>(53)</sup> reported transmission of intravascular "sound" by the arterial wall but noted the occurrence of resonant peaks with *in vitro* stenoses of dog iliac arteries. Lees and Dewey<sup>(102)</sup>, however, recorded from the skin surface just above carotid and femoral arteries distal to stenoses and showed no such resonant peaks *in vivo*. Different techniques were used and the reason for the discrepancy is not clear.

In summary, it is apparent, from work published to date that most murmurs when recorded on the chest surface have a frequency spectrum varying from about 30 Hz to about 600 Hz with the occasional "musical" murmur reaching 1000 Hz. A frequency analysis of this spectrum will not give a true picture of the frequencies with which a specific vessel or chamber is vibrating due to attenuation by the thorax of frequencies below 100 Hz and above 350-400 Hz. Turbulent pressure fluctuations within a vessel likely produce vibration of the vessel wall of similar frequencies to that recorded by a phonocatheter. The response of the

vessel wall with regard to resonance peaks is unresolved.

No reports are available which mention the presence or absence of *in vivo* poststenotic dilatation accompanying the vascular murmurs being analyzed. It is, therefore, necessary to ensure that poststenotic dilatation, *in vivo*, does occur when frequencies used in section (ii) are present as part of a murmur.

### CHAPTER III

METHODSMethod (i)*Turbulence without Stenosis*

We are going to compare the elastic properties of normal pulmonary vessels with those of (i) the dilated pulmonary trunk distal to pulmonary valve stenosis and (ii) the pulmonary arteries in atrial septal defect (Fig. 8). If turbulence and a murmur, wherever they occur, result in alteration of the vessel wall elastic properties, the pulmonary arteries in these two abnormal conditions should show similar changes in elasticity.

Catheter studies

Patients selected for this study had routine cardiac catheterization and angiography performed. Radiopaque dye was injected into the outflow tract of the right ventricle or into the main pulmonary artery just distal to the pulmonary valve<sup>(108)</sup>. The injections were recorded on 35 mm film at a shutter speed of 50 to 64 frames per second, via either a 5 or 9 inch image intensifier. The patient lay in a rotating cradle at least 60 cm above the X-ray source. The input phosphor (receiver) was located about 25 cm above the chest wall. The films were taken mainly in the postero-anterior position or the right anterior oblique but the left anterior oblique was also used occasionally.

To avoid problems arising from the changing elastic properties of arteries with age<sup>(31,65,70,142,149)</sup> all patients selected ranged in age from 6 months to 20 years, with a mean age of 9.7 years. They

### Figure 8

Schematic diagrams and X-rays for the 3 types of patients used in the study of pulmonary artery elastic properties.

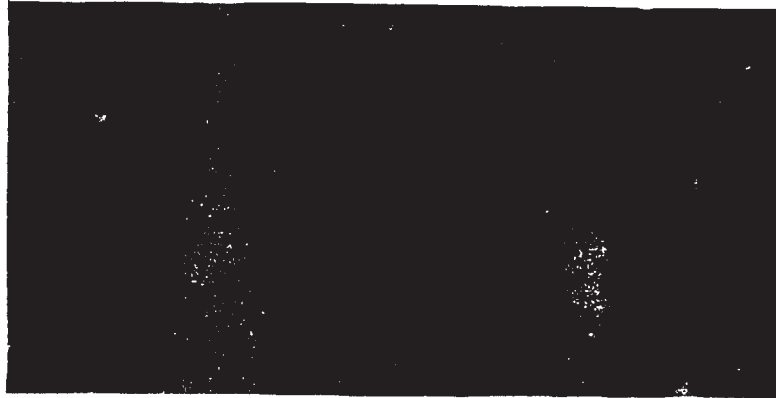
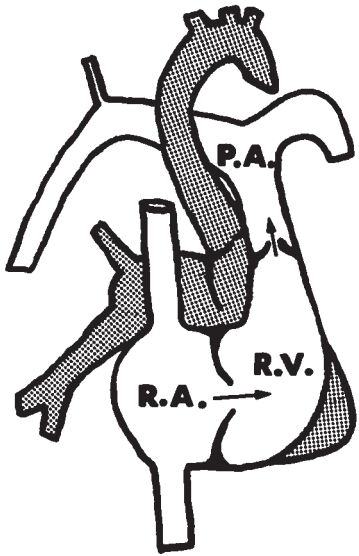
The top diagram illustrates a normal heart with no chamber or vascular enlargement (R.A. = right atrium, R.V. = right ventricle, P.A. = pulmonary artery). The chest X-rays show the normal heart in the postero-anterior (p.a.) and left anterior oblique (l.a.o.) projections.

The middle diagram illustrates pulmonary valve stenosis with poststenotic dilatation. An enlarged right ventricle is common. The chest X-rays show the enlargement of the pulmonary conus along the upper left portion of the cardiac silhouette on the p.a. projection. The enlarged right ventricle is seen on the l.a.o. projection.

The lower diagram shows an atrial septal defect with enlargement of the right atrium and ventricle and dilatation of the pulmonary arteries. The chest X-ray shows enlargement of the pulmonary conus and a bilateral increase in pulmonary vascular markings.

[schematic diagrams after Simon (161)]

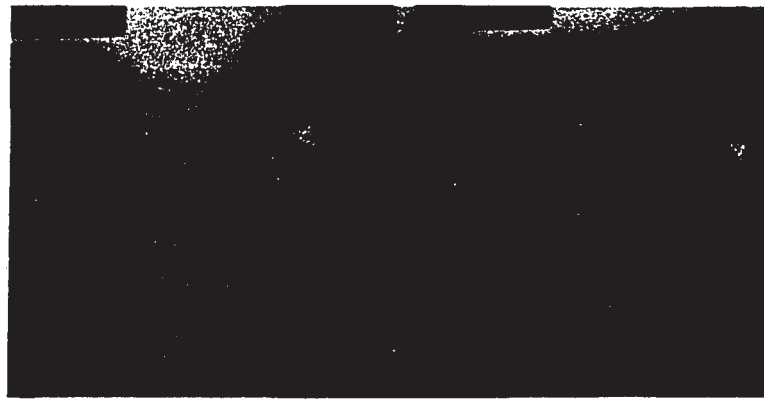
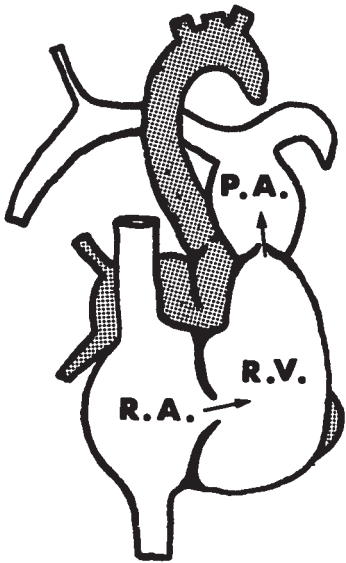
**NORMAL**



p. a.

l. a. o.

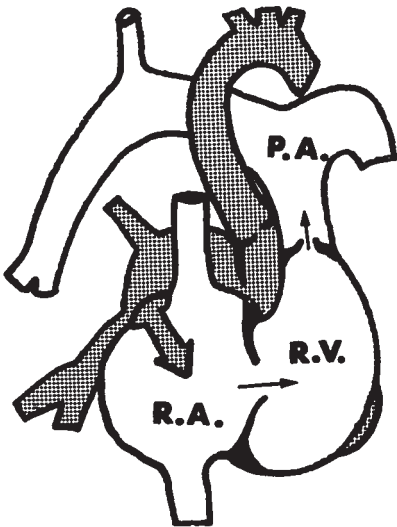
**PULMONARY STENOSIS**



p. a.

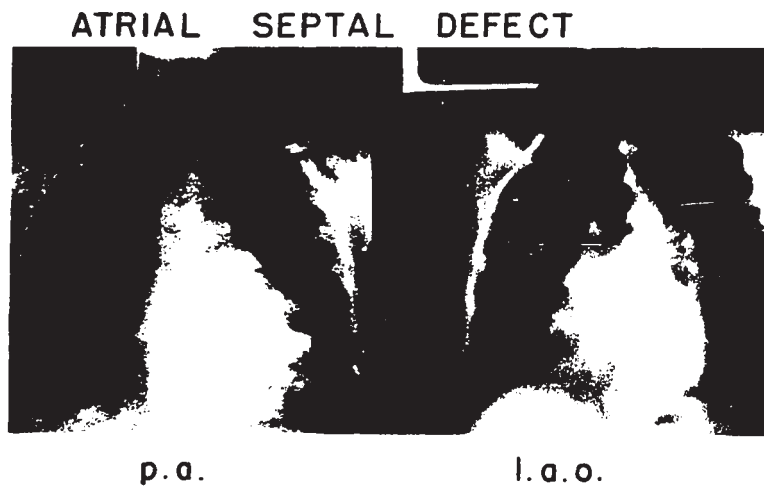
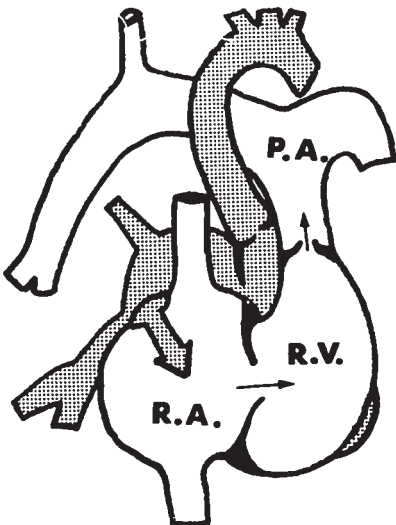
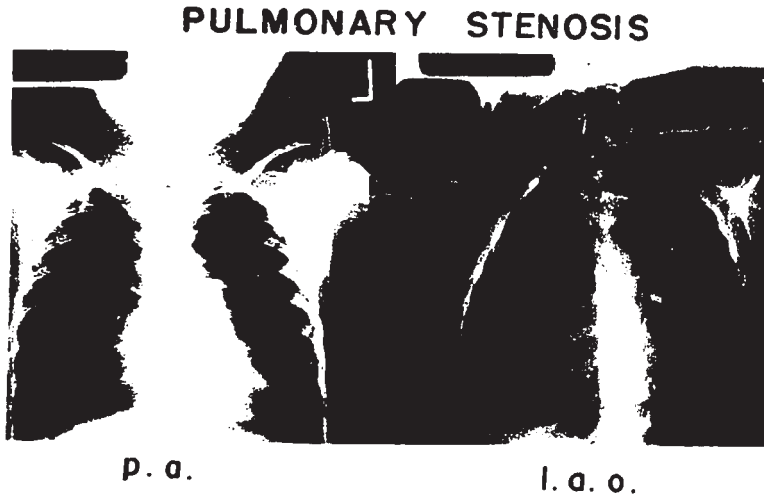
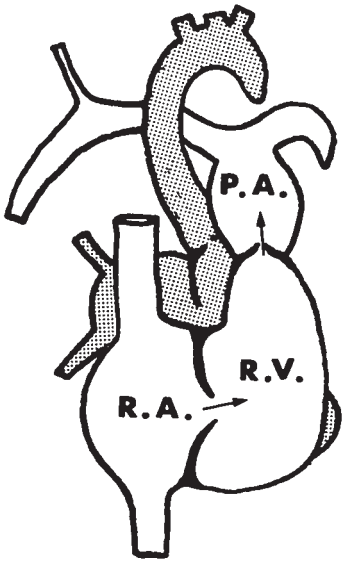
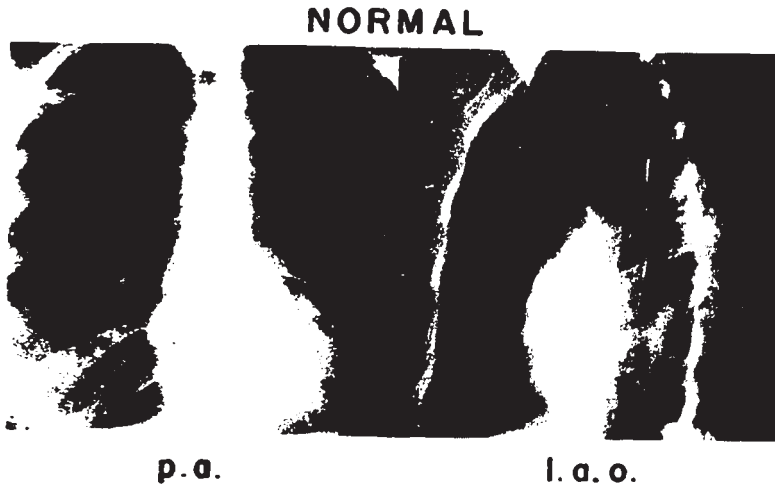
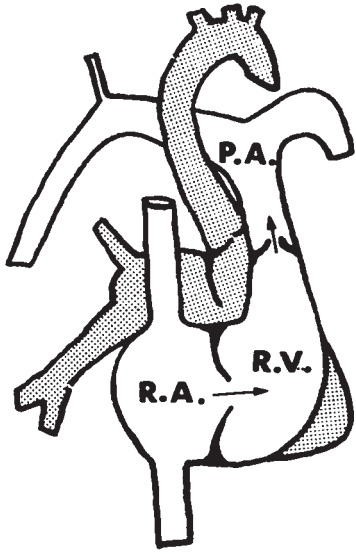
l. a. o.

**ATRIAL SEPTAL DEFECT**



p. a.

l. a. o.



were divided into three groups:

- ( i) 6 patients with normal pulmonary arteries, mean age 11.7 years (range 4 to 20 years).
- ( ii) 9 patients with moderate to severe pulmonary stenosis, mean age 8.7 years (range 5 to 13 years).
- (iii) 10 patients with atrial septal defects, mean age 7.3 years (range 6 months to 15 years).

All of the patients with pulmonary stenosis and atrial septal defect had a murmur over the left sternal border at the second interspace.

In each case the film record of the dye injection was played back without knowledge of the intraluminal pressures. Two frames were selected where good opacification of the vessel lumen was present, one frame representing systole (ventricle contracted, valve open) and the other representing diastole (ventricle relaxed, valve closed) (Fig. 9). These frames were projected onto white drawing paper and the outlines of the main pulmonary artery, the right and left pulmonary arteries and the initial portion of their major branches were then carefully traced. The length of these vessels available depended on the view recorded. Only vessels with complete opacification and clear outlines were used for the measurements and care was taken not to use injections accompanied by irregularity or premature contractions.

#### Diameter and Pressure Measurements

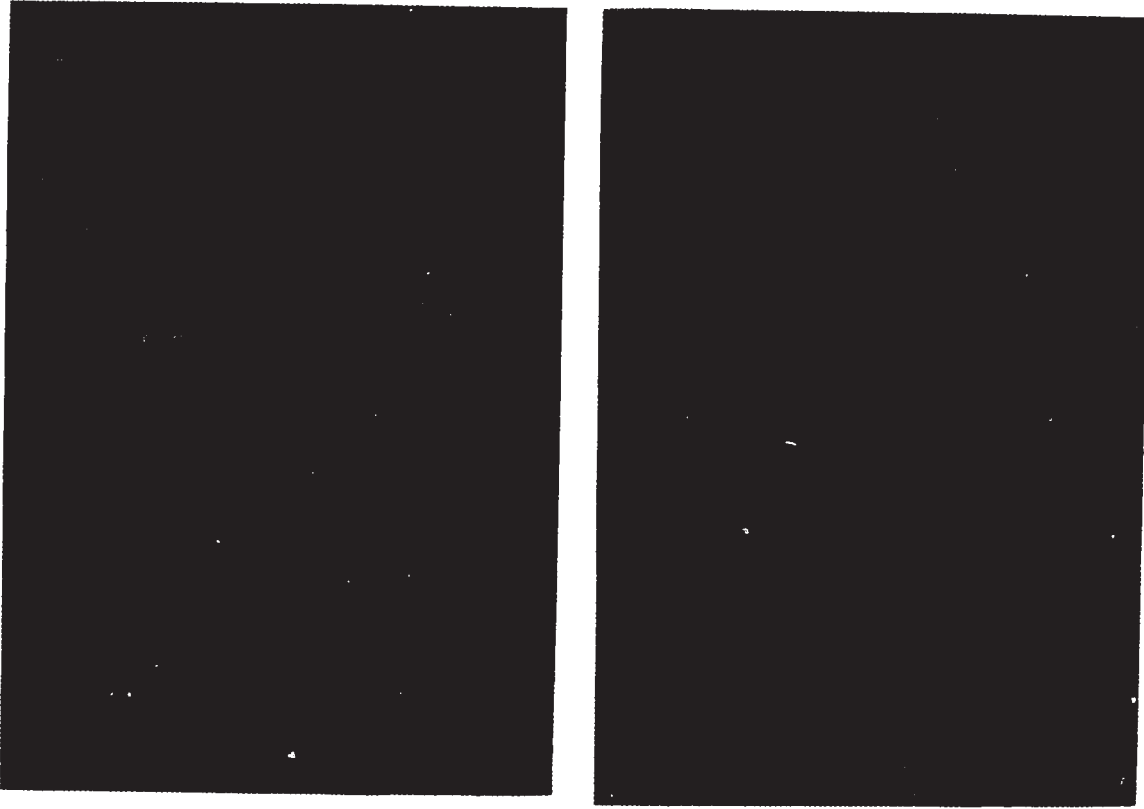
Diameters of the vessels at various comparable points along their course were measured with a ruler ( $\pm 0.5$  mm). To ensure that measurements were made at the same points in both the systolic and diastolic projections, various landmarks were used (e.g., identical



Figure 9

Angiograms in a patient with pulmonary stenosis. One frame illustrates systole (valve open) and one diastole (valve closed). The frames were then projected and enlarged, as shown, and the diameter of the vessels (D) at the same point were measured for each.

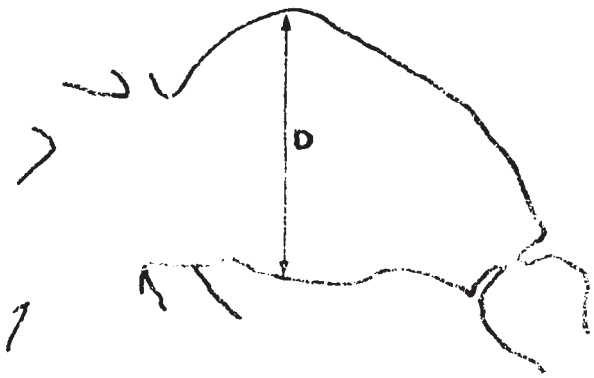
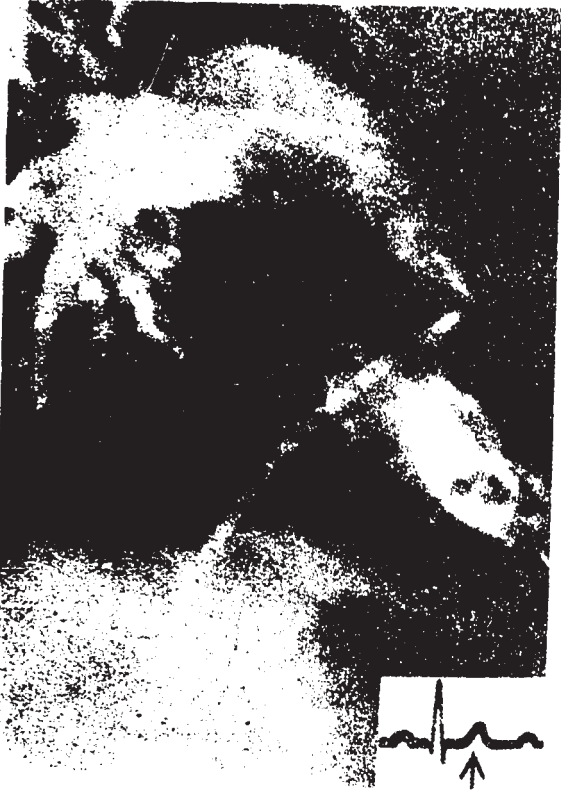
[photographs from Lind, Boesen and Wegelius (108)]



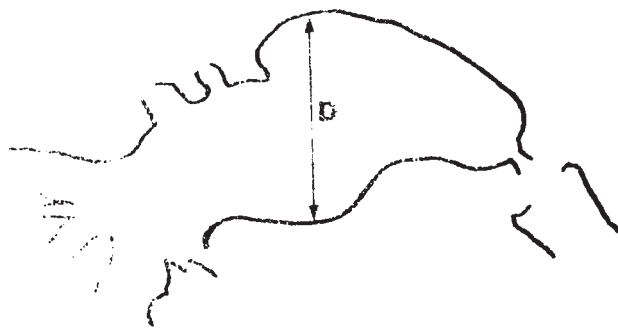
SYSTOLE

DIASTOLE

PULMONARY STENOSIS



SYSTOLE



DIASTOLE

PULMONARY STENOSIS

distances from the pulmonary valve, identical distances from a branching vessel, etc.). No measurements were made beyond the third branch of the left pulmonary artery or beyond the second bifurcation of the right pulmonary artery since the dye was frequently diluted distal to these points and complete opacification of the vessels was not common.

The catheter records were then consulted for the intraluminal pressure in systole and diastole recorded prior to the injection. In all cases the pressures lay within the normal range; i.e., less than 30 mm Hg systolic<sup>(54)</sup>. The pressures were obtained with a Statham, Model P23 series transducer (frequency response flat  $\pm 5\%$  to 20 Hz) connected to the catheter lying within the pulmonary vessels and had been recorded on either a Sanborn Model 150 Polyviso, 4-channel recorder (frequency response flat 0-80 Hz, manufacturers specifications) or an Electronics for Medicine DR8 (frequency response flat 0-30 Hz). It was not possible to routinely record the intraluminal pressure at the same time as the injection was being made since this would require a second venous cutdown on another extremity for the insertion of another catheter. Radiopaque dye injected into either the right or left heart has been shown to produce an elevation in both systolic and diastolic pressures<sup>(18,19)</sup>. This rise occurs about one minute after the injection and the percent increase in both systolic and diastolic pressures is similar (about 40%). Since our diameter measurements were made during the injection period it was therefore necessary to verify that no pressure rise occurred as the dye was filling the pulmonary vessel.

One patient with a small ventricular septal defect and minimal shunt was studied. Two venous cutdowns were made and two catheters inserted into the pulmonary trunk, one for the dye injection and one for continuous monitoring of pressure. Over 1.5 sec, 37.5 cc of dye were injected through a #8 N.I.H. catheter with the pressure injector set at 300 P.S.I. The patient had mild pulmonary hypertension, 40/8 mm Hg, and during the injection no measurable increase in either systolic or diastolic pressures occurred (Fig. 10). Between 5 and 10 minutes later the pressure rose to 50/12 mm Hg.

Using the values obtained for systole ( $21.9 \pm 3.8$  (S.D.) mm Hg) and for diastole ( $8.1 \pm 2.4$  (S.D.) mm Hg) combined with the measured radii of the vessels (Figs. 11, 12, 13) two points on the elastic diagram were calculated from the Law of Laplace ( $T = P \times R$  where  $T$  = wall tension,  $P$  = intraluminal pressure and  $R$  = radius).

#### Plotting of Results

Although this method gives two numerical values for points on a tension-radius diagram for each artery, comparison of these values from one vessel to the next is complicated by several factors. First, the unstretched radius of any vessel decreases peripherally. Therefore, although an identically shaped elastic diagram will be present at any point along the course of a normal vessel, the actual numerical values for the wall tension and radius will differ. The same problem arises in attempting to compare these values from different patients. Finally, the degree of magnification of the vessels will vary slightly depending upon the exact distance from X-ray source to patient and patient to receiver.

Figure 10

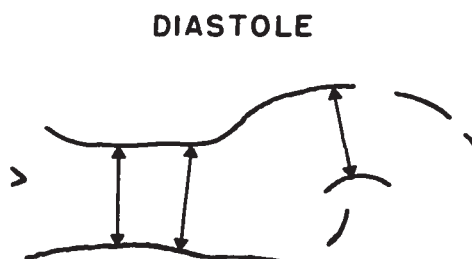
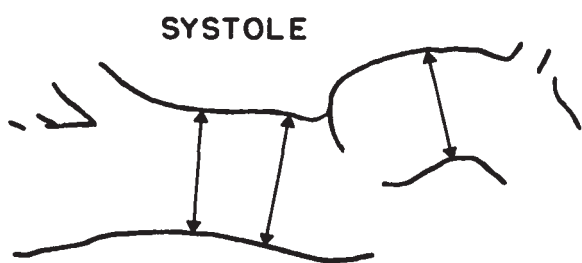
Pressure tracing from main pulmonary artery during injection of 37.5 cc radiopaque dye into the same vessel. No measurable change in pressure occurred during the injection. Patient had a small ventricle septal defect with minimal shunt.



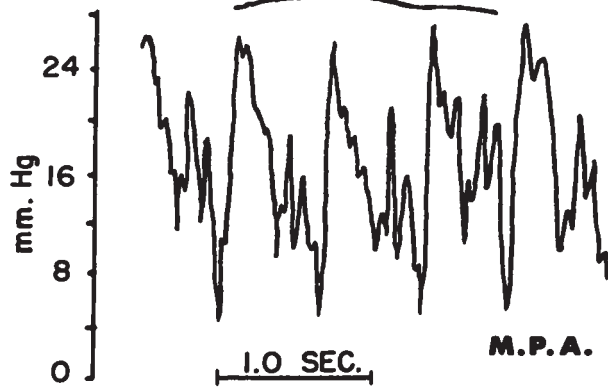
Figure 11

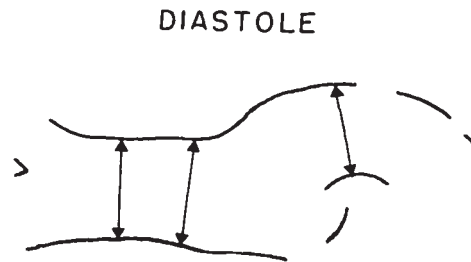
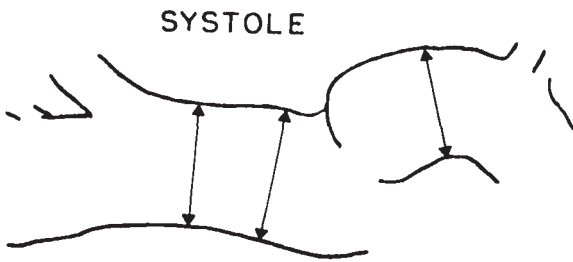
Two frames representing systole and diastole from the angiogram film of a male patient age 15 with normal pulmonary arteries. Illustrated are the vessel outlines used for the diameter measurements and the pressure tracing from the main pulmonary artery (M.P.A.).





Pt. M. G.  
Age 15  
Normal Pulmonary  
Arteries





Pt. M.G.  
Age 15  
Normal Pulmonary  
Arteries

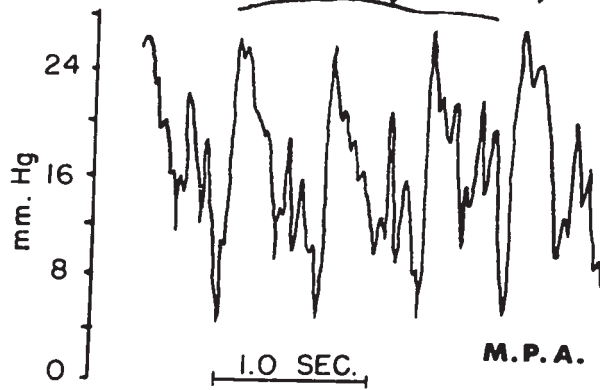
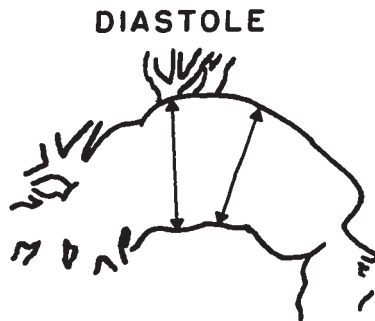
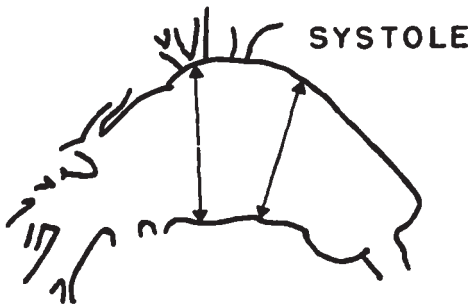


Figure 12

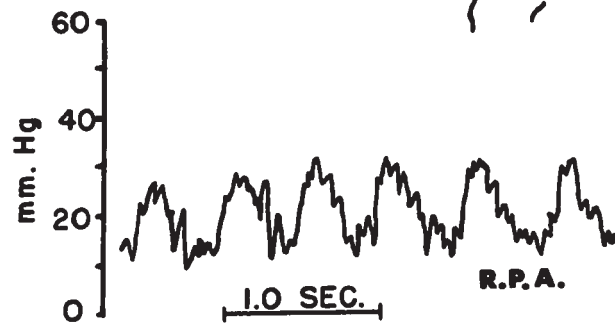
Two frames representing systole and diastole from the angiogram film of a female patient age 7 with pulmonary valve stenosis and post-stenotic dilatation. Dye injection is into the outflow tract, right ventricle. Illustrated are the vessel outlines for the diameter measurements and the pressure tracing from the right pulmonary artery (R.P.A.).

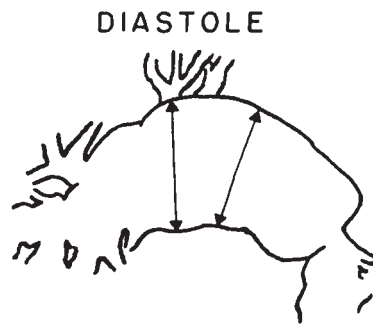
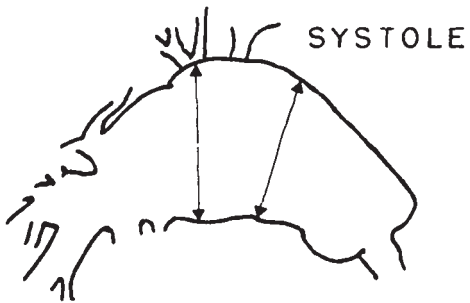
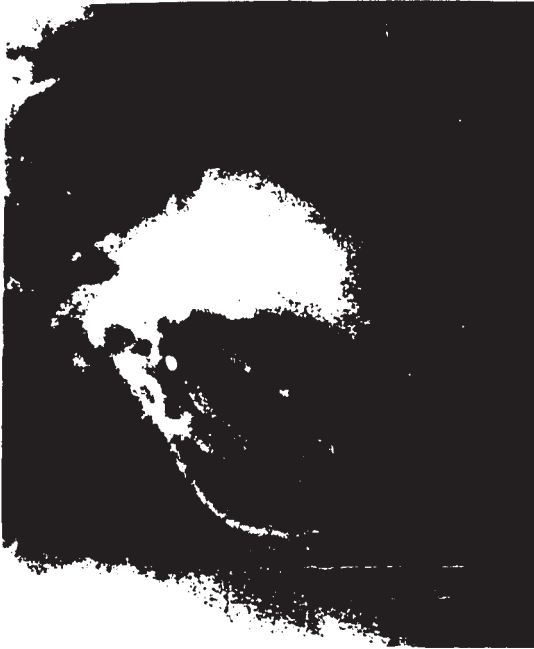


Pt. A.H.

Age 7

Pulmonary Stenosis





Pt. A.H.  
Age 7  
Pulmonary Stenosis

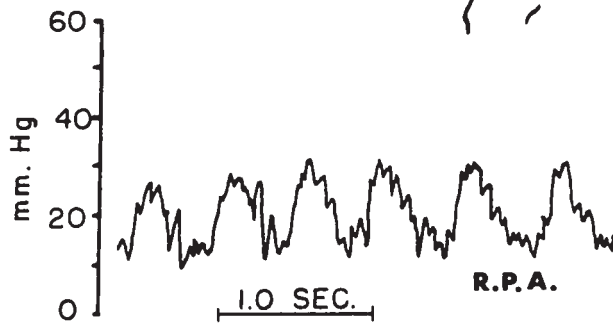
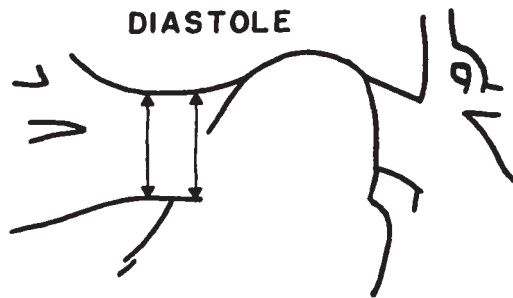
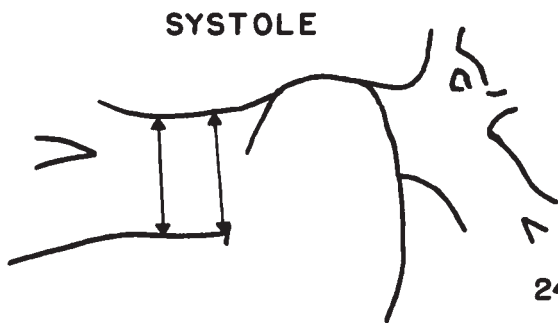
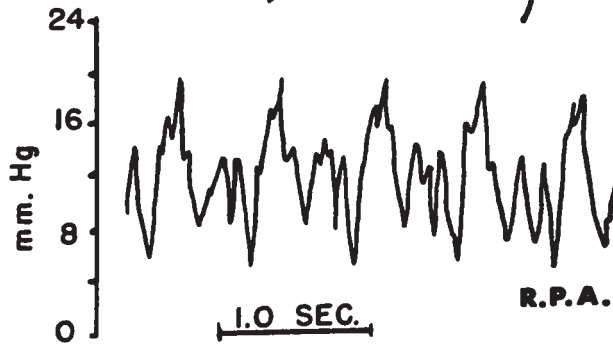


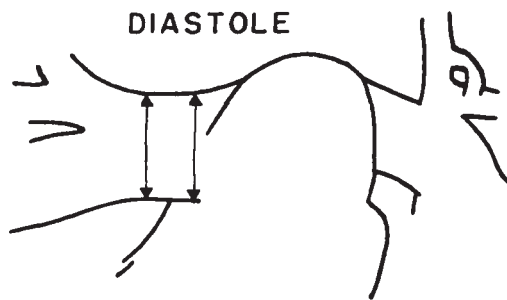
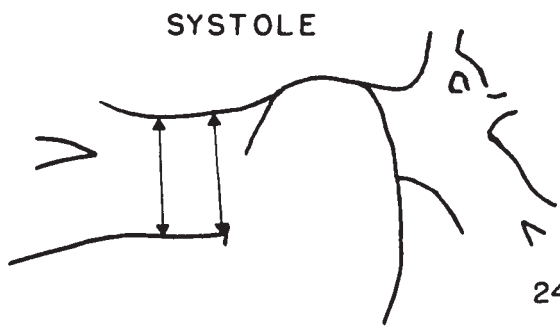
Figure 13

Two frames representing systole and diastole from the angiogram film of a male patient, age 15 with atrial septal defect. Dye injection into the outflow tract, right ventricle. Illustrated are the vessel outlines used for the diameter measurements and the pressure tracing from the right pulmonary artery (R.P.A.).



Pt. D.N.  
Age 15  
Atrial Septal  
Defect

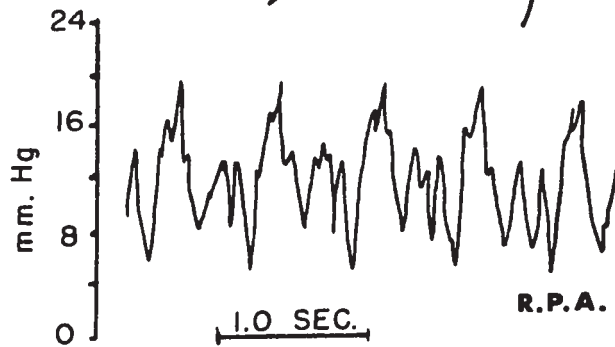




Pt. D.N.

Age 15

Atrial Septal  
Defect





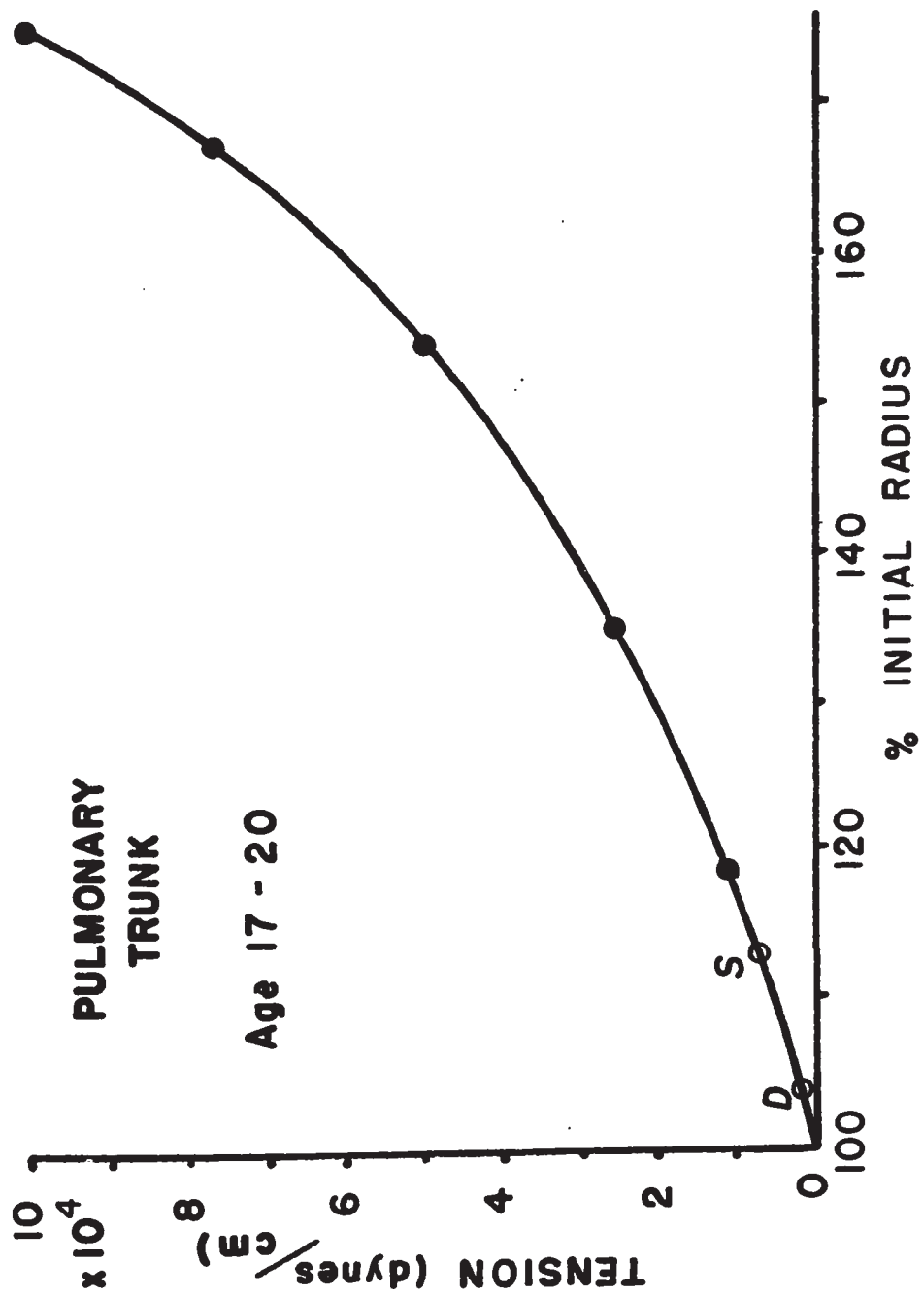
However, these pairs of points do represent a measure of the distensibility of the vessel over the normal pressure range. The slope of a line joining these two points would give a good approximation of the slope of that portion of the elastic diagram. This is because the low systolic and diastolic pressures found in the pulmonary arteries place the vessel on the initial, nearly linear, portion of the tension-length curve<sup>(70)</sup> (Fig. 14). Also, since it is this portion of the curve which is altered in poststenotic dilatation (143,144,146) we would expect this slope to be decreased for the artery distal to pulmonary valve stenosis, if poststenotic dilatation was present, even though the slope might be normal at systemic pressures.

The fact that systolic and diastolic pressures lie on the initial linear slope (Fig. 14) is useful for normalizing our measured values of radius ( $R$ ). A line passing through both points and projected to the abscissa (zero tension) will give an approximation of the unstressed or resting radius ( $R_0$ ). By dividing each value of  $R$  by the corresponding  $R_0$  we obtain an approximation of the wall strain ( $R/R_0$ ) at the various wall tensions. This allows us to plot a tension-strain diagram which makes possible the comparison of the elastic properties of normal pulmonary arteries with those showing poststenotic dilatation and those of atrial septal defect.

However, our values of wall strain ( $R/R_0$ ) will have a probable error that depends primarily on the accuracy of measurement of vessel radius. Considering film resolution and the quality of

Figure 14

Tension-strain diagram (strain expressed as percent extension) for the pulmonary trunk (mean age of patients, 18.3 years) plotted from values published by Harris *et al* (70). Systole (S) and diastole (D) lie on the initial nearly linear slope of the curve.



the tracings the probable error in R was estimated to be  $\pm 0.3$  mm. This value then affects the probable error in our calculation of  $R_0$ . A narrow pulse pressure (i.e., little difference between systolic and diastolic pressures) and a low slope of the elastic diagram will both increase this error in  $R_0$  and, therefore, increase the probable error in calculated wall strain ( $R/R_0$ ). The usual error in wall strain was about  $\pm 2.5\%$  but ranged from about  $\pm 0.5\%$  to  $\pm 7.0\%$ . This error was not great enough to alter the interpretation of our results but was sufficient to account for much of the scatter in our calculated points.

Tension was used for our graphs rather than wall stress (tension/unit thickness) since wall thickness was not measured. Also, by our methods it is not possible to measure changes in vessel wall thickness between systole and diastole. These changes were assumed to be the same for all groups and to be negligible in comparison to the changes in intraluminal radius since pulmonary wall thickness is about 1 mm at rest<sup>(71)</sup>. In this study we have assumed that the static elastic properties of the large vessels depend on the two structural components, elastin and collagen, as shown for human iliac arteries by Roach and Burton<sup>(142)</sup>. Muscle, which has a rather low elastic modulus<sup>(30)</sup> and which is present in relatively small quantities in the large pulmonary vessels, cannot be assessed by our methods but does not show any histological changes in patients with A.S.D. unless pulmonary hypertension has developed<sup>(79)</sup>.

In summary, a method is available for comparing the elastic

properties of the normal pulmonary artery with the same artery showing poststenotic dilatation beyond a pulmonary valve stenosis and also dilatation related to atrial septal defect. Due to the unusually low pressures found in the pulmonary arteries, values of tension and radius calculated at normal systole and diastole both lie on the initial linear slope of the elastic diagram. It is this slope which decreases if turbulence and a murmur develop beyond a stenosis and if the pulmonary artery dilatation seen with A.S.D. is on the same basis as poststenotic dilatation a similar decrease in the elastic modulus should be evident.

Method (ii)Vibration of Arteries

McDonald<sup>(112)</sup> found no evidence to suggest that the physical properties of either elastin or collagen were altered after blood flow ceased. Roach and Harvey<sup>(146)</sup> produced poststenotic dilatation in perfused, artificially stenosed *in vitro* preparations of human external iliac arteries and showed the characteristic alterations in the elastic properties of the distal segments illustrated in Figure 7. Foreman and Hutchison<sup>(53)</sup> could not reproduce this but, because of asymmetry and parallax, their use of a travelling microscope could have missed the small changes in radius produced.

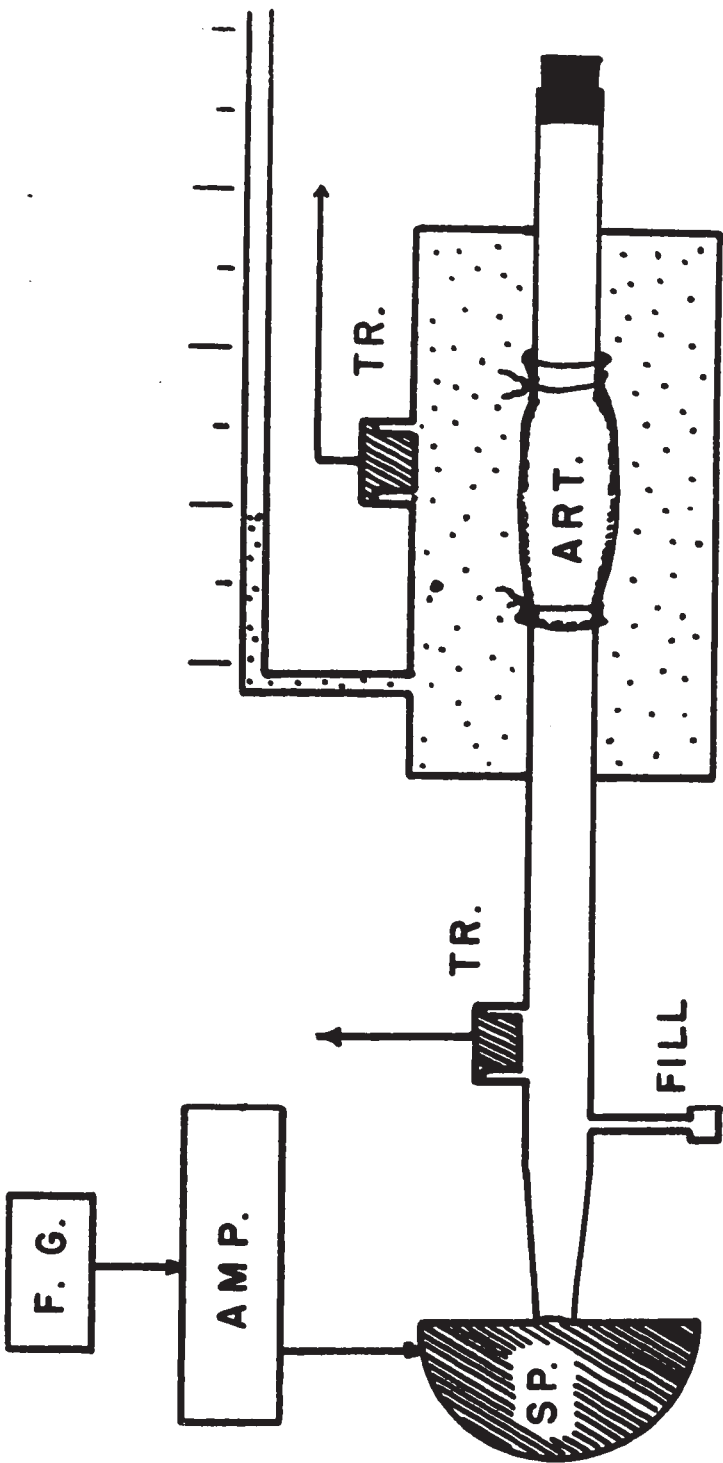
To determine whether specific vibrations could create these alterations, human external iliac arteries were obtained from autopsies and immediately immersed in a solution of 1:10,000 aqueous merthiolate in normal saline which had an osmolarity of approximately 250 mOsm/litre. These were stored in a refrigerator at 4°C until use. This solution has been previously shown to preserve the static elastic properties of an artery for several days<sup>(142)</sup> and in our experience a normal tension-length curve could still be obtained on the tenth day after removal.

Mounting the arteries

Most arteries were used within a few hours of autopsy and were mounted in a closed chamber (plethysmograph) containing the same merthiolate solution. The chamber was open to atmospheric pressure along a calibrated tube (Fig. 15). The artery was filled from a

Figure 15

The arteries were mounted in a plethysmograph which was open to atmospheric pressure along a calibrated tube. The vessels were filled from a variable pressure reservoir. Vibrations were produced within the artery by a loudspeaker (SP) driven by an amplifier (AMP) which received a signal from a frequency generator (F.G.). A transducer (TR) was mounted in the wall of the tube leading to the vessel and monitored the output of the loudspeaker. A second transducer was mounted in the wall of the plethysmograph to determine the characteristics of transmission of vibration by the artery.



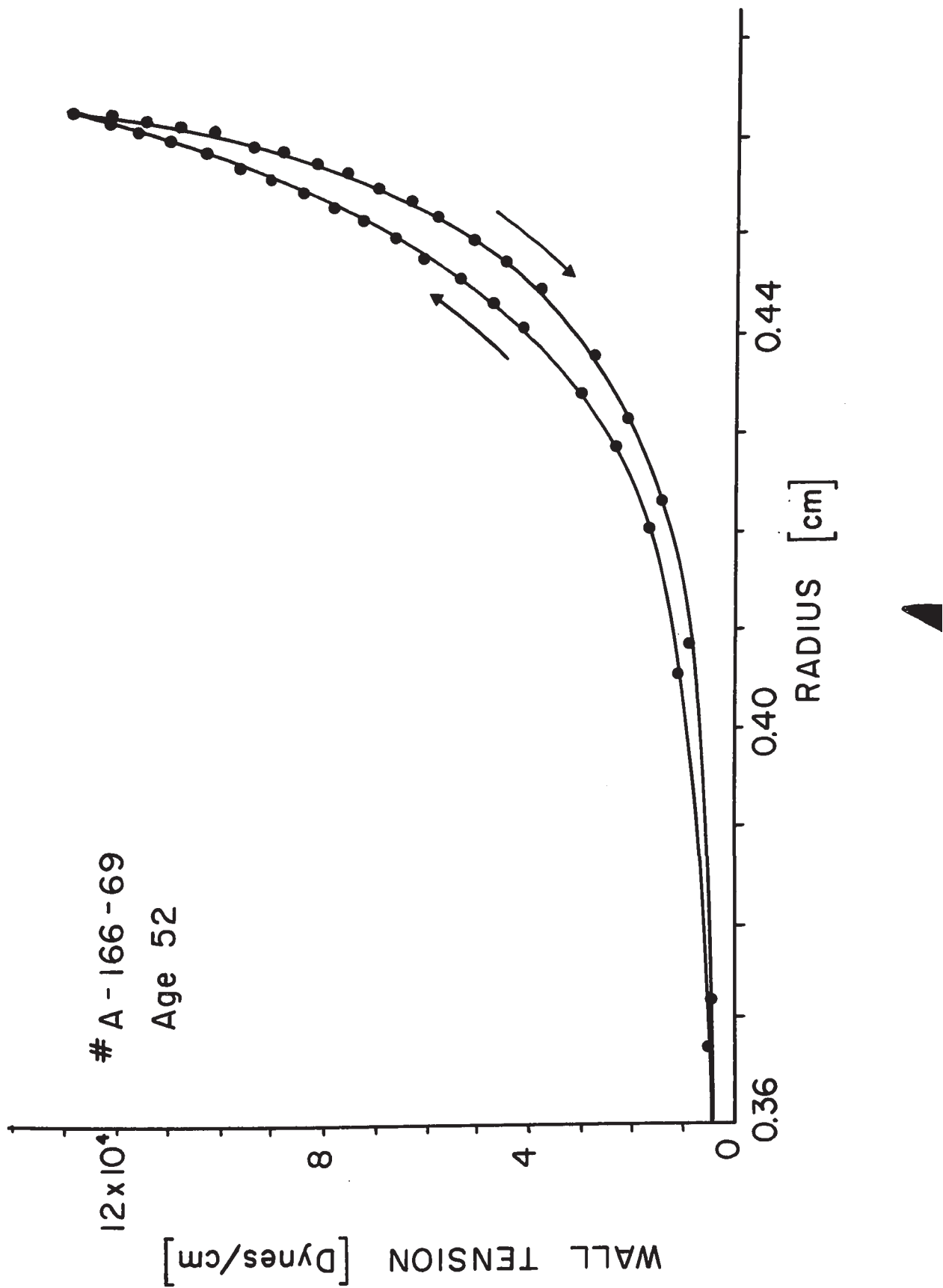


variable pressure reservoir and the volume of the artery could be measured for any given pressure by fluid displacement along the calibrated tube. Changes in volume reflected only changes in radius since the wall can be considered incompressible<sup>(34)</sup> and the length was held constant. Using the Law of Laplace as modified for arteries (25,27) ( $T = P \times R$  where  $T$  = wall tension,  $P$  = intraluminal pressure and  $R$  = vessel radius) an "elastic diagram" (Fig. 16) was constructed for the arterial wall before and after vibration. The artery was distended from 0 to 300 mm Hg pressure several times before commencing measurements. This provided a stable and reproducible curve as shown previously by Bergel<sup>(13)</sup>. This graph was not a stress-strain diagram. Since the vessel was enclosed in the plastic, fluid-filled chamber the opening pressure for each artery could not be assessed with sufficient accuracy to give a value of the radius at zero wall tension. Thus the exact radius of the vessel at each pressure was used rather than strain. In addition wall thickness at the various pressures could not be evaluated so wall tension (dynes/cm) was used rather than wall stress (dynes/cm<sup>2</sup>).

The artery was mounted on a rigid plastic tube connected directly to a loudspeaker (Fanon HOA-5A-8) with a plastic coated diaphragm. The tubing on which the vessel was mounted had a terminal "lip" over which the vessel was slipped and behind which the vessel was tied. This "lip" assured that the vessel when distended maintained a shape as close to cylindrical as possible so that end effects which might alter the calculations of radius from volume of a cylinder were avoided. Measurements of vessel length were made between these easily

Figure 16

Elastic diagram of an external iliac artery (age 52) as calculated using the plethysmograph and the Law of Laplace. Note the narrow hysteresis loop indicating viscous properties of the wall.



visible bulges. The mounted vessel length was made to approximate the *in vivo* length as closely as possible. Excision of the external iliac artery produced little measurable change in the vessel length (about 1-2%). The artery was therefore measured with a ruler before mounting and, when mounted under a slight degree of longitudinal tension, it closely approximated the *in vivo* length.

### Loudspeaker characteristics

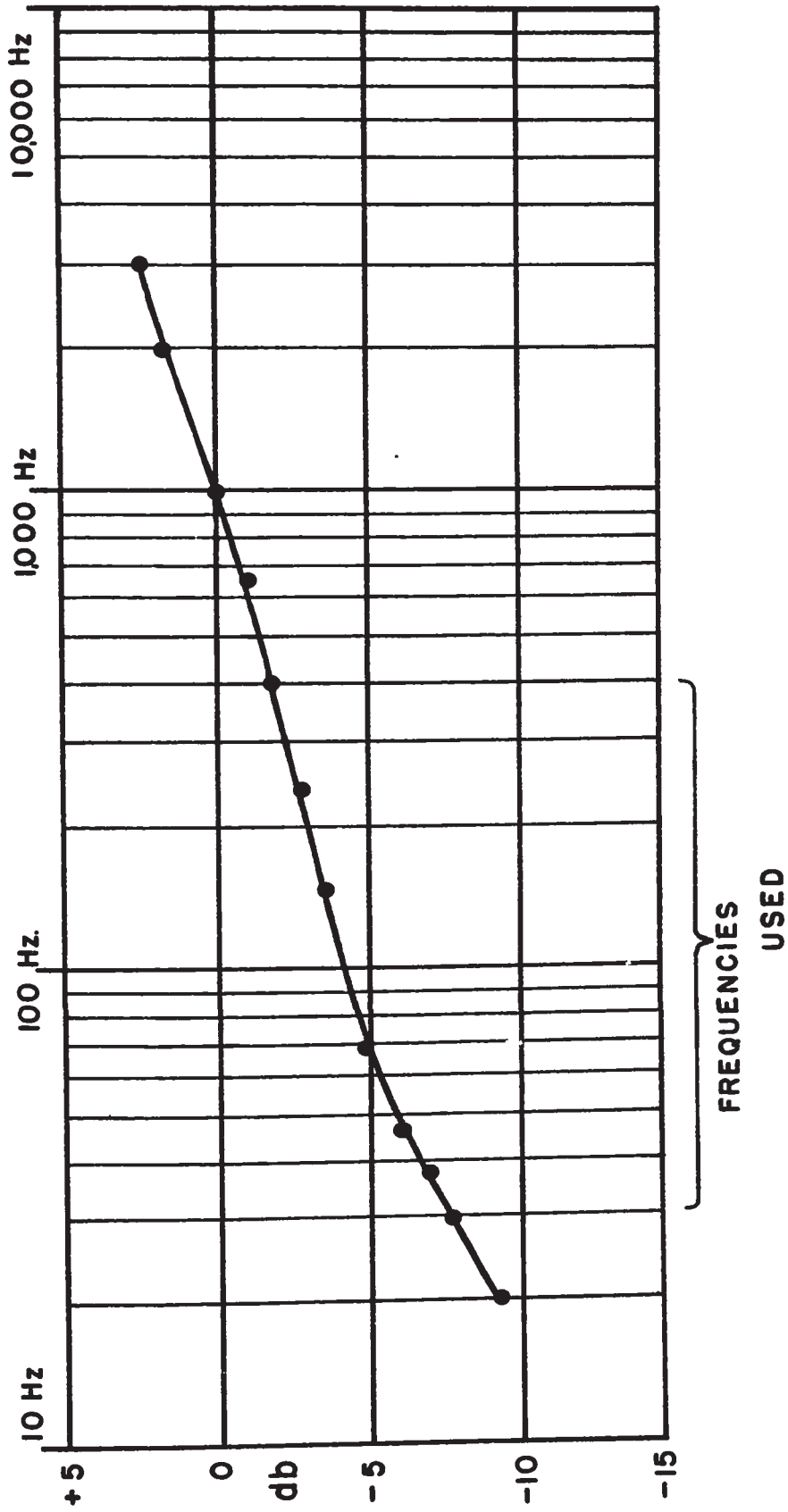
The loudspeaker used to vibrate the artery was driven by a Pako amplifier which received a signal from a frequency generator (Heathkit Model IG-18). The magnet and coil were immersed in fluid under the identical pressures to allow the diaphragm to move when exposed to the high pressures within the artery. This fluid was circulated and therefore also acted as a coolant for continuous operation of the speaker.

The frequency response curve (Fig. 17) shows the calculated amplitude output of the loudspeaker for each frequency setting. This graph was constructed by setting a specific amplitude input for the speaker at 1000 Hz and considering the output, as measured in the intra-arterial fluid, to be 100%. Then by changing only the frequency setting we determined the speaker output for frequencies above and below 1000 Hz. As shown, the amplitude decreased as the frequency decreased, and increased as the frequency was raised.

The measurements of the amplitude and frequency of the vibration within the intra-arterial fluid were made with a transducer (Stow Laboratories, Pitran Model PT-2) mounted in the wall of the plastic tubing leading from the speaker to the vessel. This transducer had a

Figure 17

The frequency response of the Fanon, Model HDA-5A-8 loudspeaker is illustrated with 100 mm Hg pressure in the tubing leading to the vessel. The output at 1000 Hz was considered to be 100%. By changing the input frequency only the speaker output was determined relative to 1000 Hz. Amplitude is seen to decrease over the range of frequencies used for vibration of the artery.



flat frequency response from 1 Hz to 150 KHz. A matching Pitran PT-2 transducer was mounted in the wall of the plethysmograph to monitor the vibrations transmitted to the fluid surrounding the artery. However, its usefulness in this regard was limited. Vibrations transmitted from the length of plastic tubing upon which the vessel was mounted and extending into the plethysmograph could not be differentiated from vibrations passing through the vessel wall.

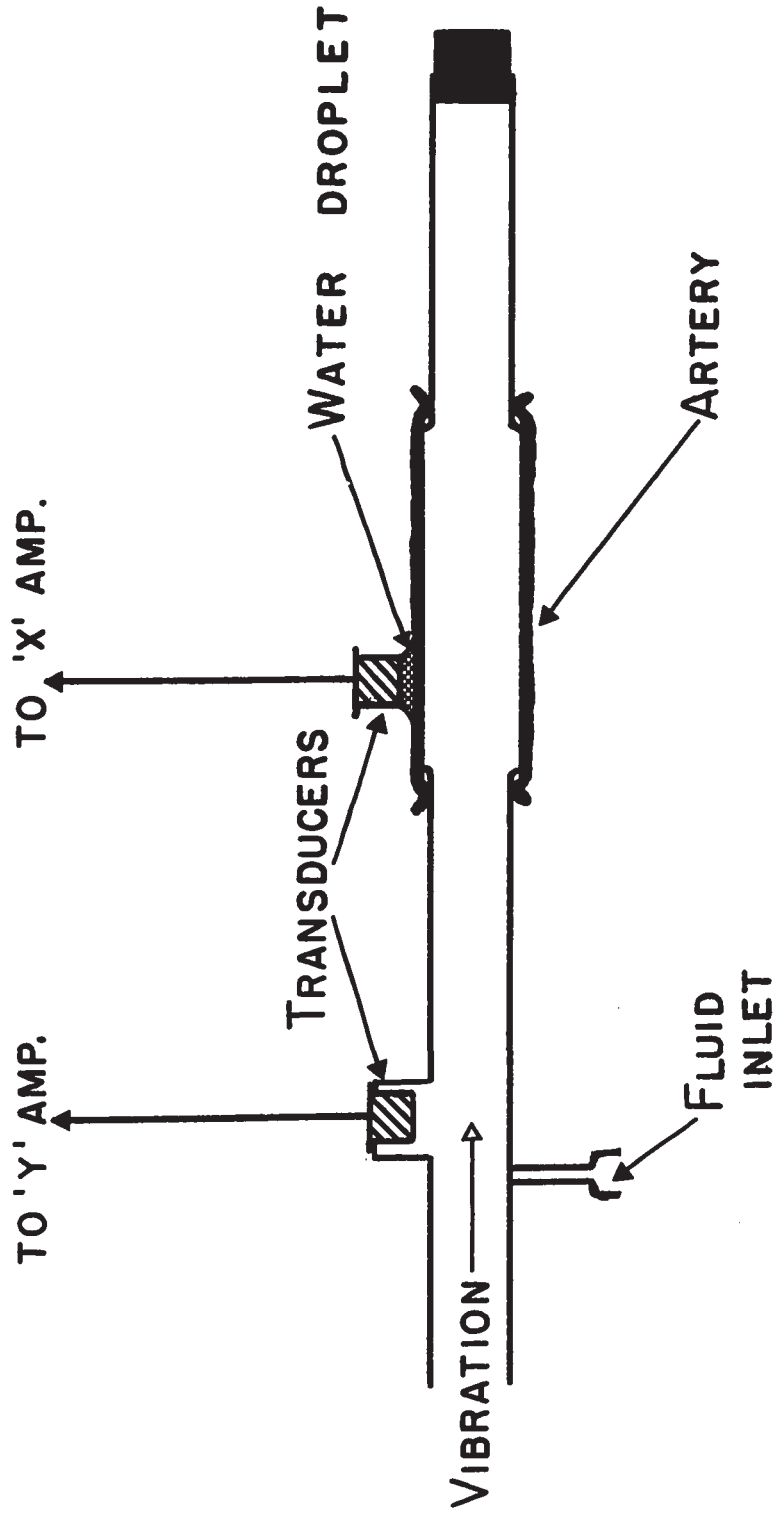
#### Arterial response

This second transducer was utilized, however, by altering the physical set-up of the apparatus (Fig. 18). Arteries were attached to the lengths of plastic tubing, filled with fluid at variable pressure and suspended, under a slight degree of longitudinal tension, in air. They were kept from drying by applying the merthiolate solution from a dropper two or three times per minute. The second transducer was removed from the wall of the plethysmograph and suspended just above, but not touching, the arteries. A drop of fluid introduced between the artery and the transducer made the contact by surface tension. The response of the arterial wall from 10 to 1000 Hz could then be recorded and compared to the intraluminal vibrations. The outputs from the matching transducers were connected to the 'X' and 'Y' matching amplifiers of a Dumont Model 401B oscilloscope. The relative amplitudes of the frequencies inside and outside the vessel were measured. In addition the transducer outputs were connected to a two-channel recorder (Sanborn Twin-Viso Model 60-1300). The response of this recorder was flat only to 30 Hz so it was not used for amplitude measurements.

Figure 18

To measure transmission of vibration through the arterial wall the plethysmograph was removed and the external transducer was coupled directly to the wall by the surface tension of a drop of water. The vessel was distended a 100 mm Hg pressure and kept from drying by periodically applying the aqueous merthiolate solution with a dropper. Vibrations from 10 to 1000 Hz were introduced into the vessel. The amplitude of the vibration within the artery was compared with that recorded by the external transducer at representative frequencies over the range noted. An oscilloscope with matching 'X' and 'Y' amplifiers was used for the display.





Both recorders demonstrated that the vibrations were transmitted readily through the arterial wall and were of identical contour on both sides of the vessel wall. There was no evidence of reflections within the wall (Fig. 19) despite its multi-layered structure.

The amplitude of the frequencies used to vibrate the vessels was selected arbitrarily since no information is available on the energy content of murmurs. At 100 Hz, when a stethoscope was applied to the apparatus, the amplitude was similar to that of a grade 3/6 murmur<sup>(105)</sup> (see Appendix 1). The settings on the amplifier and frequency generator were not altered from this output when the different frequencies were used.

The actual vibration of the arteries took place while the vessels were distended with an intraluminal pressure of 100 mm Hg. This high pressure, for a period of hours, caused some "creep" (a progressive extension) so that the circumference, and therefore the vessel volume, gradually increased with time due to this viscous property of the wall. The rate of this increase varied from one vessel to another but usually assumed a characteristic change with time (Fig. 20). The duration of this creep was repeatedly verified and was of a much longer duration than expected. The rate was very rapid over the first hour, so volume measurements were usually not begun until about 4 hours after mounting. Over the succeeding 24 hours the creep continued at a moderately rapid rate and thereafter slowed greatly but was rarely complete before 60 hours. To interpret our results, this predicted increase in volume was used as a baseline and dilatation due to vibration could be shown only by a significant

Figure 19

No change in the shape of the generated sine wave was noted on passage of the vibrations through the vessel wall suggesting that reflections did not occur despite the multilayered structure of the wall. Recordings were taken on the Sanborn Twin Viso recorder. Amplitude settings are random and cannot be used for measurement. A slight phase lag is evident from internal to external recording due to the distance between the transducers.

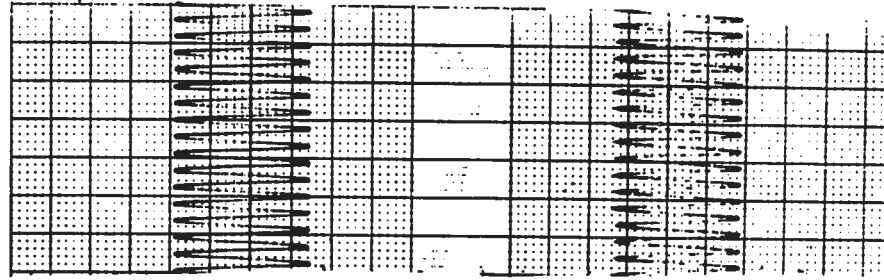
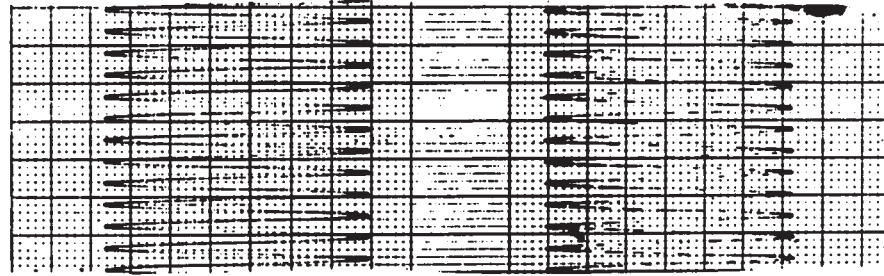
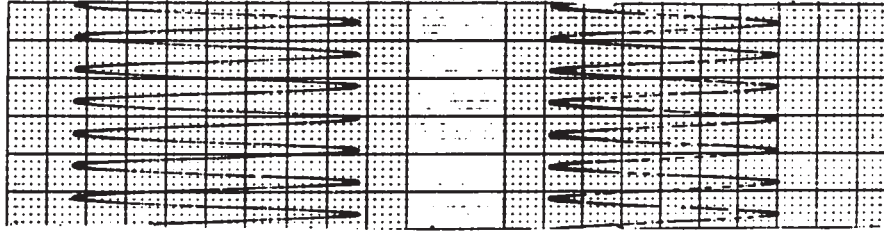
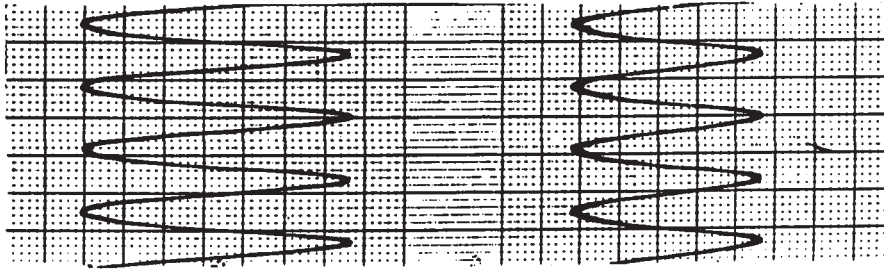
FREQUENCY

10 Hz

20 Hz

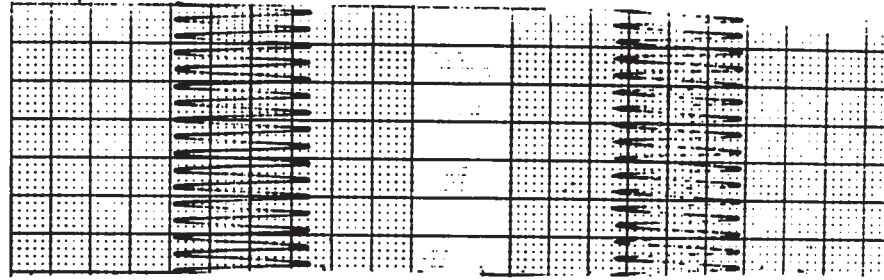
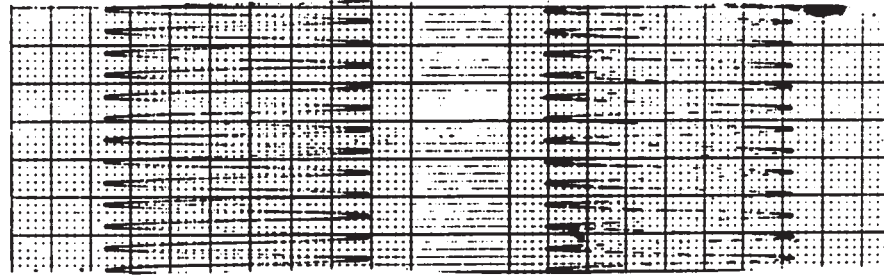
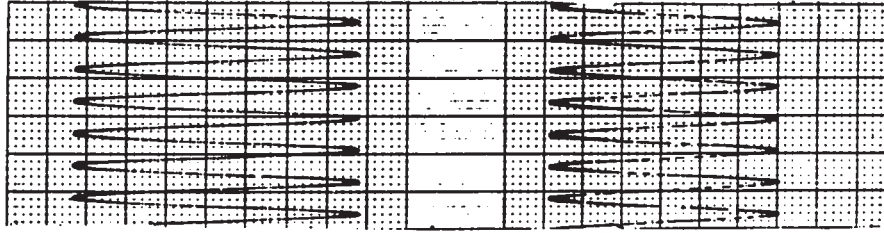
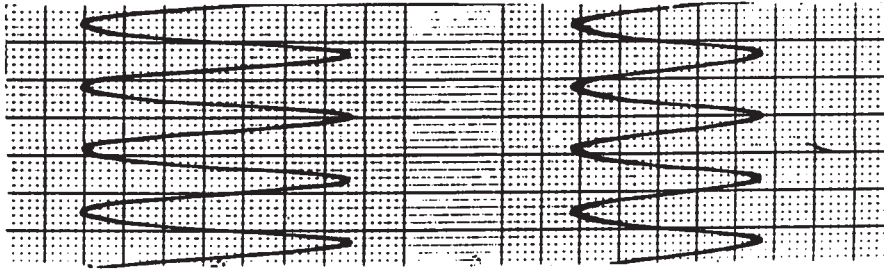
30 Hz

40 Hz



External

Internal

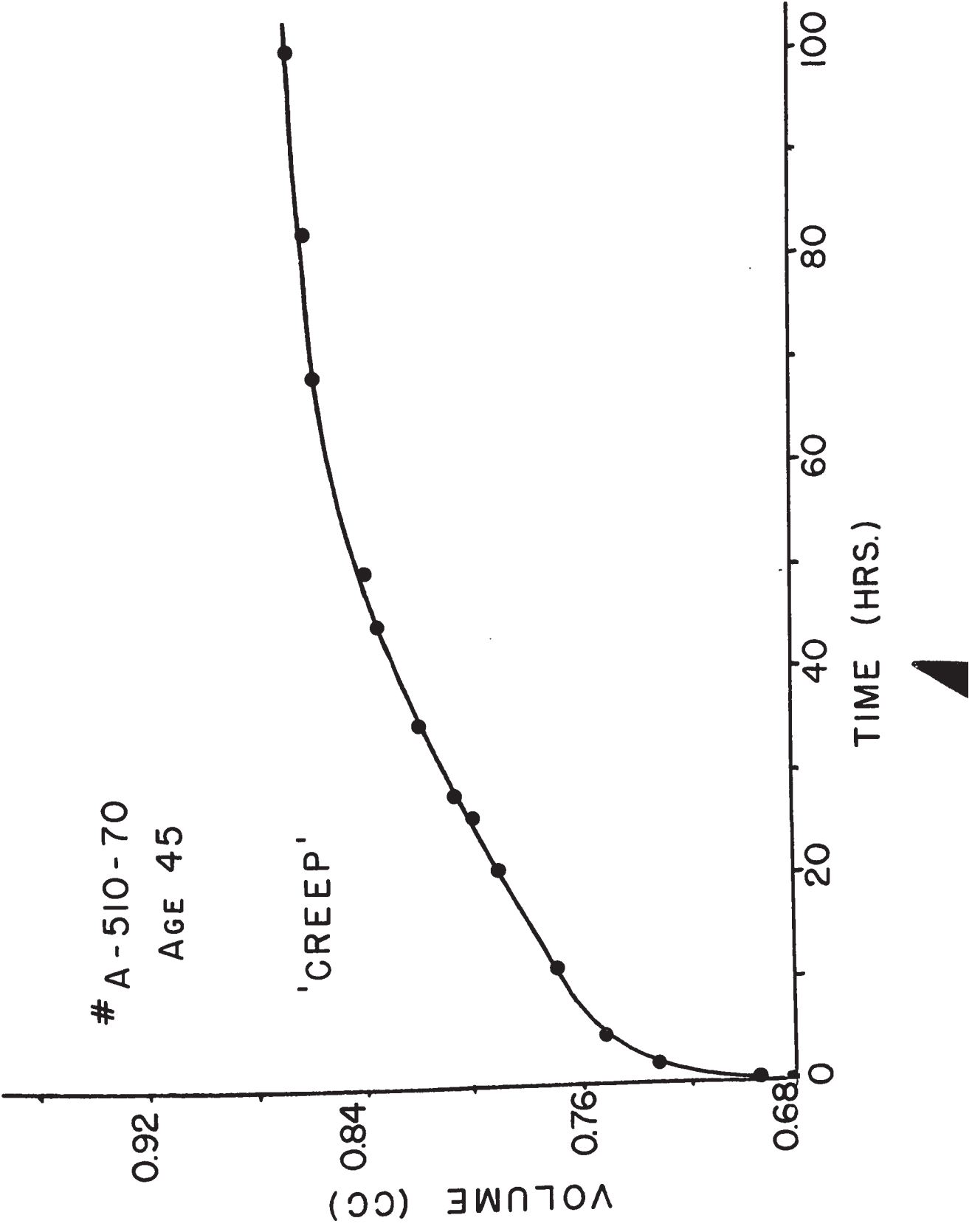


# A - 510 - 70 Age 45

Figure 20

"Creep", a viscous property of the arterial wall, produces a gradual increase in the vessel volume (or radius) when the vessels are held at 100 mm Hg pressure for a period of hours. The general shape of this curve is consistent from vessel to vessel with an initial rapid increase in volume followed by a slow distension. However, the exact rates are variable.

A significant deflection from this curve must be produced by vibration.



deviation from this line.

The frequencies selected to vibrate the arteries fell within the range of frequencies reportedly contained in murmurs<sup>(32, 115,174)</sup>. We divided these frequencies, for the purpose of interpretation, into three groups; (i) frequencies less than 100 Hz, (ii) frequencies from 100-200 Hz, (iii) frequencies greater than 200 Hz.

#### Histological examination

Following vibration, the vessels were examined under light microscopy for evidence of structural alterations. The vibrated vessels were compared to controls which consisted of either the opposite external iliac artery or another short segment of the same vessel.

The vessels were fixed at various intraluminal pressures ranging from 30 mm Hg to 100 mm Hg by the method described by Wolinsky and Glagov<sup>(177)</sup> (Fig. 21). After flushing the vessels with normal saline solution they were mounted on a plastic bracket with a plastic tube inserted in each end. They were then flushed again with normal saline and distended by increasing the pressure in the normal saline flask. The tube leading to the vessel was then clamped and the saline flask exchanged for one containing fixing solution. The vessels were perfused with the 10% formaldehyde, 1% calcium chloride fixing solution and their intraluminal pressure maintained. Finally the distended vessel was immersed in a plastic chamber containing the same formaldehyde and calcium chloride solution. It was left to fix for one hour.

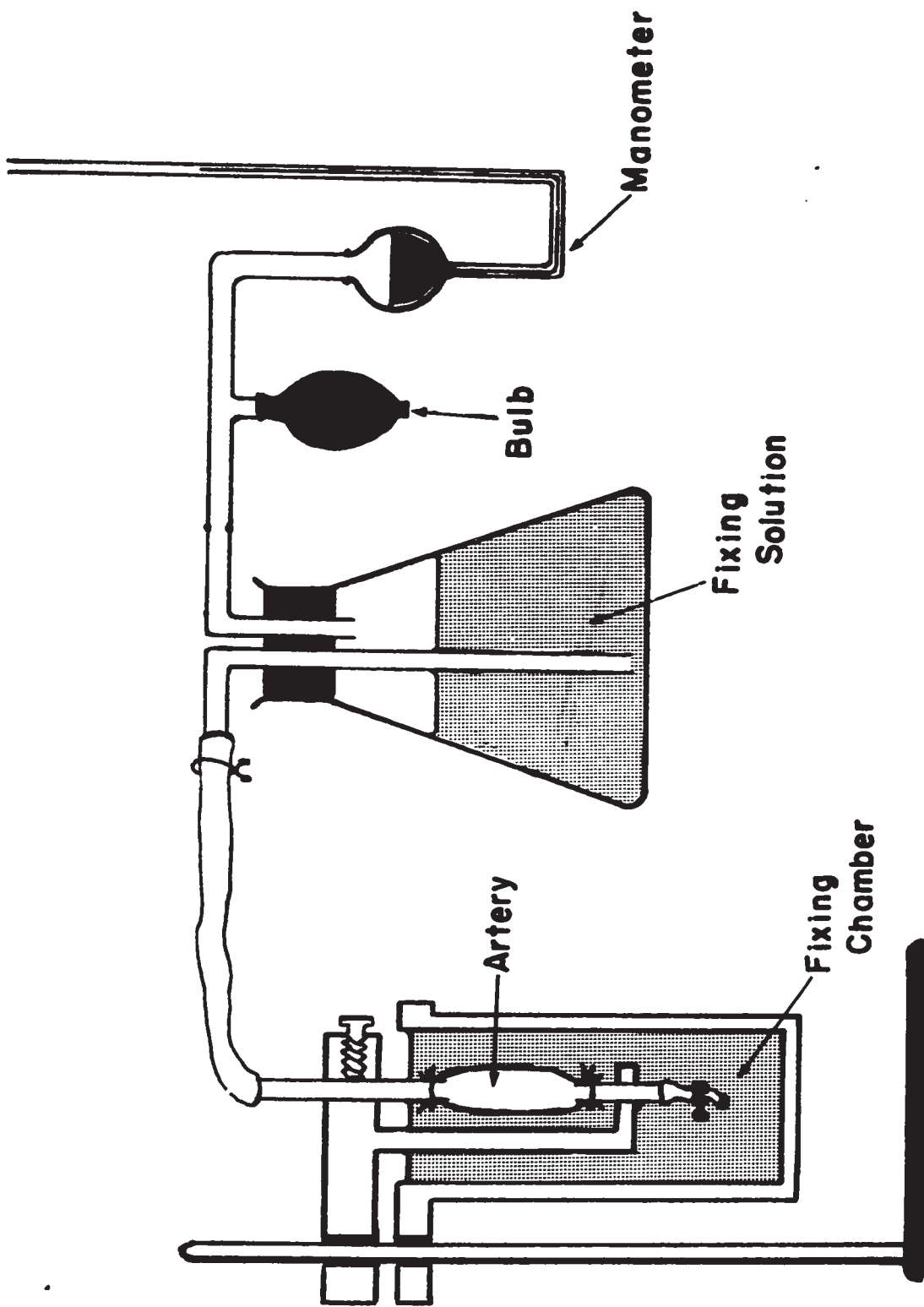
The vessels were later sectioned, mounted and stained with Weigert's stain in order to examine the elastin network and its architecture at various intraluminal pressures.

Figure 21

To fix arteries at various distending pressures they were attached to two lengths of plastic tubing and mounted on a plastic holder. The lower tube could be clamped off. The upper tube was connected to a flask containing, first, normal saline then, second, fixing solution (10% formaldehyde and 1% calcium chloride).

The artery was flushed with normal saline and distended to the desired pressure. Fixing solution was then substituted for the saline and flushed through the vessel. The vessel was immersed in the same fixing solution for one hour while distended and then mounted and stained with Weigert's stain.





Method (iii)Frequency Content of Murmurs

Several authors (80,81,144,145,146) have suggested that arterial wall vibration by the intravascular turbulence distal to a stenosis results in a form of structural fatigue, i.e., poststenotic dilatation. However, little is known about the actual frequency spectrum to which such vessels are exposed. The published reports on the frequency content of murmurs refer mainly to recordings made from the chest surface (32,115,116,119,174,175) and this literature does not include any mention of accompanying poststenotic dilatation. Since the thorax apparently attenuates a variety of frequencies (50,81), the available information is inadequate for my purposes. The choice of frequencies in section (ii) and the interpretation of the arterial response requires further support. It is therefore necessary to show that arterial dilatation *in vivo* does accompany the frequencies used *in vitro*. This means that an analysis of the frequency spectra of intravascular turbulence beyond a stenosis is needed.

Selection of patients

Pulmonary stenosis and aortic stenosis are two relatively common cardiac lesions which produce poststenotic dilatation (16,22,35,40,85,89,152). However, in section (ii) human iliac arteries were vibrated when distended with a pressure of 100 mm Hg *in vitro*. Since, for the pulmonary arteries, the intravascular pressure is normally much lower than that value and the structure of the elastin significantly different from iliac vessels, it was decided that aortic murmurs would

be the most suitable for a frequency analysis. These are available in reasonable numbers and usually have adequate angiographic studies performed to determine whether or not poststenotic dilatation is present.

Seven patients were selected for this study on the basis of an audible systolic murmur at the second right intercostal space<sup>(100)</sup> and the presence of a systolic gradient across the aortic valve.

#### Apparatus used

To determine the frequencies to which the aortic wall was being exposed, a double lumen phonocatheter (American Electronics Laboratories, Model 192) was inserted via the brachial artery to the root of the aorta where the murmur of aortic stenosis originates<sup>(49)</sup>. The catheter tip was placed about 3-6 cm distal to the aortic valve. The piezoelectric crystal in this instrument is pressure sensitive and transforms small pressure fluctuations into electric energy for recording as "sound"<sup>(106)</sup>. It has a flat frequency response from 20 to 10,000 Hz. By photographing the motion of spherical polystyrene beads in the turbulent area beyond a model stenosis Foreman and Durie<sup>(52)</sup> have demonstrated a good correlation between these "particle tracer frequencies" and the pressure spectra recorded with a microphone set-up. The frequency analysis of the output from our phonocatheter would, therefore, give the required information on the frequency spectrum to which the vessel wall was exposed.

An Electronics for Medicine DR8 recorder was used to display the patient's electrocardiogram as well as the murmur picked up by the

phonocatheter. The TPD-5 amplifier on the DR8 was set at 50-500 Hz bandwidth to display the unfiltered heart sounds and murmur (upper trace, Fig. 22). This made correct timing of the filtered murmur easier (centre trace, Fig. 22). The paper speed for all recordings was 50 mm/sec.

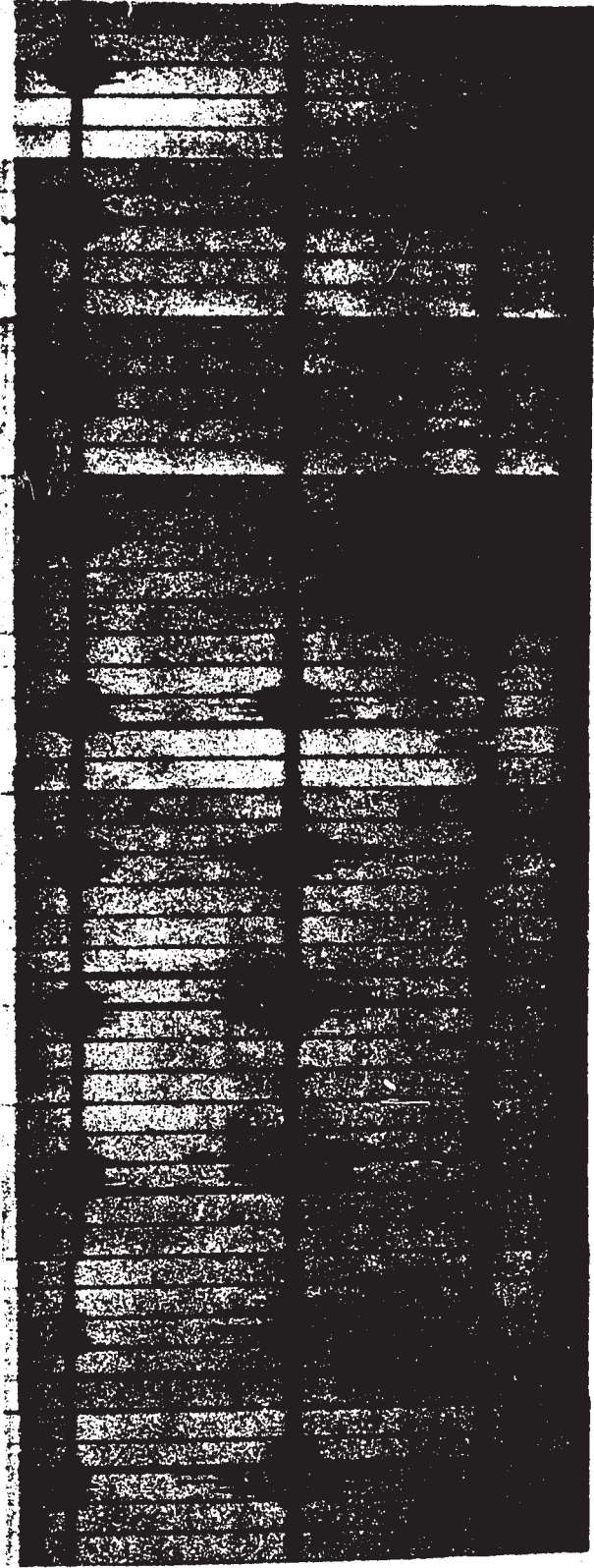
The filtration of the murmur was accomplished by arranging two Krohn-Hite Model 310AB and one model 3500 in series. The output from the phonocatheter was passed directly through these filters and into the EEP-8 amplifier of the DR8 recorder (Fig. 23). The frequency response of this amplifier, set at the bandwidth of 12 to 2000 Hz, was flat  $\pm 3$  db from 40-460 Hz and  $\pm 10$  db from 40-910 Hz (Fig. 24). This was determined by putting a known input from a frequency generator (Heathkit, model IG 18) through the filters and amplifier in series. The amplitude output for each frequency was then measured on the recorded print-out.

Each band pass filter had an attenuation of 24 db per octave and by connecting the three filters in series their effectiveness in narrowing the output band can be increased<sup>(143)</sup>. With the high and low pass settings at the same frequency the gain of each filter was reduced 6 db giving a total amplitude loss of 18 db  $\pm 1$  db for the three filters. For each filter the 3 db down points, measured from the pass band peak, occur at 0.77 and 1.30 times the cut-off frequency according to factory specifications. This was verified by using the Heathkit frequency generator to put the limits of this one-third octave through each filter and recording the output on a RMS

Figure 22

Samples of an intraaortic murmur recorded from a phonocatheter (patient N.M.). The upper trace is the unfiltered murmur used only for timing. Amplitude settings are independent of the centre trace which displays the murmur filtered at each of the 'centre' frequencies. This centre trace was used for amplitude measurements for construction of a histogram representing the murmur's frequency spectrum. The lower trace is the electrocardiogram (E.C.G.).

40 Hz 55 Hz 80 Hz 120 Hz 160 Hz 210 Hz 300 Hz 460 Hz 670 Hz 910 Hz

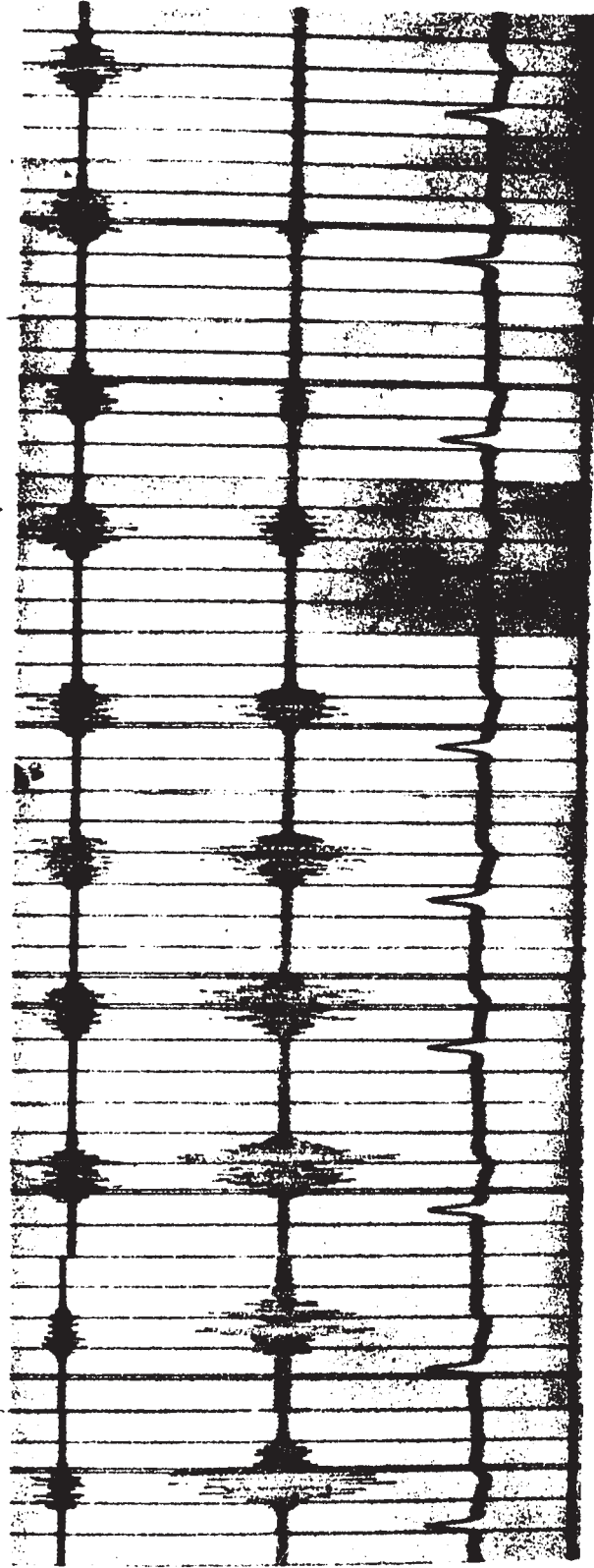


Unfiltered

Filtered

E.C.G.

40 Hz 55 Hz 80 Hz 120 Hz 160 Hz 210 Hz 300 Hz 460 Hz 670 Hz 910 Hz



Unfiltered

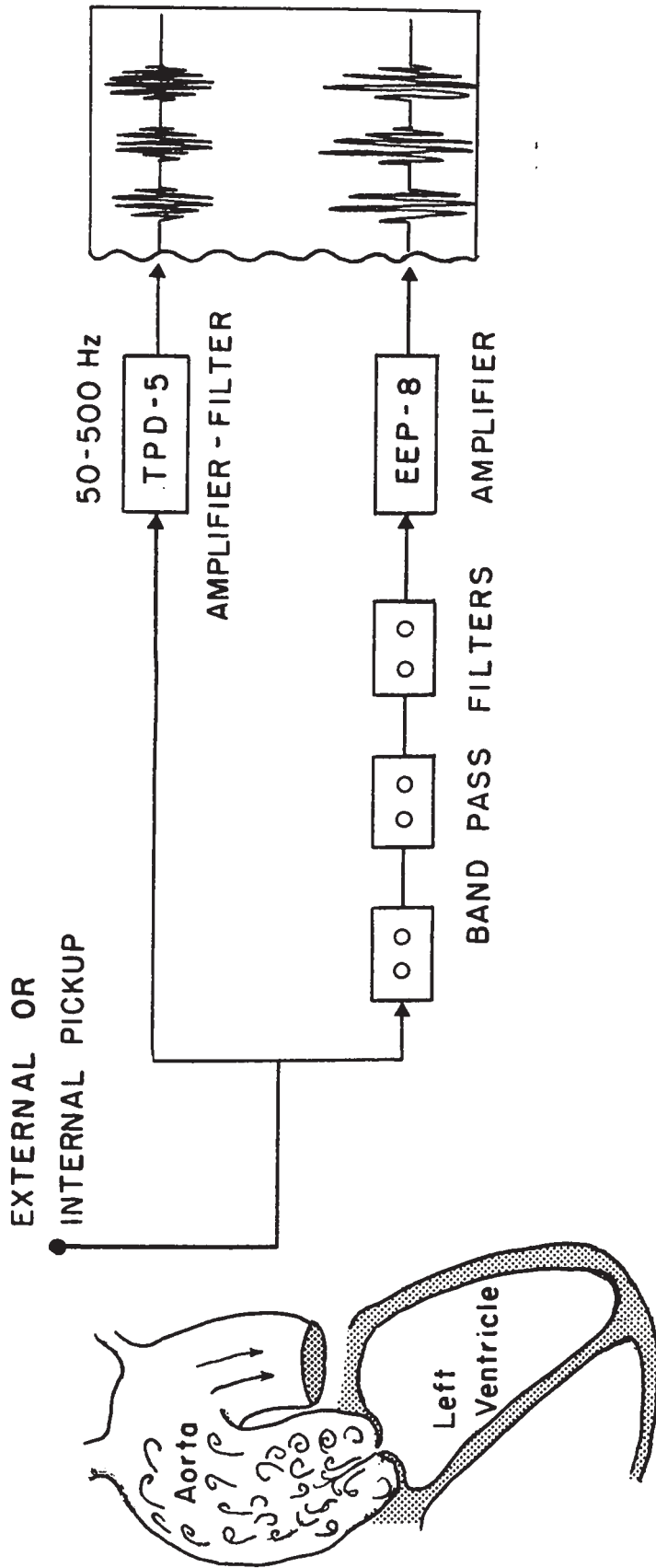
Filtered

E.C.G.

Figure 23

Schematic diagram illustrating the equipment used for the frequency analysis of aortic murmurs. The output from the intraaortic phonocatheter or external crystal microphone passed: (i) to the TPD-5 amplifier of the Electronics for Medicine recorder and directly onto light sensitive paper, and (ii) to the three Krohn Hite band pass filters in series, set at one of the ten 'central' frequencies, then to the EEP-8 amplifier and directly onto light sensitive paper.





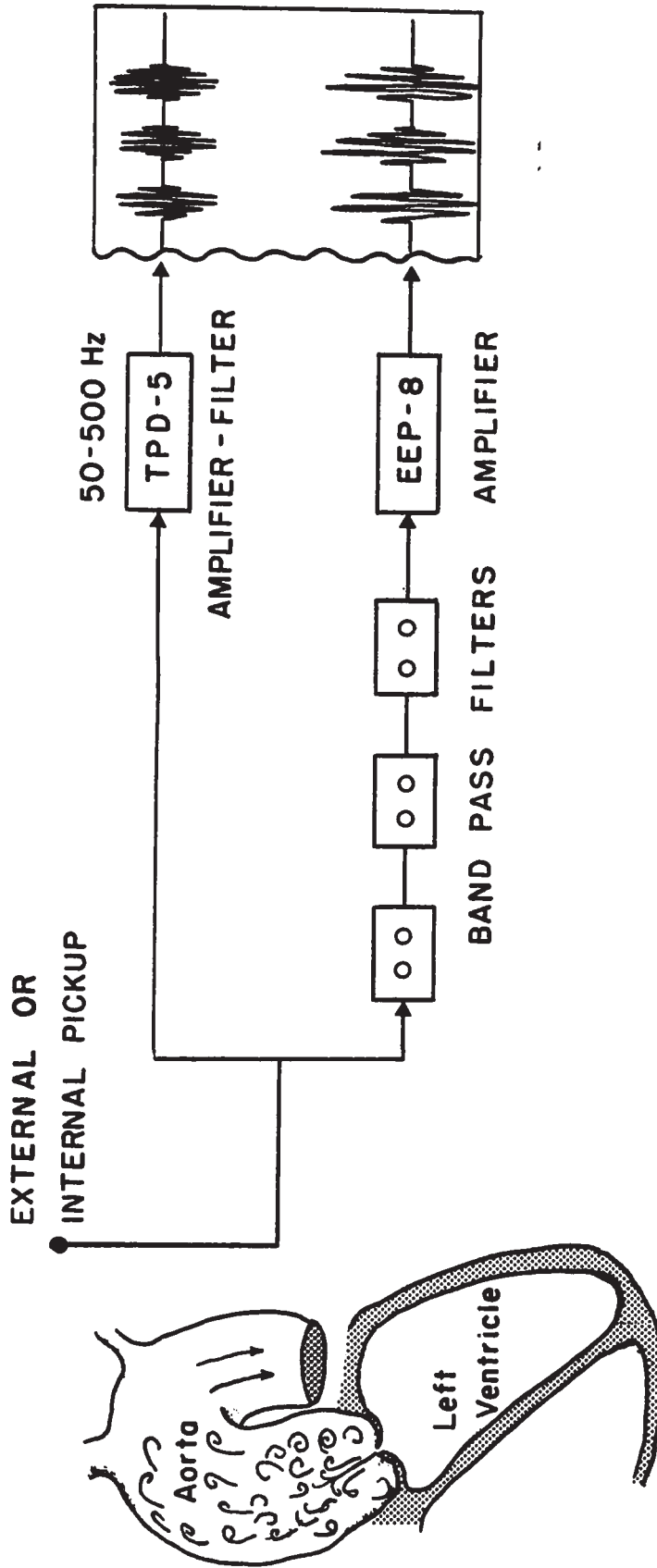
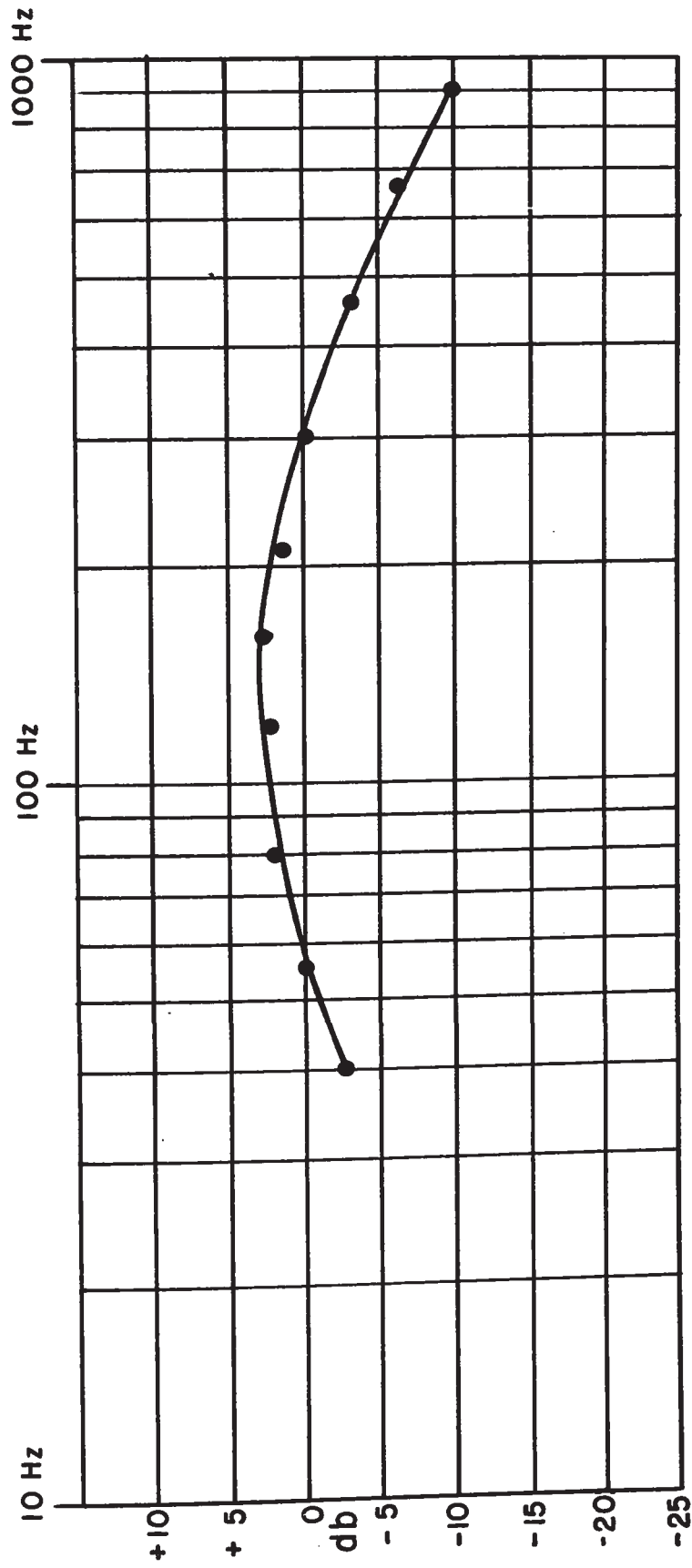


Figure 24

The frequency response curve for the three band pass filters and EEP-8 recorder amplifier in series. This was calculated by providing a reference input from the Heathkit IG-18 frequency generator and measuring the output on the print out paper of the recorder.



voltmeter. The three filters in series, therefore, produced a verified 9 db drop from their peak over the one-third octave (Fig. 25). Pulsed inputs showed an initial transient response varying with the frequency input. The duration of this transient, except at the lowest frequencies, was not significant when compared to the duration of a murmur (Fig. 26).

The "central frequencies" chosen for filtering the murmur were selected so that the narrow pass bands resulted in a good picture of the frequency spectrum of the murmur when plotted. The frequency settings used were 40 Hz, 55 Hz, 80 Hz, 120 Hz, 160 Hz, 210 Hz, 300 Hz, 460 Hz, 670 Hz, and 910 Hz.

#### Internal and external recordings

With the phonocatheter in position in the aorta, the murmur was serially filtered at the above frequencies. The filtered signal was amplified by the EEP-8 amplifier of the recorder with a direct write-out on light sensitive paper. The amount of amplification was chosen arbitrarily so that a good signal to noise ratio was present and the greatest amplitude frequencies did not go off scale. Next, the total maximum height of at least 8 and up to 25 samples of the light beam deflection (murmur) were measured with a ruler for each frequency setting. From the mean values so obtained, a histogram of the relative frequency components of the patient's murmur was constructed.

To determine whether the murmur, as recorded on the chest wall, was valid in assessing the frequency spectrum of the intravascular turbulence, a contact crystal microphone was placed in the second right intercostal space. The output from this microphone (an Electronics for

Figure 25

Pass band characteristics of the three Krohn-Hite band pass filters in series. The high and low cut-off frequencies are equal (40 Hz) and insertion loss at peak of the pass-band is about 17.5 decibels (db). The 3 db down points are at 36 and 45 Hz.

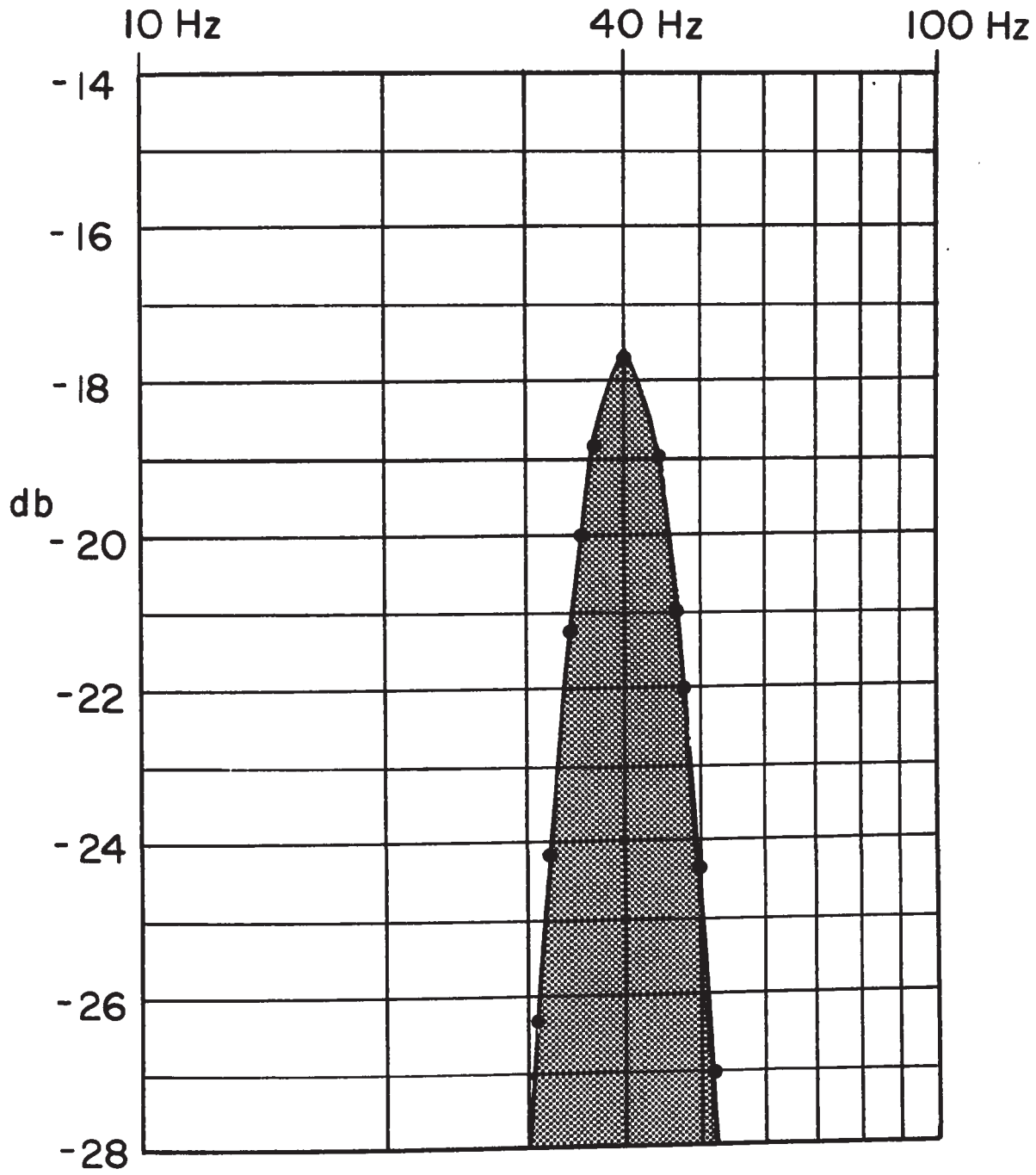
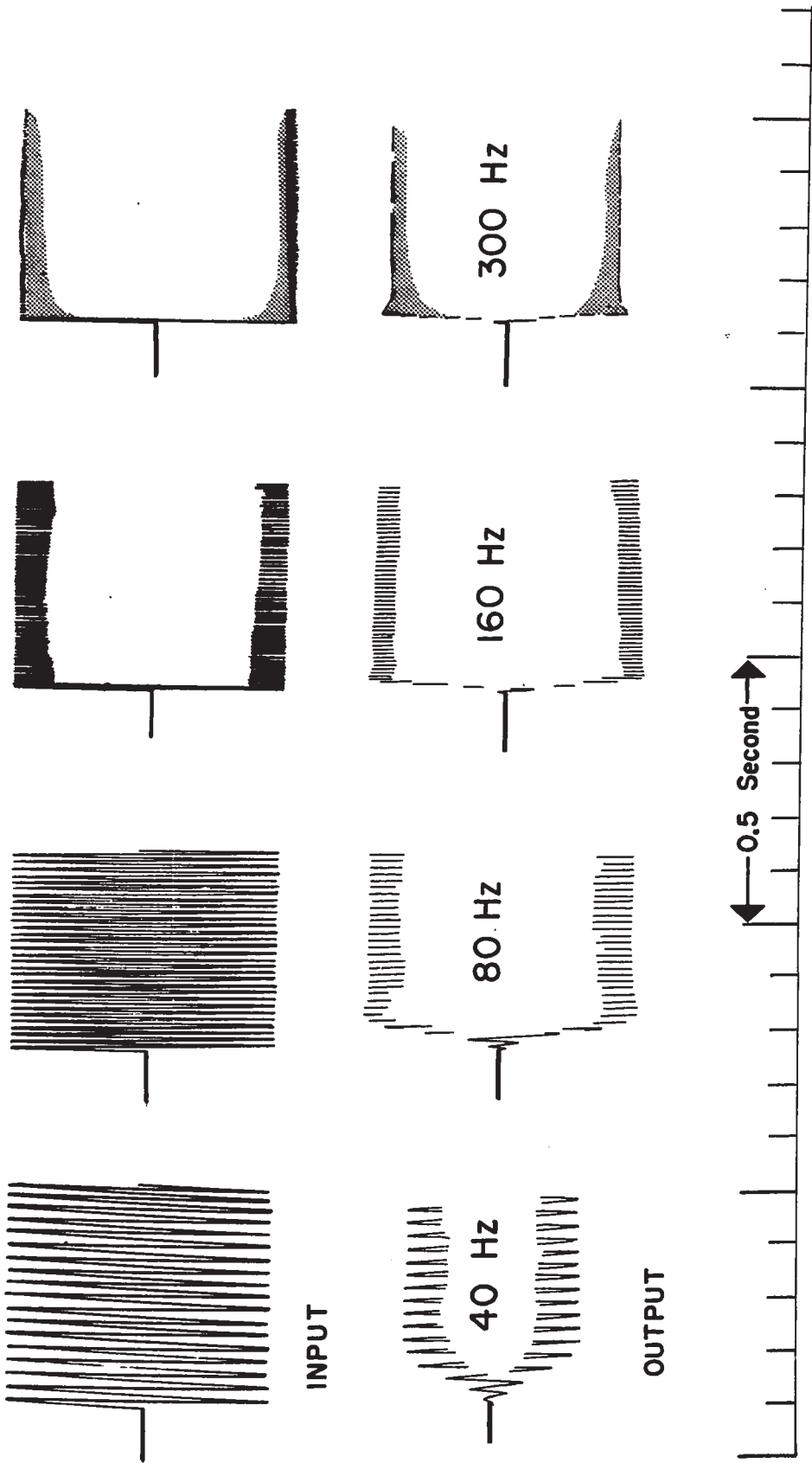


Figure 26

Illustration of the transient response characteristics of the three filters and amplifier in series. For a pulsed input (upper trace) the output (lower trace) shows a period of instability during which time the amplitude slowly rises to a peak higher than the final steady state output. The duration of this transient decreases with the higher frequencies. At 40 Hz it last approximately 0.1 sec but by 120 Hz has decreased to about 0.03 sec. The duration of a systolic murmur is about 0.4-0.5 sec so this transient should not interfere with our amplitude measurements which were usually taken at about mid-systole.





TRANSIENT RESPONSE  
(FILTERS and AMPLIFIER)



Medicine crystal microphone, frequency response flat 30-1000 Hz 3 db) was filtered and recorded in an identical manner to that outlined above for the phonocatheter. This recording was taken after the catheter study was complete. Intravascular and chest wall recordings could not be done simultaneously since another matching EEP-8 amplifier would have been necessary and this was not available.

#### Assessment of stenosis and dilatation

In addition to the frequency analysis of the murmur each patient had a left heart catheterization performed. The left ventricular and aortic pressures were measured by a pressure transducer (Statham Model P23 series) connected to the tube lying in either the chamber or vessel. The pressures were recorded on paper by the Electronics for Medicine DR8 and the aortic gradient calculated.

Injections of radiopaque dye were made at the root of the aorta, just distal to the valve, and the aorta was visualized to the level of the left subclavian in the left anterior oblique position. The injection was recorded on 35 mm film at a shutter speed of 54-60 frames per second and reviewed later by a cardiac radiologist. The degree of poststenotic dilatation was graded by him as (i) none, (ii) minimal, (iii) mild, (iv) moderate, or (v) severe (i.e., grades 0 to 4), without knowledge of the frequency components of the murmur.

A total of seven patients with aortic valvular stenosis were analyzed in this way. It was thus possible to show whether or not the frequencies used for vibration of the vessels in section (ii) could be found in the murmurs of aortic valvular stenosis and also if poststenotic dilatation did accompany those frequencies.

CHAPTER IV



RESULTSResults (i)Turbulence without Stenosis (A.S.D.)

A total of 15 separate pairs of systolic and diastolic diameters were measured and the corresponding wall tensions calculated from the six normal pulmonary arteries and branches. In addition a further 10 pairs of measurements were made in seven patients with pulmonary valvular stenosis beyond the area of poststenotic dilatation. This second group of measurements was confined to the right pulmonary artery and accepted only if the cardiac radiologist confirmed that dilatation was limited to the pulmonary trunk. Each of these 25 pairs of values were plotted on a tension-radius graph, and  $R_0$  (the unstretched radius) was approximated by projecting a line through the points to zero tension (Fig. 27). Next, each value of radius was divided by the corresponding  $R_0$ . The wall tension-strain diagram could then be constructed by plotting wall tension ( $T$ ) versus  $R/R_0$  for all points (Fig. 28). The regression line calculated for these 50 points was  $T = 21.5 \times 10^3 R/R_0 - 21.2 \times 10^3$  with a standard error of the estimate of  $\pm 0.87 \times 10^3$  and a correlation coefficient of 0.82 (Table 1). The slope of this regression line,  $2.15 \times 10^4$  dynes/cm, is the elastance for our normal pulmonary arteries, where elastance is Young's modulus times wall thickness<sup>(141)</sup>.

The tension-strain diagram for the nine patients with pulmonary valve stenosis and poststenotic dilatation was obtained in the same manner (Fig. 29). The calculated regression line for the 48 points

Figure 27

For calculation of  $R_0$ , the pairs of radius and wall tension measurements at systole and diastole were plotted. Illustrated are the measurements at three points in a dilated main pulmonary artery of a patient with pulmonary stenosis. When the line joining the pairs of points is projected to zero wall tension, an approximation of the resting radius ( $R_0$ ) is obtained.

Patient A.H.  
Age 7  
PULMONARY  
STENOSIS

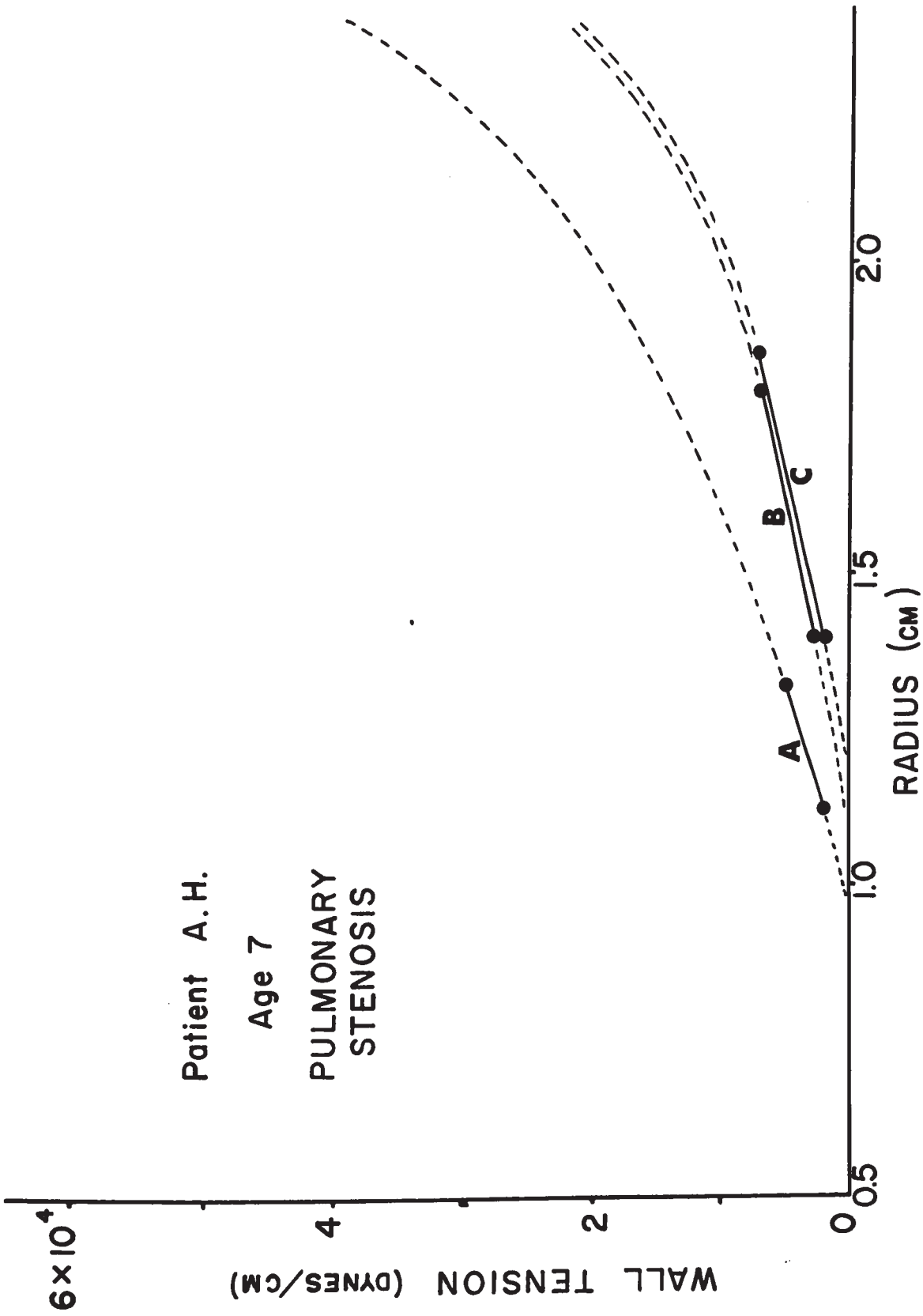


Table 1

List of the regression equations for the tension-strain measurements. Shown are: the equations for normal pulmonary arteries, poststenotic dilatation of pulmonary vessels, and the arteries in cases of atrial septal defect. The standard error of the estimates and correlation coefficients are also shown.

	Regression Equation $Y = mX + b$	Standard Error	Regression Coefficient
NORMAL	$T = 21.5 \times 10^3 R/R_0 - 21.2 \times 10^3$	$\pm 0.87 \times 10^3$	0.82
PULMONARY STENOSIS	$T = 10.0 \times 10^3 R/R_0 - 9.70 \times 10^3$	$\pm 0.65 \times 10^3$	0.93
A. S. D.	$T = 8.92 \times 10^3 R/R_0 - 8.52 \times 10^3$	$\pm 0.87 \times 10^3$	0.86



was  $T = 10.0 \times 10^3 R/R_0 - 9.7 \times 10^3$  with a standard error of the estimate of  $\pm 0.65 \times 10^3$  and correlation coefficient of 0.93 (Table 1). The elastance for pulmonary vessels with normal pressures and post-stenotic dilatation was  $1.00 \times 10^4$  dynes/cm which is statistically different from normal ( $p < 0.01$ ). The standard method for comparing two regression lines was used<sup>(9)</sup>.

For the third group of 10 patients with atrial septal defects 25 pairs of systolic and diastolic radii were measured. The resulting plot of T versus  $R/R_0$  (Fig. 30) had the regression equation  $T = 8.92 \times 10^3 R/R_0 - 8.52 \times 10^3$  with a standard error of the estimate of  $\pm 0.87 \times 10^3$  and a correlation coefficient of 0.86 (Table 1). Therefore the elastance of the pulmonary vessels in A.S.D. with normal intraluminal pressures was calculated to be  $0.89 \times 10^4$  dynes/cm. This elastance is statistically different from normal ( $p < 0.01$ ) but not different from that of poststenotic dilatation ( $p > 0.1$ ).

Since we did not measure the pressure during the dye injection some error might be introduced if the pressure changed during this time. However, no measurable change was demonstrable during the injection (Fig. 10) but a slight rise, within minutes, is reported<sup>(18,19)</sup> and was verified. This rise will not affect the majority of our samples. In three patients however (two normal and one pulmonary stenosis) the pressure recording had been taken prior to a previous injection and no pressures were available prior to the injection used for our measurements. The problem this poses is not great for, in fact, the effect should only be to increase the scatter about the regression lines. Both the systolic and diastolic pressures have been shown to

Figure 28

For normal pulmonary arteries:

- (a) A plot of measured vessel radius at maximum systole (solid circles) and diastole (open circles) versus the corresponding systolic or diastolic pressures.
- (b) Tension-strain diagram. Tension is used rather than stress because wall thickness was not measured. The points representing wall tension versus normalized radius ( $R/R_0$ ) give the regression line and standard error of the estimate shown. Elasticity for normal pulmonary arteries approximates the slope of this line,  $2.15 \times 10^4$  dyne/cm.

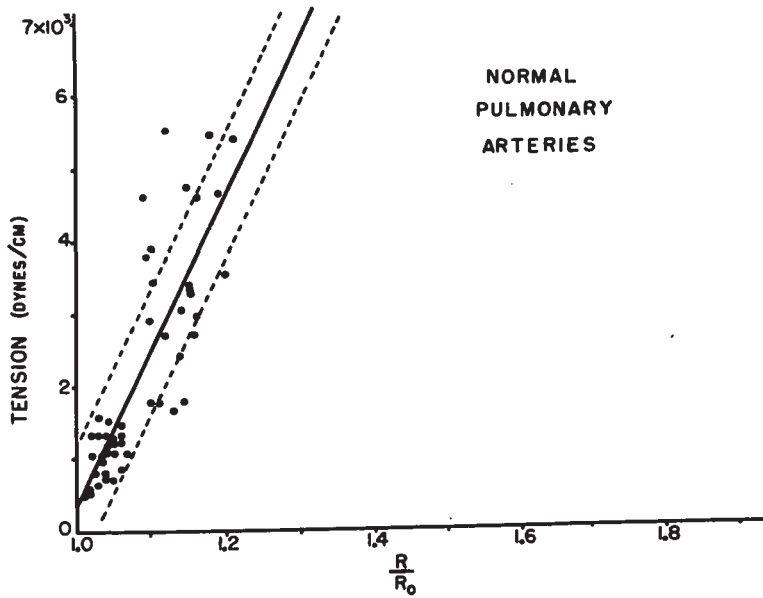
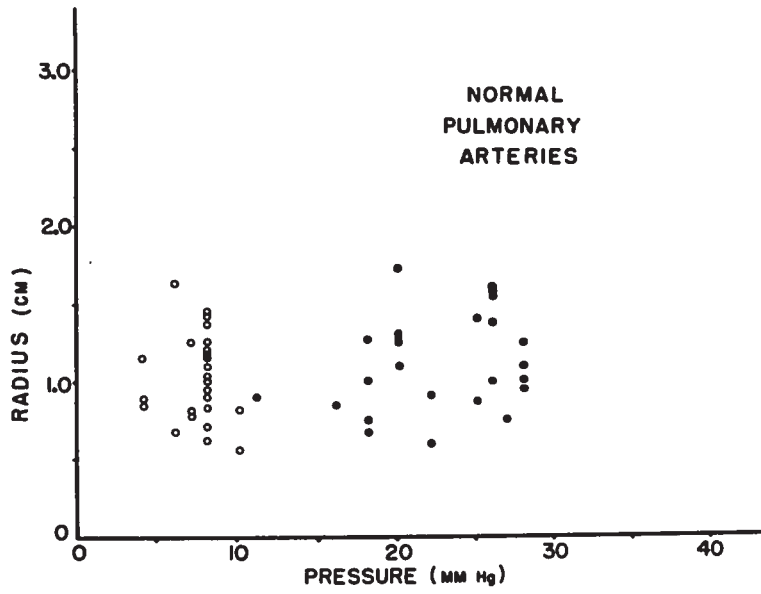


Figure 29

For poststenotic dilatation distal to stenosed pulmonary valves:

- (a) A plot of measured vessel radius at maximum systole (solid circles) and diastole (open circles) versus the corresponding systolic or diastolic pressures.
- (b) Tension-strain diagram. Tension is used rather than stress because wall thickness was not measured. The points representing wall tension versus normalized radius ( $R/R_0$ ) give the regression line and standard error of the estimate shown. Elasticity for pulmonary arteries showing poststenotic dilatation approximates the slope of this line,  $1.00 \times 10^4$  dyne/cm. This is statistically different from normal ( $p < 0.01$ ).

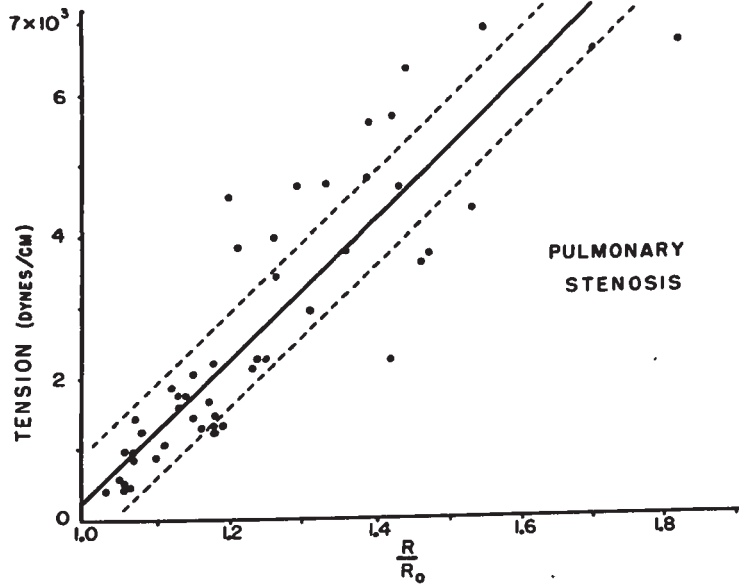
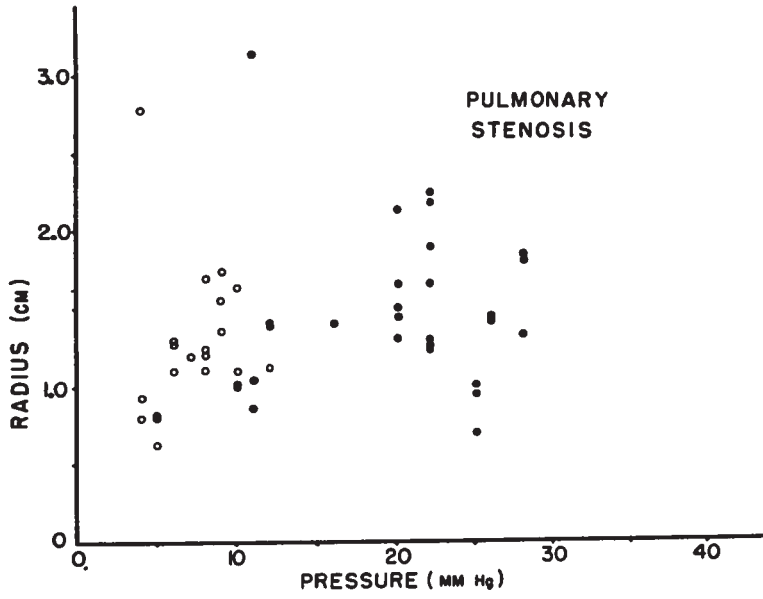
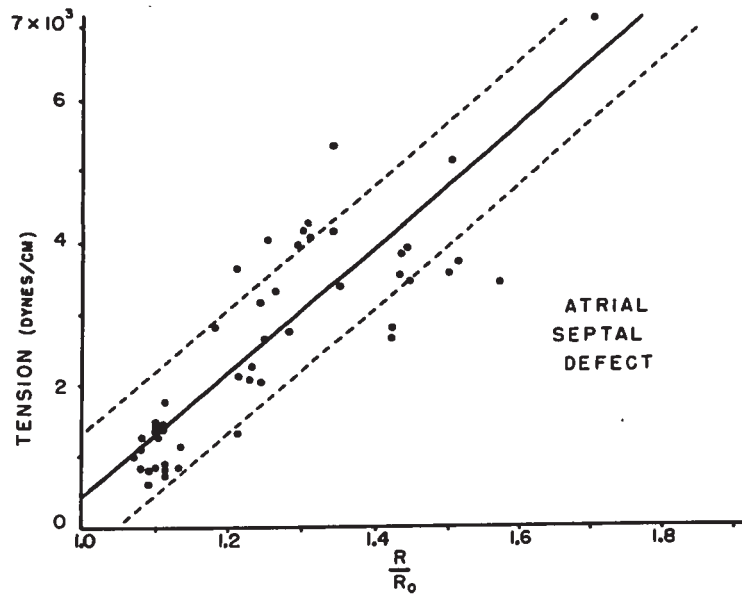
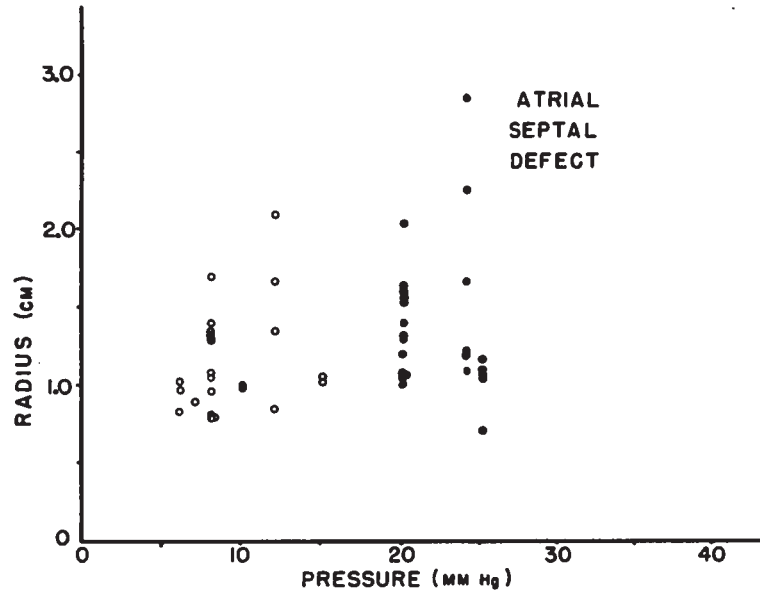


Figure 30

For pulmonary arteries in atrial septal defect:

- (a) A plot of measured vessel radius at maximum systole (solid circles) and diastole (open circles) versus the corresponding systolic or diastolic pressures.
- (b) Tension-strain diagram. Tension is used rather than stress because wall thickness was not measured. The points representing wall tension versus normalized radius ( $R/R_0$ ) give the regression line and standard error of the estimate shown. Elasticity for pulmonary arteries in patients with atrial septal defect approximates the slope of this line,  $0.89 \times 10^4$  dyne/cm. This is statistically different from normal ( $p < 0.01$ ) but not different from poststenotic dilatation ( $p > 0.1$ ).



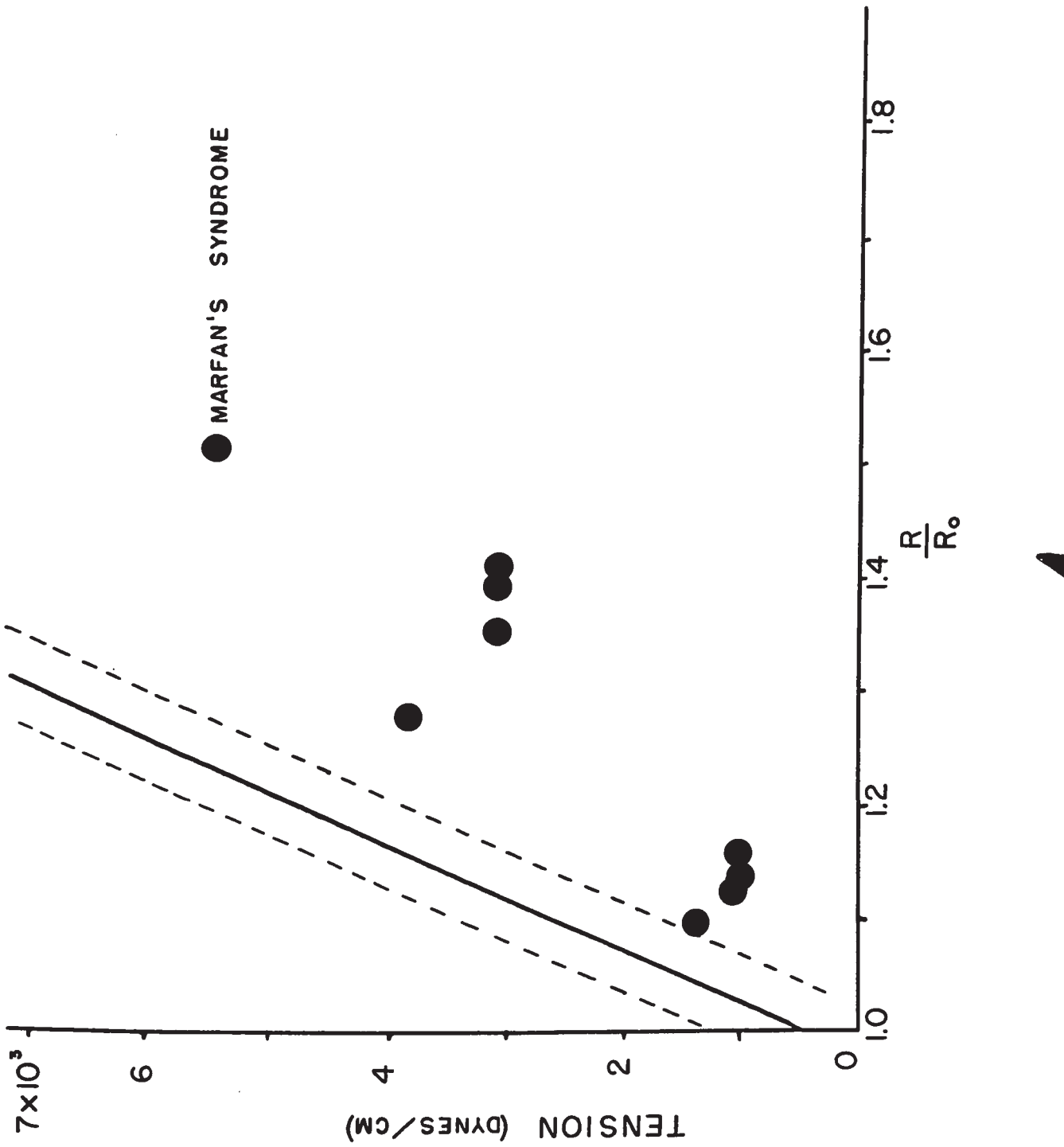
rise about 45% (mean values 43% and 46%, respectively)<sup>(19)</sup>. This rise, even from a 30 mm Hg pressure, will not put the vessel off the linear portion of the elastic diagram for our age group. Since we use our measured values of R versus P or T to obtain  $R_0$  (Fig. 27) the true values of P would place the two real points for systole and diastole directly and proportionately above the calculated values, in this group of three patients. Connecting these two real points would give the same slope as calculated but a value of  $R_0$  less than that calculated. The vessel strain ( $R/R_0$ ) for systole and diastole would be larger, corresponding to the increased pressure. Thus the true values of wall tension versus strain would be proportionately greater but should still fall along the course of the calculated regression line, i.e., the slope of the elastic diagram should be no different for greater pressures as long as the values do not leave the linear portion of the curve.

One additional case, originally felt to fall into the "normal" group, since the angiogram and cardiac output were reported as normal, was of interest. The patient, a 17 year old boy, presented with a low amplitude murmur over the pulmonary artery for which he was investigated. All values of T versus  $R/R_0$  fell outside the normal range (Fig. 31) indicating increased distensibility of the vessels. Examination of this patient's old records revealed that he had been previously diagnosed as a Marfan's syndrome. In 34 cases of this connective tissue disorder studied by Goyette and Palmer<sup>(62)</sup>, a consistent deficiency of aortic elastin fibres was noted. These were replaced with loose collagenous tissue. Involvement of the pulmonary



Figure 31

Tension-strain values for one case of  
Marfan's syndrome compared to the regression  
line for normal pulmonary arteries.  
Increased distensibility is indicated.

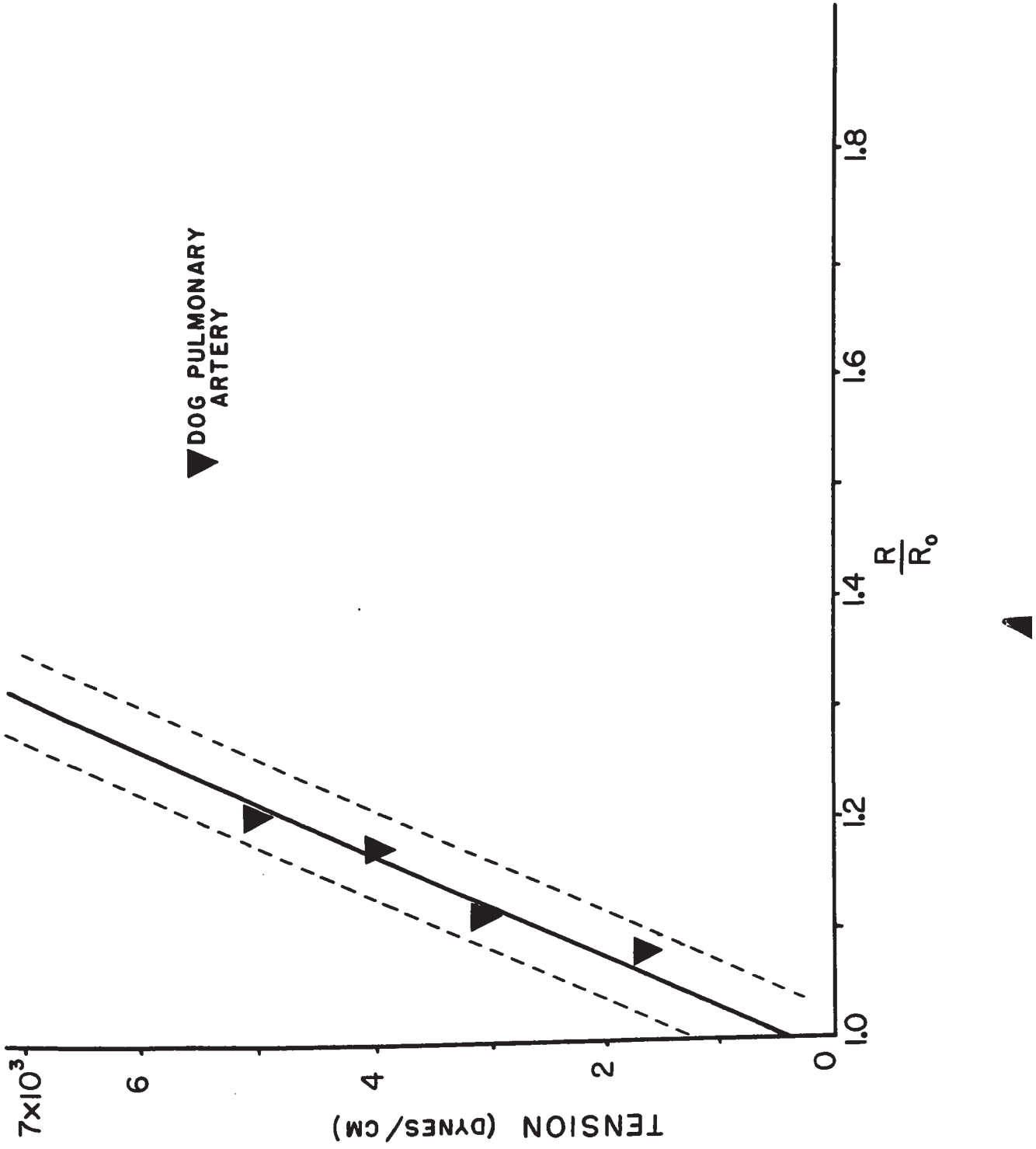


arteries occurs<sup>(8,118)</sup> but usually does not produce symptoms<sup>(120)</sup>. Since elastin is responsible for the initial slope of the elastic diagram<sup>(141)</sup>, the finding of abnormally distensible pulmonary vessels in our patient with Marfan's syndrome should not be entirely unexpected and further demonstrates the usefulness of this method.

Patel *et al*<sup>(130)</sup> have previously made *in vivo* measurements of the mechanical properties of the major pulmonary arteries in 18 normal dogs. The vessel diameter was measured with an electrical recording caliper, and plotted against intravascular pressure on an oscilloscope. They published, for one dog, an oscilloscopic plot of the pulmonary artery diameter (D) at various increasing pressures and indicated the point "D<sub>0</sub>". Calculating values of R/R<sub>0</sub> from that graph we obtained values of wall tension versus strain similar to our results for the distensibility of normal human pulmonary vessels (Fig. 32). The age of that particular dog was not recorded and the marked similarity may have been fortuitous. However, for their 18 dogs, an overall percent change in radius about the mean for a normal cardiac cycle was  $\pm 7.8\%$ . Our results show an average normal radius change of  $\pm 4.9\%$  about the mean pulmonary artery radius, while changes for poststenotic dilatation and A.S.D. were considerably larger, being  $\pm 12.1\%$  and  $\pm 12.9\%$  respectively. Patel *et al* also reported an average radius change of the right pulmonary artery in 30 human subjects of  $\pm 8\%$ . Although not clearly outlined, their method was apparently similar to ours for measuring vessel radius on angiography but no mention was made as to what lesions were present in their patients. Therefore, our measurements produce results comparable to Patel's for measuring pulmonary artery properties *in vivo*.

Figure 32

Tension-strain values for a normal dog pulmonary artery calculated from Patel *et al* (130) and compared with our regression line for normal pulmonary arteries.



Results (ii)Vibration of Arteries

Twenty-four human external iliac arteries were vibrated and 19 dilated in response to one or more of the frequencies to which they were exposed. The rate of dilatation was exceedingly slow but could be measured over a period of seven to 10 hours (Fig. 33). The percent increase in radius, in excess of that expected for creep, and projected for 24 hours was  $7.1 \pm 3.4$  S.D.%. In a series of 26 dog carotid and femoral arteries banded by Roach<sup>(145)</sup>, maximal dilatation was seen by 10 days and the total increase in diameter varied from 5 to 25%. Therefore, our *in vitro* results show more rapid dilatation but are still comparable to those found *in vivo* in dogs.

It was soon apparent that a particular artery did not dilate with every frequency to which it was exposed. An artery which failed to dilate when exposed to one frequency might very well dilate when exposed to another frequency (Figs. 34 and 35). Several variables were considered in attempting to decide what factors governed the frequency response of an artery.

Energy

The first consideration was the energy being delivered to the arterial wall. At the higher frequencies this energy was much greater than that being delivered at the lower frequencies ( $E \propto f^2 A^2$  where  $E$  = energy,  $f$  = frequency and  $A$  = amplitude). The lower amplitude being produced by the speaker at the lower frequencies made this difference even greater. However, despite this energy difference, it

Figure 33

A segment of external iliac artery from a 77 year old female was subjected to 300 Hz vibration for two time intervals, as shown. In each case the vessel segment increased in volume, and therefore in radius, over the amount expected for "creep" alone.

# A-169-69  
Age 77

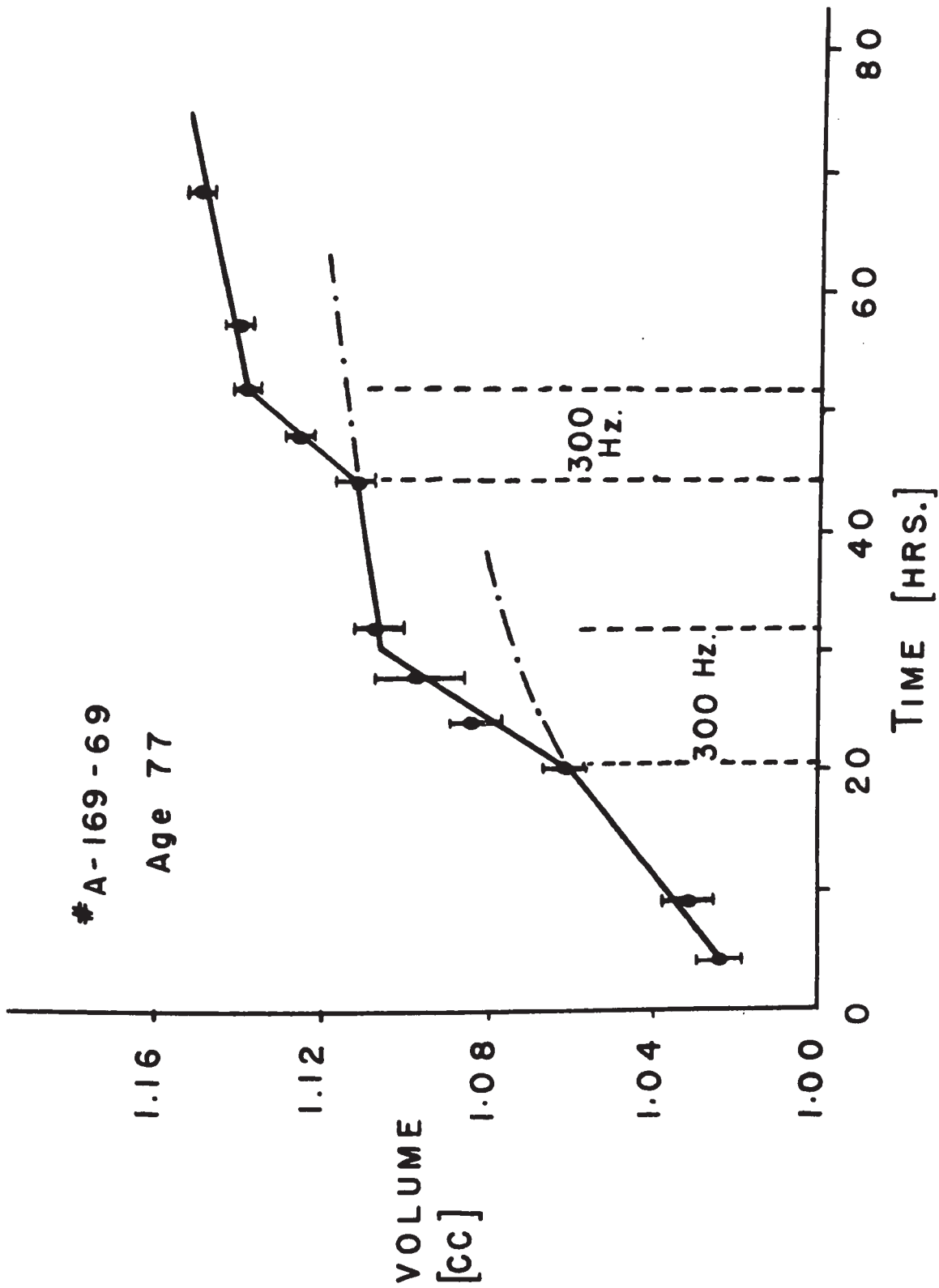




Figure 34

- (a) A segment of external iliac artery from a 33 year old male was exposed 75 Hz and then to 170 Hz vibrations. No dilatation over that expected for "creep" occurred with the 170 Hz but dilatation did occur with 75 Hz.
- (b) A segment of external iliac artery from a 52 year old male was exposed to 50 Hz and then to 120 Hz vibrations. Dilatation over that expected for "creep" occurred only with the 120 Hz vibration.

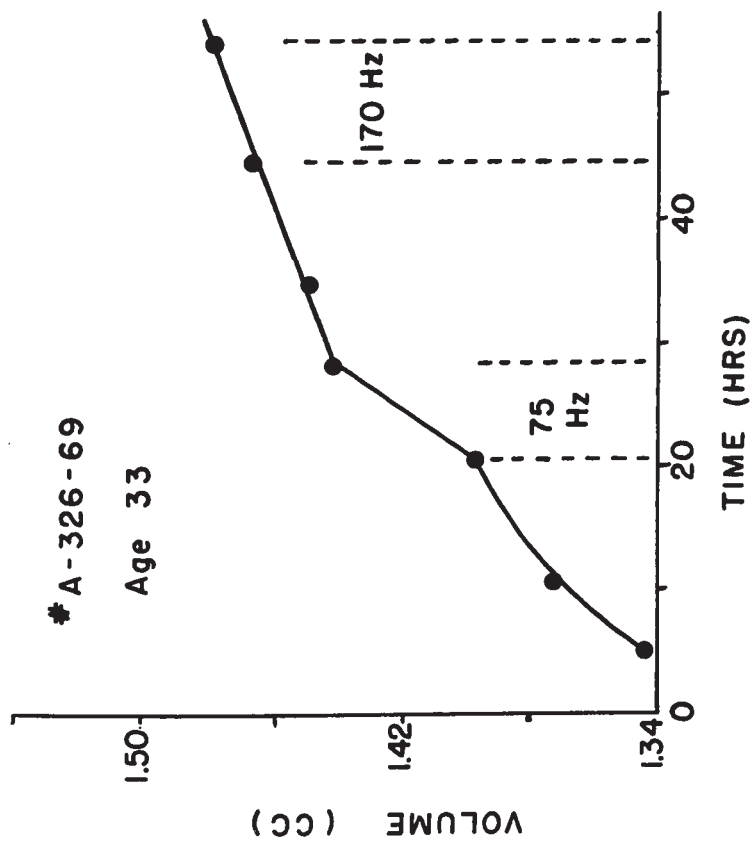
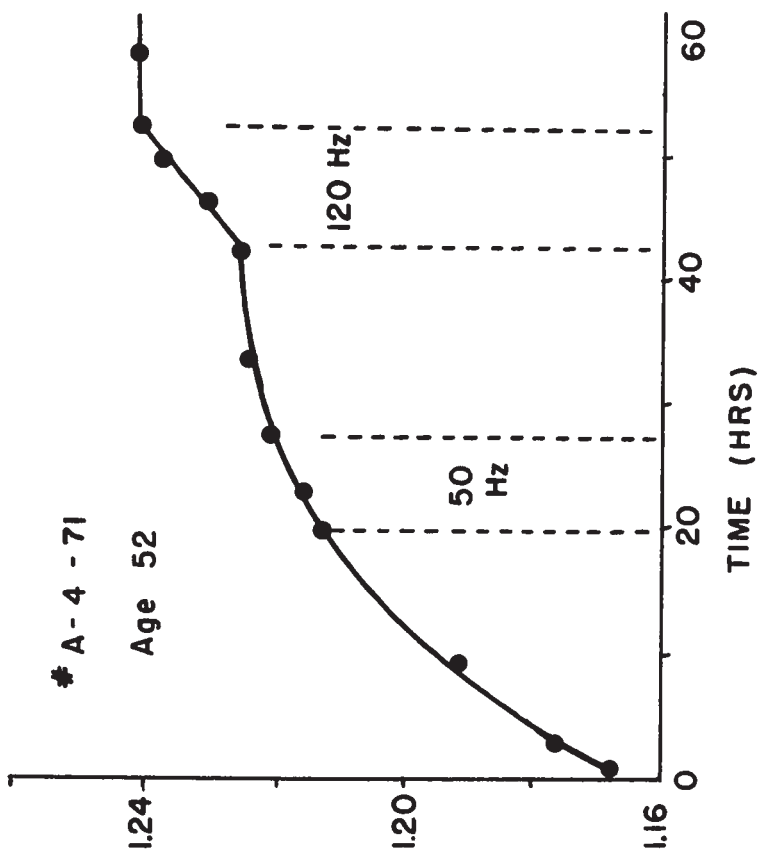
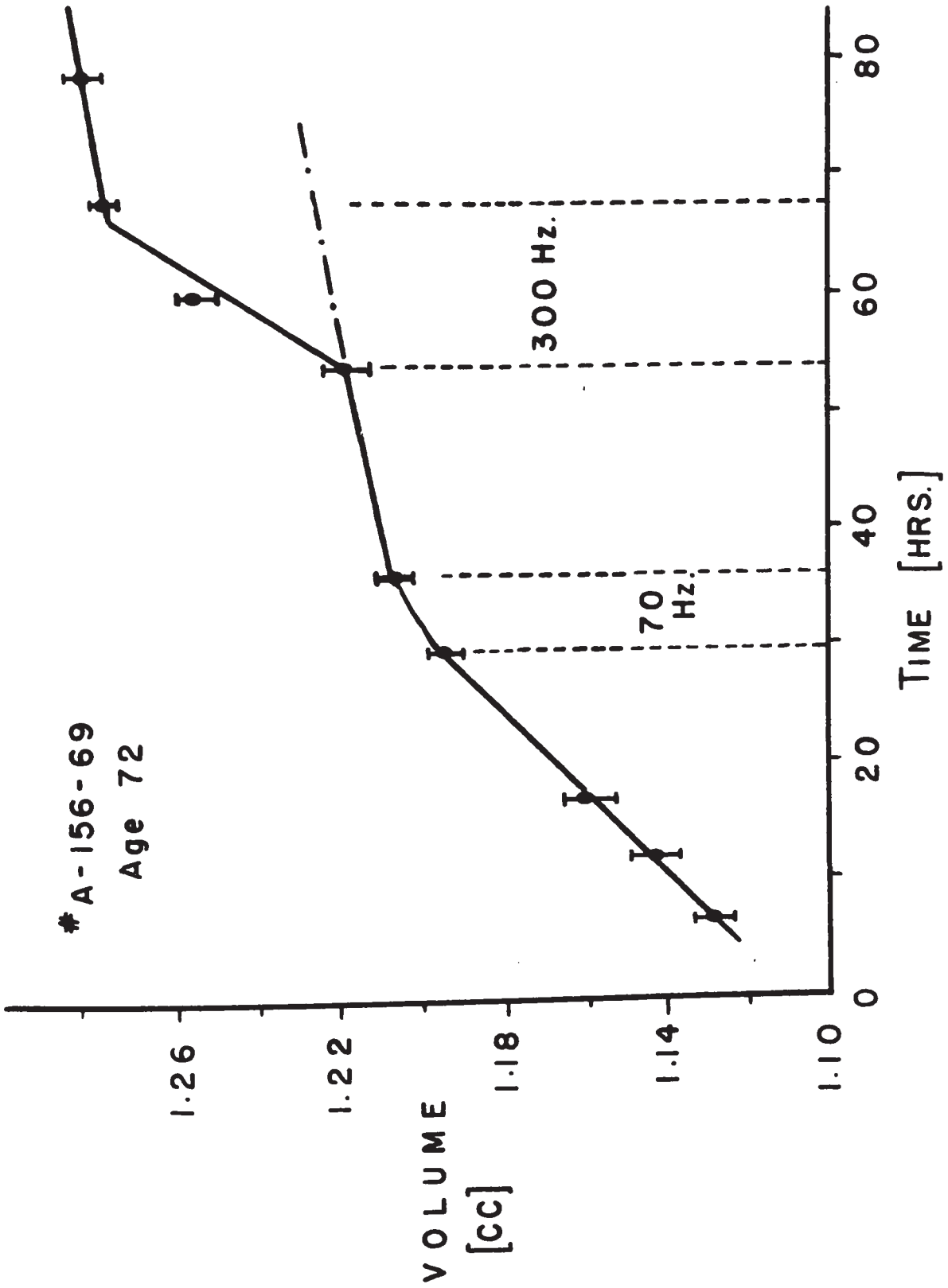


Figure 35

A segment of external iliac artery from a 72 year old female was exposed first to 70 Hz then to 300 Hz vibrations. No dilatation over that expected from "creep" occurred with the 70 Hz but dilatation did occur with 300 Hz.



▲

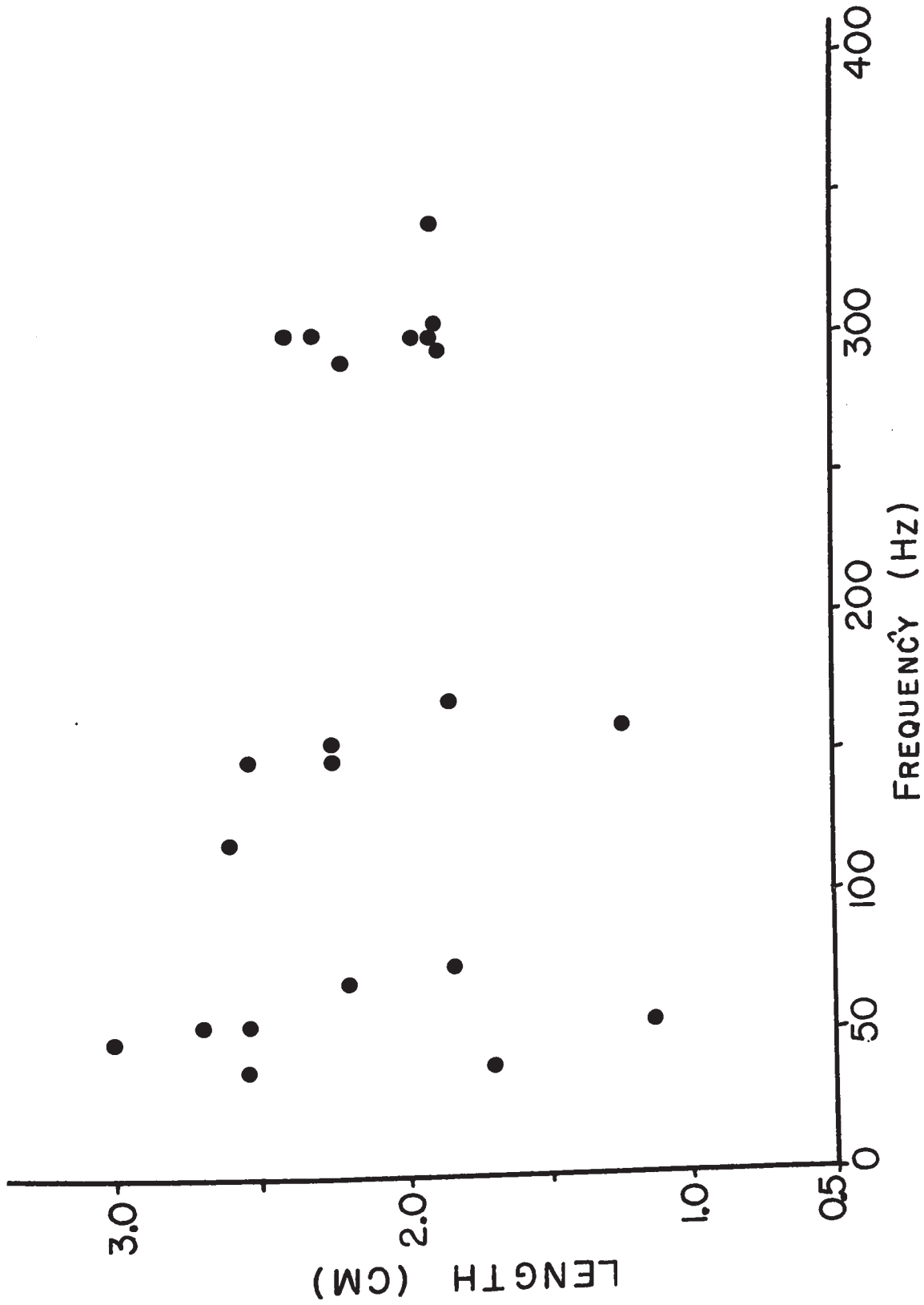
was not uncommon for an artery to dilate in response to a low frequency and not respond to a higher frequency. The reverse was also seen and it was therefore concluded that energy content was not the sole factor.

### Resonance

A second possibility was that the sound, or an overtone of it, whose wavelength corresponded to the length of the segment of vessel in use, was setting up a resonance peak resulting in the dilatation. Resonance occurs when a small amplitude periodic stimulus results in a large amplitude vibration. It occurs when the periodic stimulus has a wavelength or overtone corresponding to the length of the material that it is vibrating and will therefore be a function of wave velocity and frequency. Wavelength depends directly on the velocity of sound in the fluid medium and inversely as the frequency ( $v = f\lambda$  where  $v$  = velocity,  $f$  = frequency and  $\lambda$  = wavelength). The velocity of sound in arteries is about 5 m/sec<sup>(6,47,95,105)</sup> and depends on the properties of the walls<sup>(6)</sup>. The lengths of vessels used varied from 1.15 cm to 3.00 cm (mean length  $2.10 \pm 0.50$  cm) so a resonance peak could be a consideration. However, no evidence of resonance peaks were found either inside or outside any age of vessel where the outputs from the matching transducers were compared by the alternate set-up (Fig. 18). Also, no attenuation of the vibration for any frequency from 5 to 1000 Hz was measurable on passage of the frequencies through the vessel wall with the vessel distended at 100 mm Hg. Lateral vibration of the entire vessel segment was unlikely, due to the longitudinal tension present. A plot of the length of the

Figure 36

A plot of vessel length versus the frequency producing dilatation shows no correlation between the two variables.



vessel versus the frequency causing dilatation (Fig. 36) showed no correlation.

### Age

The elastic properties of the arteries are known to change with age (31,70,126,142) and so a third variable was considered, i.e., the age of the artery being used. By dividing the vessels into three groups (i) six patients less than 45 years, (ii) 11 patients 45-60 years and (iii) seven patients over 60 years old, a correlation appeared between frequency, age and dilatation (Fig. 37). Statistical analysis revealed the frequency response between the youngest and oldest age groups to be significantly different ( $\chi^2 < 0.05$ ). The middle aged group, although appearing to respond mainly to the middle range of frequencies, was not significantly different from either of the other two groups ( $\chi^2 > 0.20$ ). However, from these results we have concluded that the older the artery the higher is the frequency of sound to which it will likely respond with dilatation.

Changes in the elastic diagram observed after vibration and dilatation of the vessel were limited to the initial portion of the tension-radius curve (Fig. 38). The characteristic shape of the curve, in the absence of the action of muscle (38,141), is produced by the two elements collagen and elastin. Roach and Burton (141) demonstrated that the initial slope represents the elastic modulus for elastin alone and the final slope the elastic modulus for collagen alone. The non-linear portion of the curve is produced by complex rearrangements of the elastin and collagen within the wall with increasing pressure. The wavy elastin lamellae are gradually straightened and the distance



Figure 37

The vessels were divided into three age groups, as shown. The presence or absence of dilatation on exposure of the artery to a frequency from each of the three frequency ranges (<100 Hz, 100-200 Hz and >200 Hz) was used to form this histogram. Vessels which dilated are represented by the shaded bars and vessels which failed to dilate for a particular frequency are represented by the unshaded bars.

The younger vessels dilated to lower frequencies than did the older vessels ( $\chi^2 < 0.05$ ). The middle age group tended to dilate to the middle range of frequencies but were not significantly different from either the younger or older age groups.

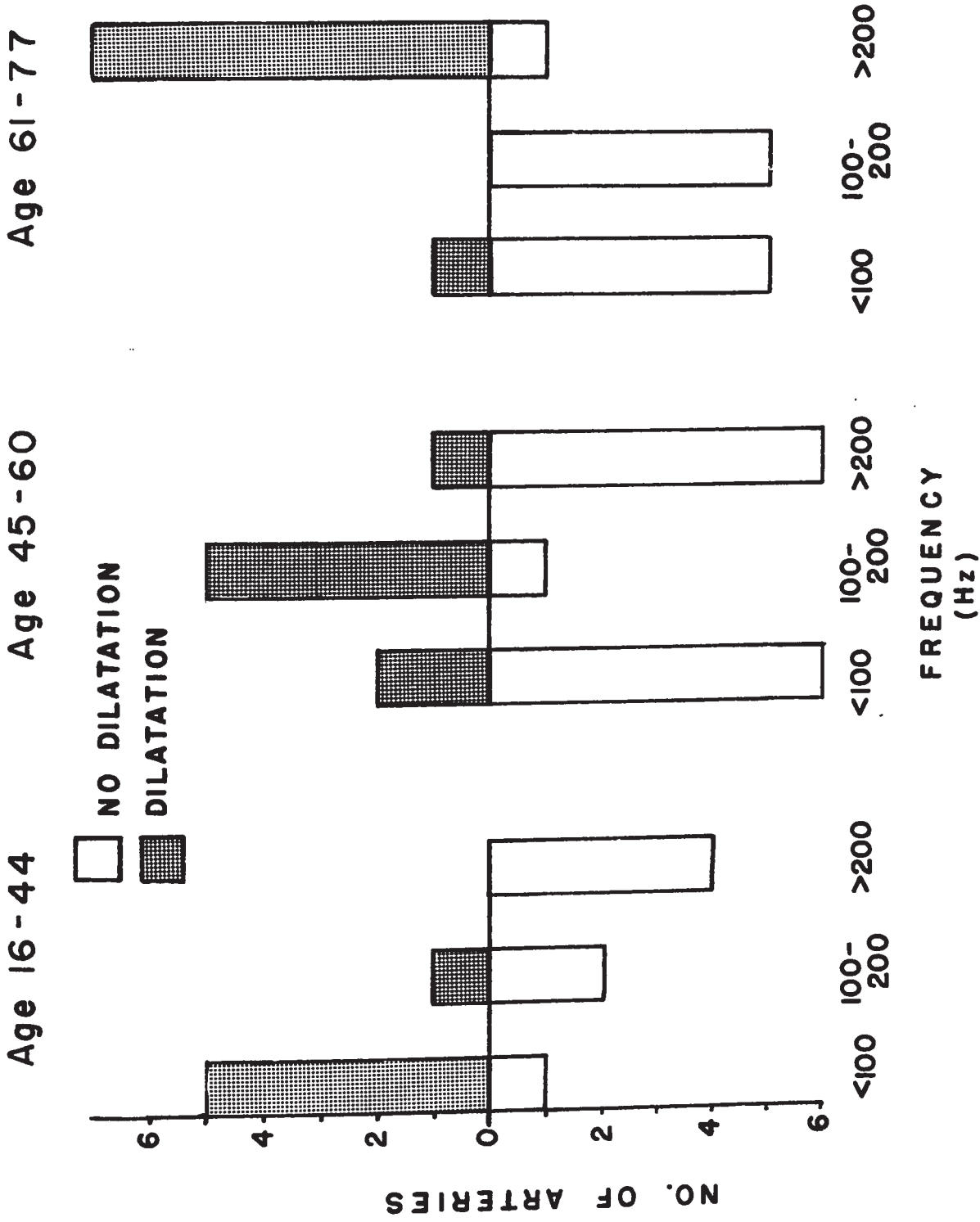
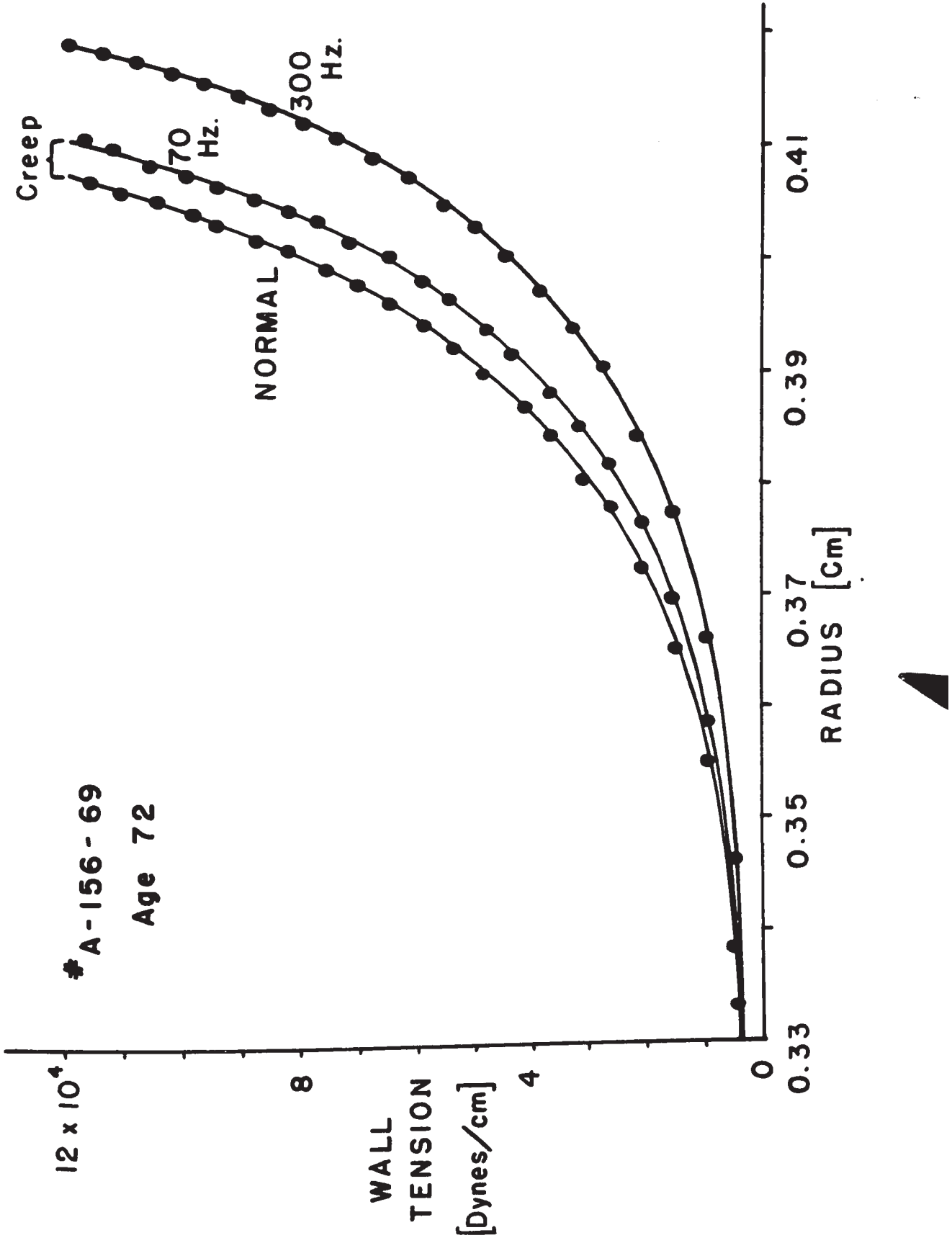


Figure 38

The changes in the elastic diagram with "creep" were identical to those produced by vibration. These elastic diagrams are from the 72 year old patient shown in Fig. 35. The shift of the curve to the right during 70 Hz vibration is due only to "creep" but the shift during 300 Hz vibration is greater than would be expected from "creep" alone as shown by Fig. 35.

The changes produced by vibration are probably related to disruption of interlamellar elastin nets resulting in a decrease in the initial slope with no change in the collagen portion of the curve. These alterations are the same as seen with poststenotic dilatation. The changes resulting in "creep" are unknown but may be of a similar nature.



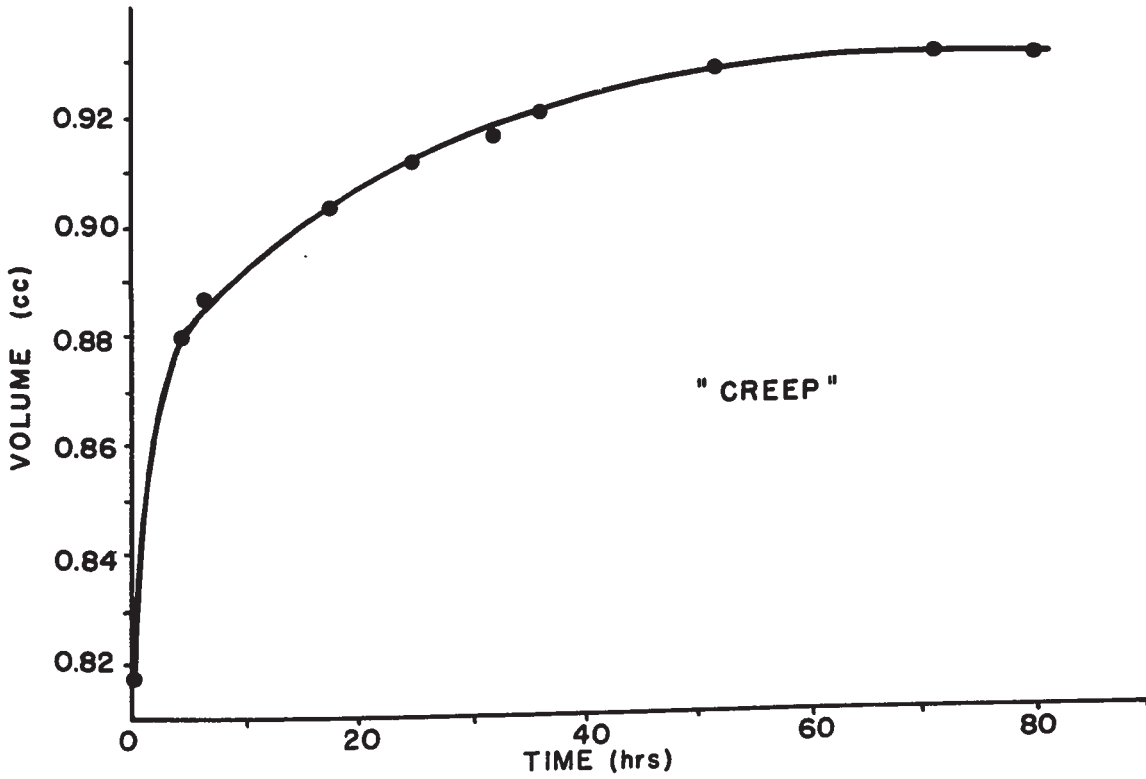
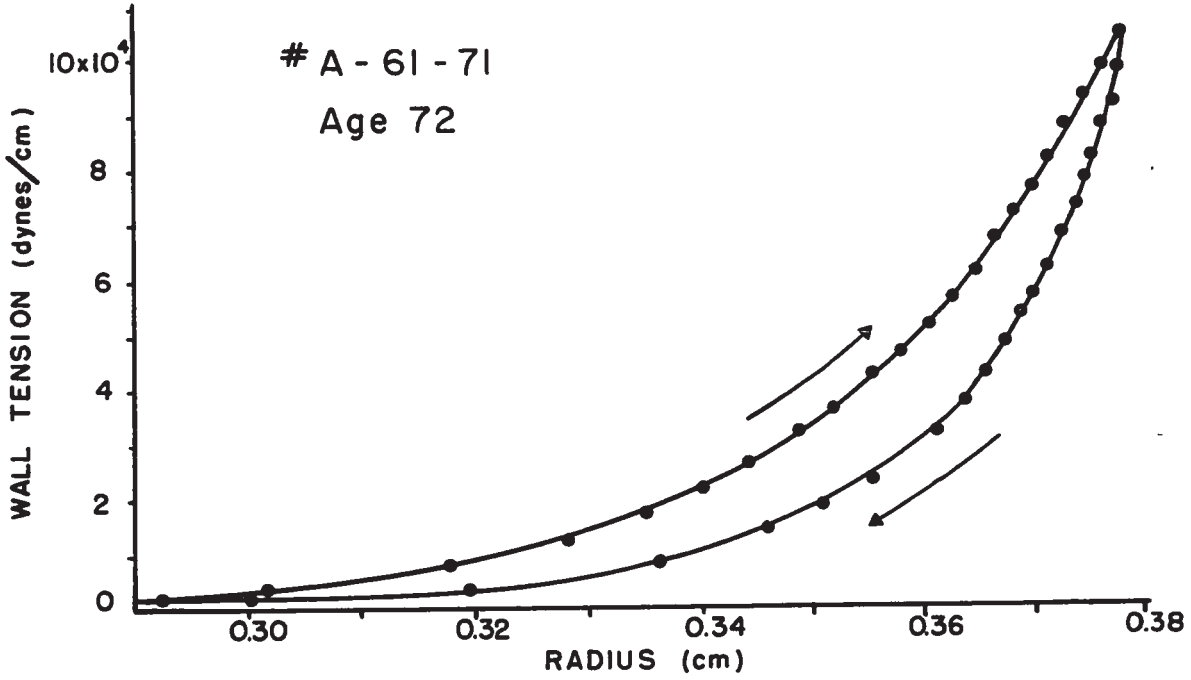
between them becomes progressively less up to about 120 mm Hg. The collagen fibres, which are randomly oriented below 70-80 mm Hg pressure are all circumferentially oriented by 120 mm Hg<sup>(59,177)</sup>. The pressure which we used (i.e., 100 mm Hg) lies within the range where changes in orientation of both elastin and collagen are incomplete, but where both are under some tension.

In all cases, when dilatation occurred, the curve was shifted to the right but the final slope appeared unchanged (Fig. 38). Vibration appeared to alter the initial part of the curve, which represents the modulus for elastin<sup>(141)</sup>, and had therefore made some alteration in the elastin network so that it became more distensible. Thus a greater radius was achieved before the unaltered collagen fibres were stressed. These changes corresponded to those found in post-stenotic dilatation of arteries both *in vitro*<sup>(146)</sup> and *in vivo*<sup>(143,144)</sup>.

It was necessary to rule out the unlikely possibility of vascular smooth muscle activity being responsible for our results. The iliac arteries demonstrated the presence of viscous properties (creep and hysteresis loop) *in vitro* which are usually attributed entirely to muscle<sup>(14)</sup>. From autopsies two vessels were obtained, age 43 and 72, and were immediately immersed in a solution of 1:10,000 aqueous merthiolate in normal saline and 0.25 gm/l sodium amytal. This concentration of sodium amytal prevents oxygen uptake<sup>(58)</sup> and therefore would prevent any possibility of smooth muscle spasm occurring when the vessel was immersed in the storage fluid. The viscous properties still remained (Fig. 39) even though the muscle

Figure 39

The viscous properties, hysteresis and creep, are still evident for an iliac artery immersed in sodium amytal and aqueous merthiolate solution immediately after autopsy. The certain elimination of smooth muscle activity by this method shows that some arterial viscous properties are related either to elastin and/or collagen.



must have been inactivated.

In addition one vessel, age 53, was mounted in the plethysmograph and its volume measured at 100 mm Hg pressure. Enough nor-epinephrine was then added to the fluid within the plethysmograph to produce a concentration of 2 mgm/litre. This concentration will produce maximal contraction of vascular smooth muscle<sup>(38)</sup> but on measurement of the vessel volume every five minutes for one half hour no change was recorded.

The decreased slope, after vibration, of the initial portion of the curve (the segment representing the elastic modulus of elastin<sup>(141)</sup>), would suggest that structural changes might be seen on histologic examination. However, the dilated vessels when fixed at various intraluminal pressures from 30 mm Hg to 100 mm Hg, showed no consistent changes compared with the controls (Fig. 40). The elastin lamellae stained with Weigert's stain and examined under light microscopy appeared to us to be normal in number and configuration. This finding coincides with the histologic findings of Roach<sup>(144)</sup> and of Clagett *et al*<sup>(36)</sup> in poststenotic dilatation.

In summary, human external iliac arteries dilated in response to low frequency vibrations, but required a higher frequency to produce dilatation the older the artery. The changes in the elastic diagram were limited to the initial elastin portion of the curve and no consistent changes were seen on light microscopy.



Figure 40

Histologic examination of the external iliac arteries fixed at various pressures and stained with Weigert's stain showed no consistent alteration from normal after vibration.

The top photographs are sections of vessel wall from a 66 year old male, fixed at an intraluminal pressure of 55 mm Hg (L = lumen). The control was taken from the opposite external iliac and was not vibrated. The lower photographs are sections of a vessel wall from a 50 year old female. The vessel was fixed at a pressure of 35 mm Hg and the control vessel was the opposite iliac artery, not vibrated.



CONTROL



55 mm Hg AFTER VIBRATION



CONTROL



35 mm Hg AFTER VIBRATION



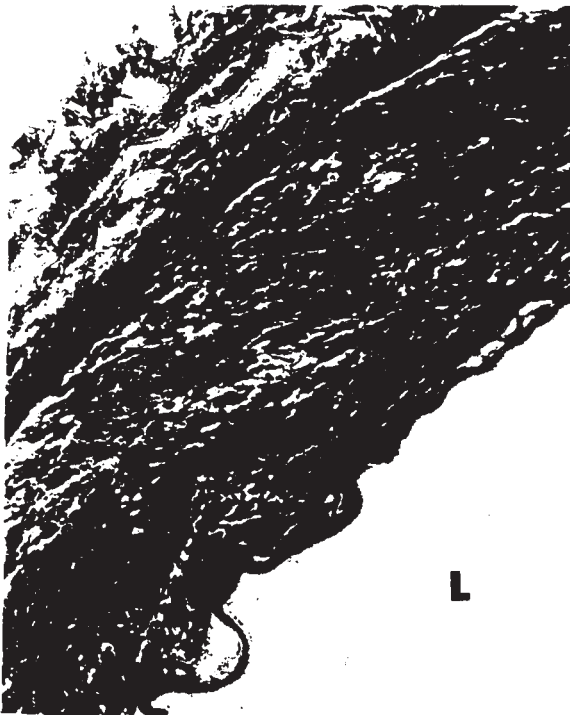
L

CONTROL



L

55 mm Hg AFTER VIBRATION



L

CONTROL



L

35 mm Hg AFTER VIBRATION

## Results (iii)

### Frequency Content of Murmurs

The murmurs from seven patients with aortic stenosis were picked up internally with a phonocatheter, and externally with a contact microphone, then serially filtered to determine their frequency content. One external recording was of inadequate quality for analysis due to a high level of background noise.

### Apparatus

The lowest 'central' frequency used (high and low pass set at the same frequency) was 40 Hz. Frequencies below 15 Hz are related to left ventricular contraction (i.e., gross pressure changes) and between 15 and 30 Hz catheter artifact appears due to catheter movement (92). The 40 Hz setting, with a band width from 35 to 47 Hz at the 3 db down point (Fig. 26), was the lowest at which frequencies could be attributed solely to intravascular turbulence.

Also, on examining the lower frequencies (Fig. 22) from the phonocatheter an apparent delay in transmission was noted when compared to the unfiltered recording. This corresponds to earlier observations by Faber<sup>(47)</sup> that different frequencies are transmitted by these devices at different rates. This factor did not interfere with the measurement of murmur amplitude at the various 'central' frequencies.

### Analysis

The frequency spectrum of each aortic murmur was filtered at each of the 'central' frequencies. Then the mean maximal amplitude at each setting was calculated and plotted in the form of a histogram.

The bar widths of the histogram were determined by first setting the three filters at each of the 'central' frequencies. Next, several test frequencies above and below these 'central' frequencies were introduced from the Heathkit frequency generator. The output for each test frequency was measured on an RMS voltmeter, compared to the input and converted to decibel loss. The shape of each pass band was plotted (Fig. 41) and the 3 db down point of -21 db was taken for the width of each bar of the histogram. Minor variation was noted in the exact decibel loss (from -17 to -18 db) at the various 'central' frequencies for the three filters in series. This may have been due to slight inaccuracies in the Krohn-Hite filter dial markings.

The calculated widths of each histogram bar are shown in Table 2. Some small gaps will be noted but were not likely of sufficient width to permit any important information to be missed.

#### Internal recordings

The frequency distributions of the seven intraaortic murmurs are shown in Figures 42, 43, 44 and 45. All had the majority of their frequency components from 50-200 Hz. Two had their peak amplitude at less than 50 Hz and most had frequency components extending up to about 800 Hz.

Poststenotic dilatation was seen on angiography in all of the seven patients, although in one patient this was graded as minimal. Of the remainder, one was graded as moderate to severe and the other five showed either mild or moderate dilatation as well as relatively high amplitude frequency components within the ranges expected to

Figure 41

Illustration of the filtration characteristics of the band pass filters set at each of the ten 'central' frequencies. The insertion loss at peak of each pass band varied slightly probably due to minor inaccuracies in the dial markings. The band widths at -21 db were taken for the bar widths on the frequency analysis histogram.

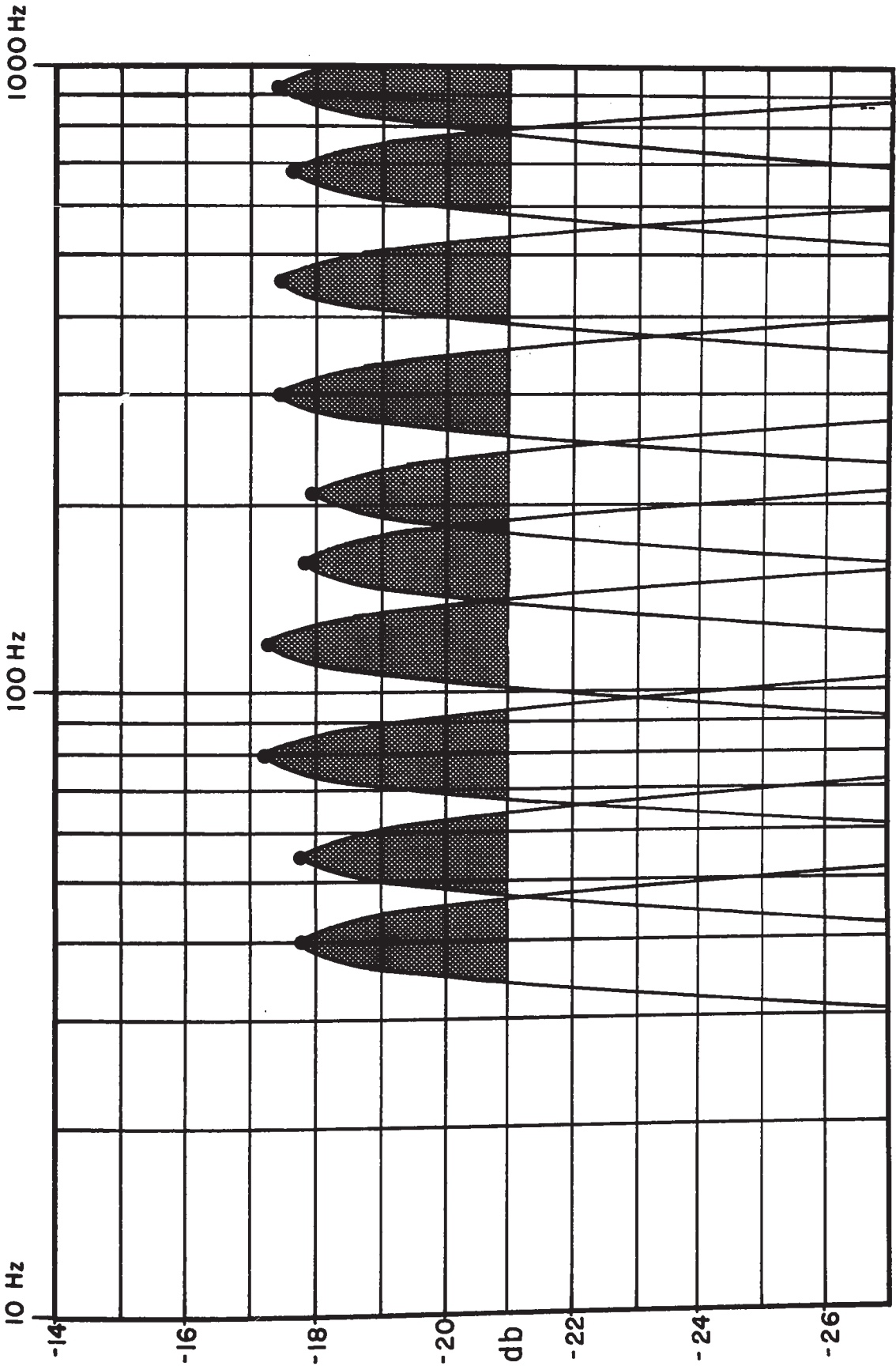


Table 2

Band widths at -21 db for each of the 'central'  
frequency settings.



"CENTRE" FREQ. (at -18 db $\pm$ 1 db )	BAND WIDTH (at -21 db )
40 Hz	35 - 47 Hz
55	47 - 65
80	67 - 97
120	105 - 145
160	145 - 190
210	190 - 260
300	260 - 360
460	390 - 560
670	580 - 800
910	800 - 1150

produce dilatation in their age groups.

The patient with minimal dilatation (Mr. A. H.) was 63 years of age and showed calcific aortic stenosis with a gradient of 40 mm Hg across the aortic valve. The frequency content of his murmur lay primarily below 190 Hz and contained the fewest high frequency components recorded (Fig. 44b). The patient with the most marked degree of poststenotic dilatation (Mr. N. M.), age 42, had a gradient of 100 mm Hg. His murmur contained largely low frequency vibrations with a peak amplitude lying below 50 Hz.

#### External recordings

A comparison of the frequency spectrum recorded within the aorta and that recorded on the chest wall was of interest. Although the arterial wall attenuates high frequencies transmitted along it (6,47) the results in section (ii) demonstrate that frequencies are not altered as they pass transversely through the wall. When the aortic murmurs were recorded on the chest wall the frequency spectra were found to lie predominantly between 70 and 190 Hz with marked changes in their relative amplitude content compared to the intravascular frequencies. The changes observed strongly suggested resonance peaks, especially Figures 42a, 43a, 44b and 45. These were not apparent intravascularly, so it is apparent that a murmur recorded on the chest surface should not be used to indicate the frequencies to which the vessel is being exposed.

In summary, the frequencies used for vibrating arteries in section (ii) are found in intravascular turbulence *in vivo* and are

Figure 42

- (a) Frequency spectrum for a murmur of aortic valve stenosis from a female, aged 33, with moderate poststenotic dilatation. The murmur was recorded from within the aorta (solid line) and from the chest wall (shaded area) and the frequencies of about 70-100 Hz appear to have been transmitted best through the thorax. The histogram bars represent relative amplitudes. Only the shape of the histogram for internal and external recordings can be compared.
- (b) Frequency spectrum for a murmur of aortic valve stenosis from a male, aged 40, with mild poststenotic dilatation. The murmur was recorded from within the aorta (solid line) and from the chest wall (shaded area). The histogram bars represent relative amplitudes and only the shape of the histogram for internal and external recordings can be compared.

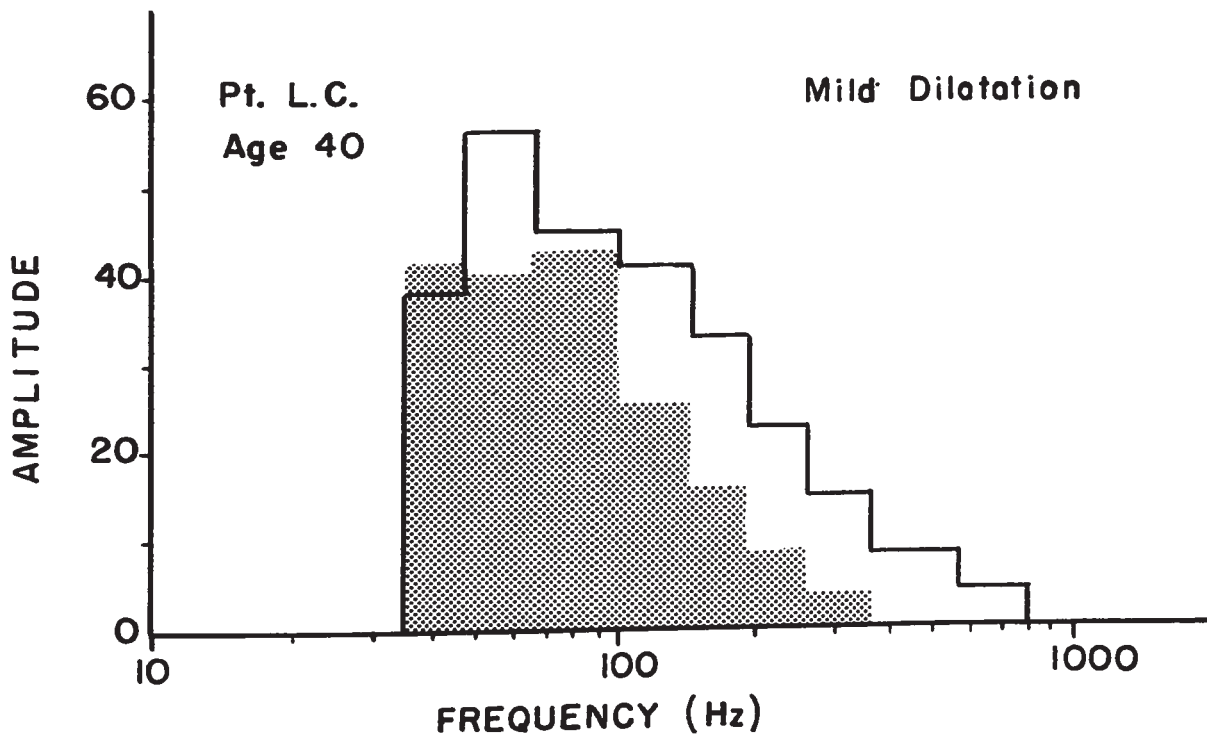
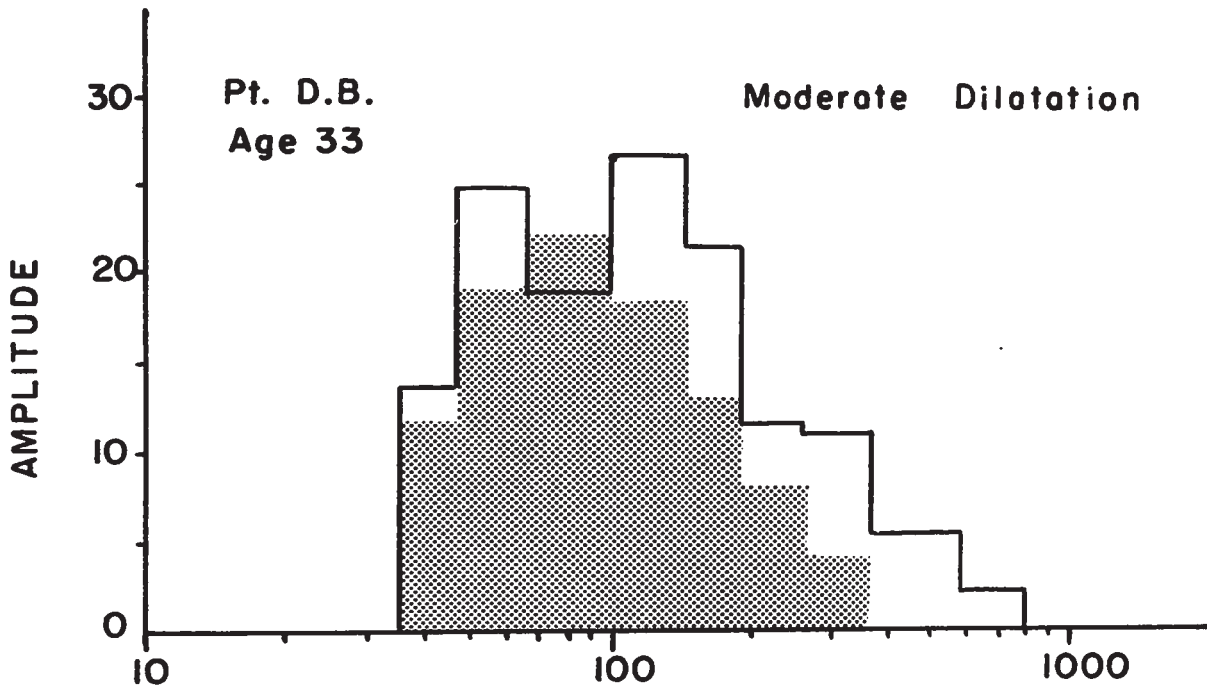


Figure 43

- (a) Frequency spectrum for a murmur of aortic valve stenosis from a male, aged 42, with severe poststenotic dilatation. The murmur was recorded from within the aorta (solid line) and from the chest wall (shaded area). Frequencies between 70 Hz and 200 Hz were transmitted best. Amplitudes are relative and only the shape of the histograms for internal and external recordings can be compared.
- (b) Frequency spectrum for a murmur of aortic valve stenosis from a male, aged 42, with mild poststenotic dilatation. Only the analysis of the murmur as recorded from within the aorta is shown. The external recording was of inadequate quality for use. The histogram bars represent relative amplitudes and the standard deviation of each bar is shown. These are typical of the standard deviations for the majority of our measurements.

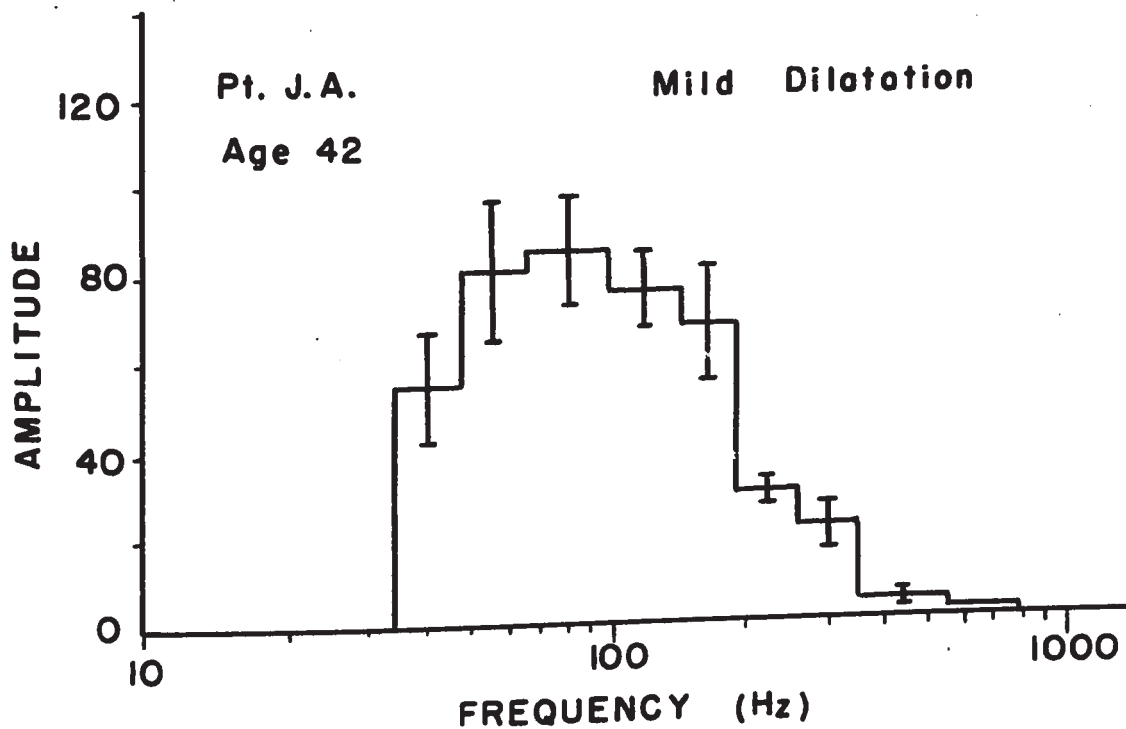
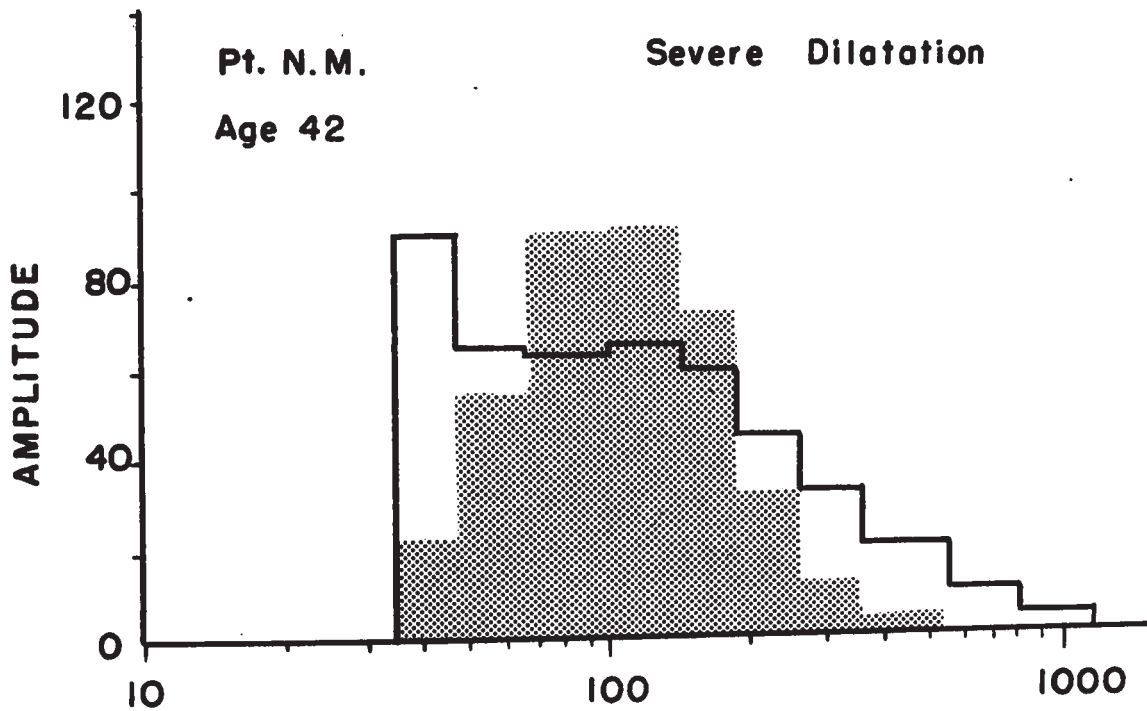


Figure 44

- (a) Frequency spectrum for a murmur of aortic valve stenosis from a female, aged 50, with mild poststenotic dilatation. The murmur was recorded from within the aorta (solid line) and from the chest wall (shaded area). Amplitudes are relative and only the shape of the two histograms can be compared.
- (b) Frequency spectrum for a murmur of aortic valve stenosis from a male, aged 63, with minimal poststenotic dilatation. The murmur, as recorded from within the aorta (solid line) showed few frequencies above 200 Hz. The murmur recorded on the chest surface (shaded area) showed the best transmission to be between 100 and 200 Hz. Amplitudes are relative and only the shape of the two histograms can be compared.

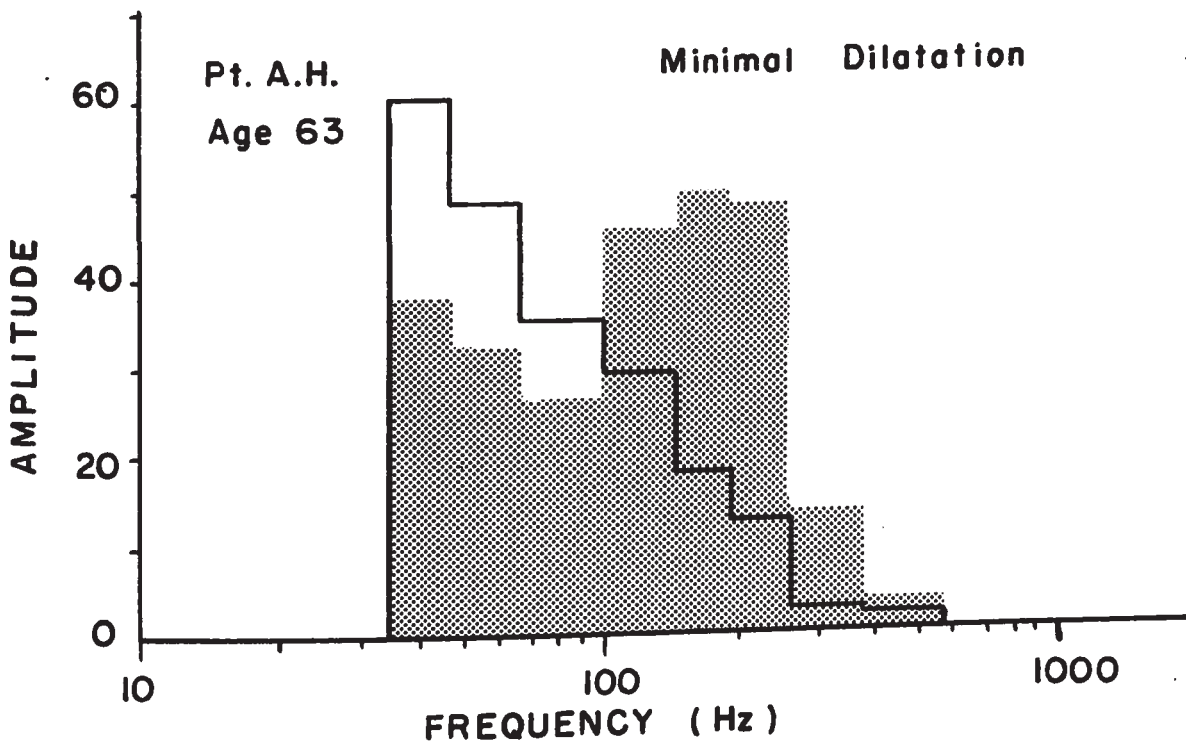
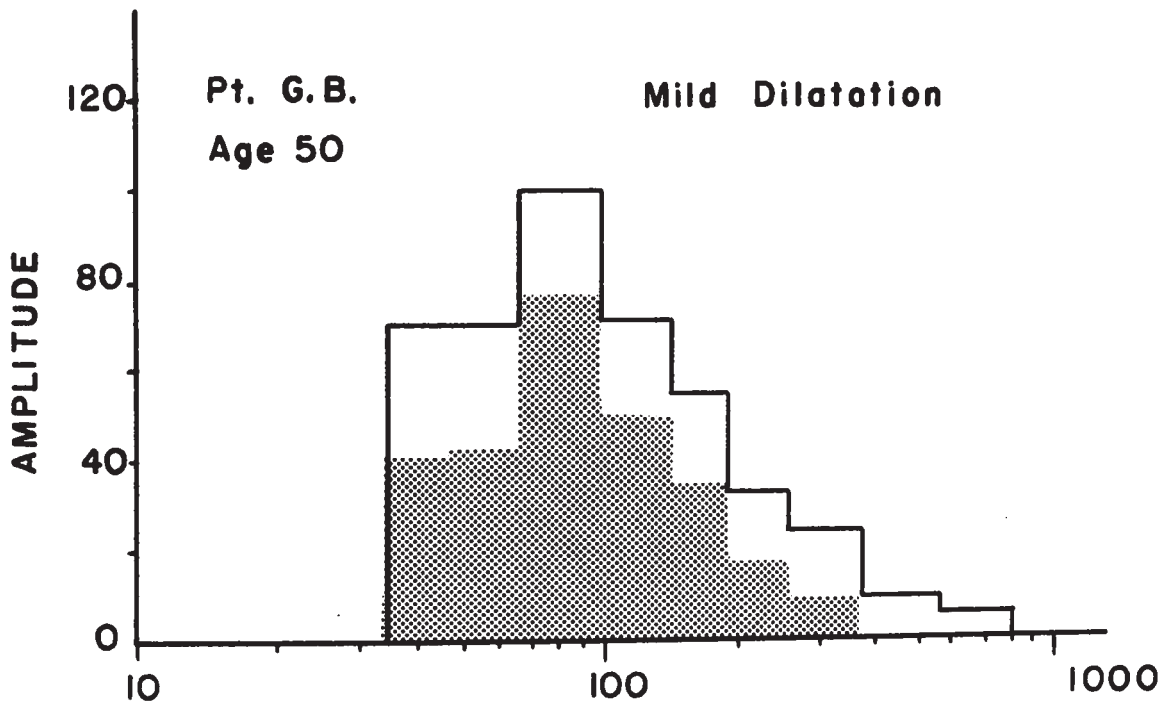
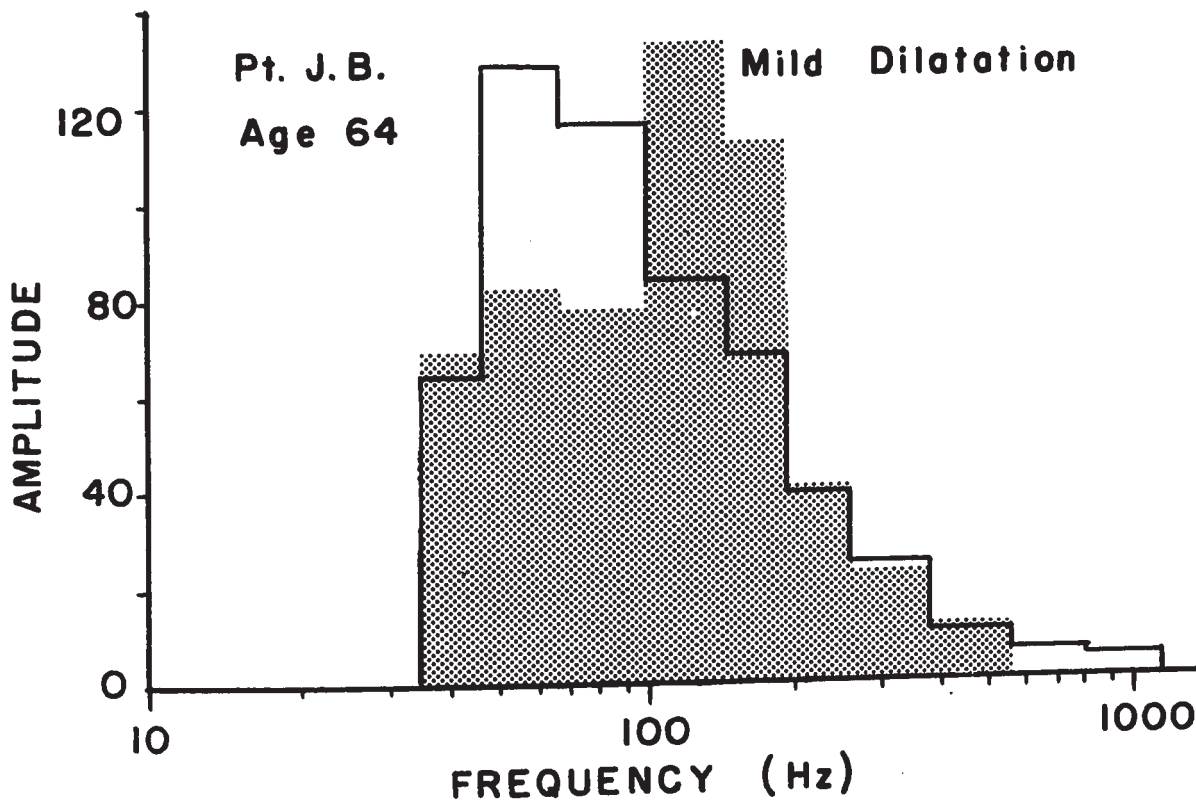




Figure 45

Frequency spectrum for a murmur of aortic valve stenosis from a male, aged 64, with mild poststenotic dilatation. The murmur was recorded from within the aorta (solid line) and from the chest wall (shaded area). Frequencies from 100 to 200 Hz were transmitted best by the thorax. Amplitudes are relative and only the shape of the two histograms can be compared.



associated with poststenotic dilatation in most cases. The relative frequency content of a murmur is altered on passage through the thorax to the chest surface.

**CHAPTER V**



DISCUSSIONDiscussion (i)Turbulence without Stenosis

Patients with atrial septal defect are known to have dilated pulmonary arteries<sup>(10,12,78,128,160,161,169)</sup>, a murmur<sup>(54,132,153,164)</sup> and a normal intravascular pressure<sup>(54,78)</sup>. I have shown that the arterial dilatation is on the basis of altered vessel wall elastic properties and is the same as poststenotic dilatation.

The slope of the normal elastic diagram for pulmonary vessels calculated by our methods produced results comparable to those obtained *in vivo* in dogs by Patel *et al*<sup>(130)</sup>. My results do not fully agree with the *in vitro* results of Harris *et al*<sup>(70)</sup> on circumferential strips of human pulmonary trunk. Their youngest age group was 17-20 years with a mean age of 18.3 years (Fig. 14). From their results, we calculated a slope of  $4.32 \times 10^4$  dynes/cm<sup>2</sup> for the section of their elastic diagram representing normal systole and diastole. This is about twice our calculated slope of  $2.15 \times 10^4$  dynes/cm for a normal group of mean age 11.7 years. However, age changes in the elastic properties of iliac arteries examined by Roach and Burton<sup>(142)</sup> showed that in five patients age 0-10 years, the initial slope of the elastic diagram was less than half that drawn for three patients aged 11-20 years. It is therefore not surprising that, for our controls, the slope we calculated is about one-half that measured by Harris *et al*<sup>(70)</sup> in their youngest age group. Thus the results obtained by our method for measuring normal pulmonary artery distensibility compare favourably with the results of other

previously reported methods.

Distal to pulmonary valve stenosis our results show the pulmonary artery to be more distensible than normal, i.e., a lower slope for this portion of the elastic diagram and a slower rate of change of wall tension with increasing radius. This is as predicted by previous *in vitro* measurements of the elastic properties of vessels showing poststenotic dilatation<sup>(143,144,146)</sup>. It also confirms that these changes are present *in vivo*. The increased distensibility of the vessel means that for any given pressure its radius will be greater than normal.

Finally, the pulmonary arteries in patients with atrial septal defect were more distensible than the controls, resulting in an increased diameter over their normal pressure range. Although the elastic properties are altered in the same way, the arterial dilatation with A.S.D. extends more peripherally than that of poststenotic dilatation. This is because the turbulence in the pulmonary vessels with A.S.D. is much more widespread, as suggested earlier.

These findings appear to rule out the previously proposed causes for the pulmonary artery enlargement in patients with atrial septal defect. The increased volume being ejected into the pulmonary artery<sup>(33,78)</sup> is seen only as an increased flow rate which cannot dilate low resistance vessels such as the large pulmonary arteries, but is indirectly responsible for the changes observed because it creates turbulence. Secondly, if the enlargement were congenital<sup>(164)</sup> the elastic properties of the wall should be normal. In addition experimental production of atrial septal defects in dogs has shown

the enlargement to be acquired<sup>(97)</sup>. Finally, the suggestion made by Baltaxe and Amplatz<sup>(10)</sup> that the enlarged vessels are a growth phenomenon resulting from increased flow is also unlikely. Our results demonstrate that larger vessels maintain a normal, predictable distensibility. Lansing<sup>(97)</sup> demonstrated in dogs that the dilatation appears within weeks of the increased flow and is associated with the appearance of a murmur. It is likely that a much longer time, in the order of months, would be necessary for true growth to occur, since the turnover rate of elastin<sup>(162)</sup> and collagen<sup>(68)</sup> is extremely slow.

The only previous measurement of pulmonary artery elastic properties in A.S.D. was done by Harris *et al*<sup>(71)</sup>. They did not find abnormal elastic properties in the two patients examined. However, both their patients were considerably older (aged 34 and 45) than our group (all less than 20 years) and were approaching the age where the pulmonary artery elastic diagram begins to show decreasing distensibility<sup>(70,142)</sup>. Also, histological examination of the pulmonary vessels in both their patients showed the marked changes associated with pulmonary hypertension, which includes increased wall thickness and muscle hyperplasia<sup>(69,79)</sup>. Their study was carried out *in vitro* by hanging weights on small circumferential strips of pulmonary artery. This is an older method for measuring arterial wall elastic properties and does not give the most accurate results since it necessitates disruption of the helical structure of the wall. In addition, they plotted predicted versus actual percent extension and considered the normal to be within twice the standard error of the estimate of the

expected line. This rather unusual method of plotting results showed the pulmonary vessels in A.S.D. to be the most distensible of all the vessels tested. Therefore, it is felt that their results in two patients with atrial septal defect cannot be considered contradictory to the much larger group reported here.

Since we have shown that altered elastic properties of the pulmonary arteries can account for their increased diameter in A.S.D. one wonders if the abnormally great pulsation of the hilar vessels seen with fluoroscopy<sup>(33,39,164,169)</sup> can also be explained.

The average radius of the vessel is larger than normal and the slope of the elastic diagram is decreased over the range representing systole and diastole (Fig. 46). Therefore the radius change between these two normal pressures will be greater than normal (i.e., about twice normal for a reduction of the slope by one-half). This is seen on fluoroscopy as "hilar dance" or abnormally great pulsations of the hilar vessels. The localized nature of the dilatation with pulmonary valve stenosis does not create the same impression. However, if carefully looked for, abnormal unilateral "expansile movement" can be seen with pulmonary stenosis in the left lower lobe branch of the left pulmonary artery<sup>(121)</sup>. This presumably results from turbulence being transmitted into this vessel but not into others due to a direct anatomical pathway from the stenosed valve.

We would predict that "hilar dance" should decrease or even disappear under two conditions. First, as the pressure rises the artery would reach the steep slope (collagen portion) of the elastic diagram occurring over 60-80 mm Hg<sup>(70,177)</sup>. This increased slope



Figure 46

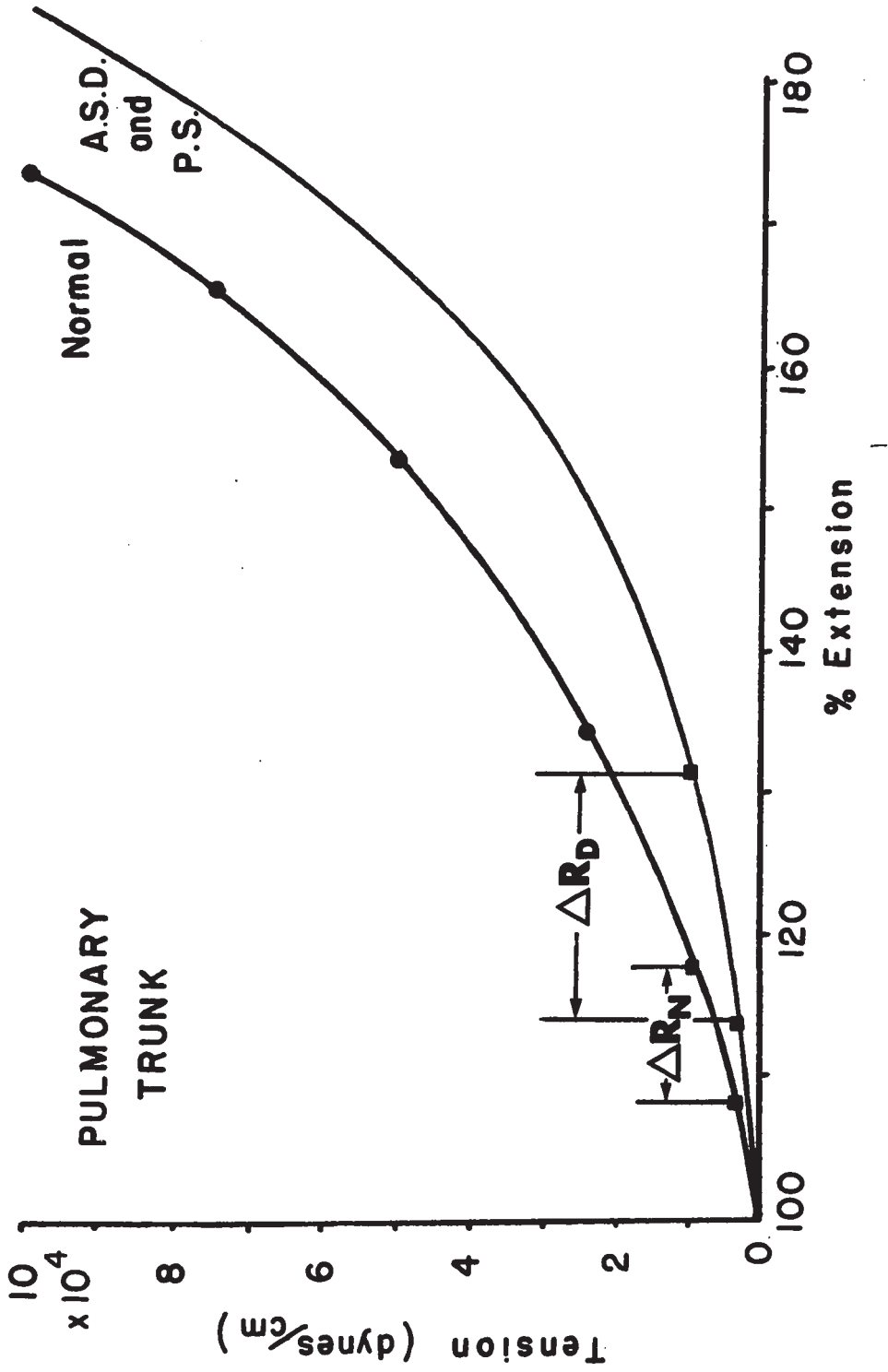
The normal elastic diagram for the pulmonary trunk is plotted from values given by Harris *et al* (70). The decrease with dilatation that we have demonstrated in the initial slope will produce a greater than normal change in radius between systole and diastole.

$\Delta R_N$  = normal change in radius

$\Delta R_D$  = change in radius after dilatation  
(due to pulmonary stenosis or A.S.D.)

On fluoroscopy this will be interpreted as "hilar dance" if dilatation extends into the smaller pulmonary arteries.

If the final portion of the curve is unaltered, as can be predicted from Roach (143,144,146), then as pulmonary hypertension develops the change in radius between systole and diastole will decrease and hilar dance should disappear.



should be associated with decreased radius change between systole and diastole. In a study using electrokymography in patients with A.S.D., Donzelot *et al*<sup>(39)</sup> concluded that "for a given flow a large kinetic pulsation corresponds to low pressures, and a reduced kinetic pulsation to raised pressures". We found one young patient, age three years, with A.S.D. and pulmonary hypertension of 100/40 mm Hg. Changes in radius between systole and diastole were small and the elastance was  $18.5 \times 10^4$  dynes/cm, a value far greater than that seen at lower pressures.

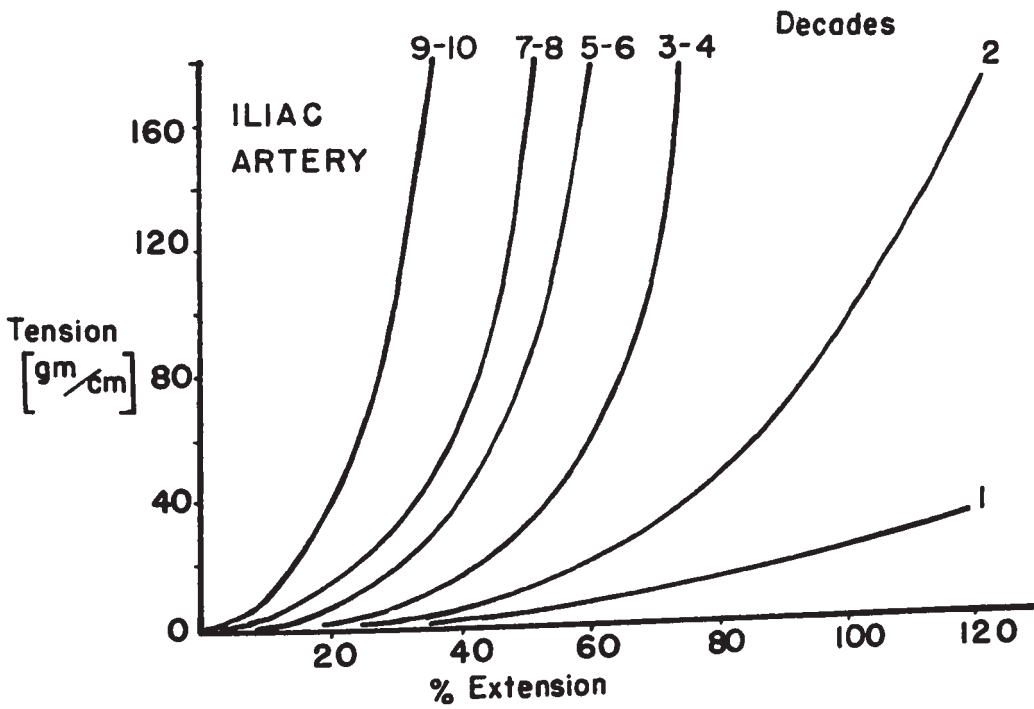
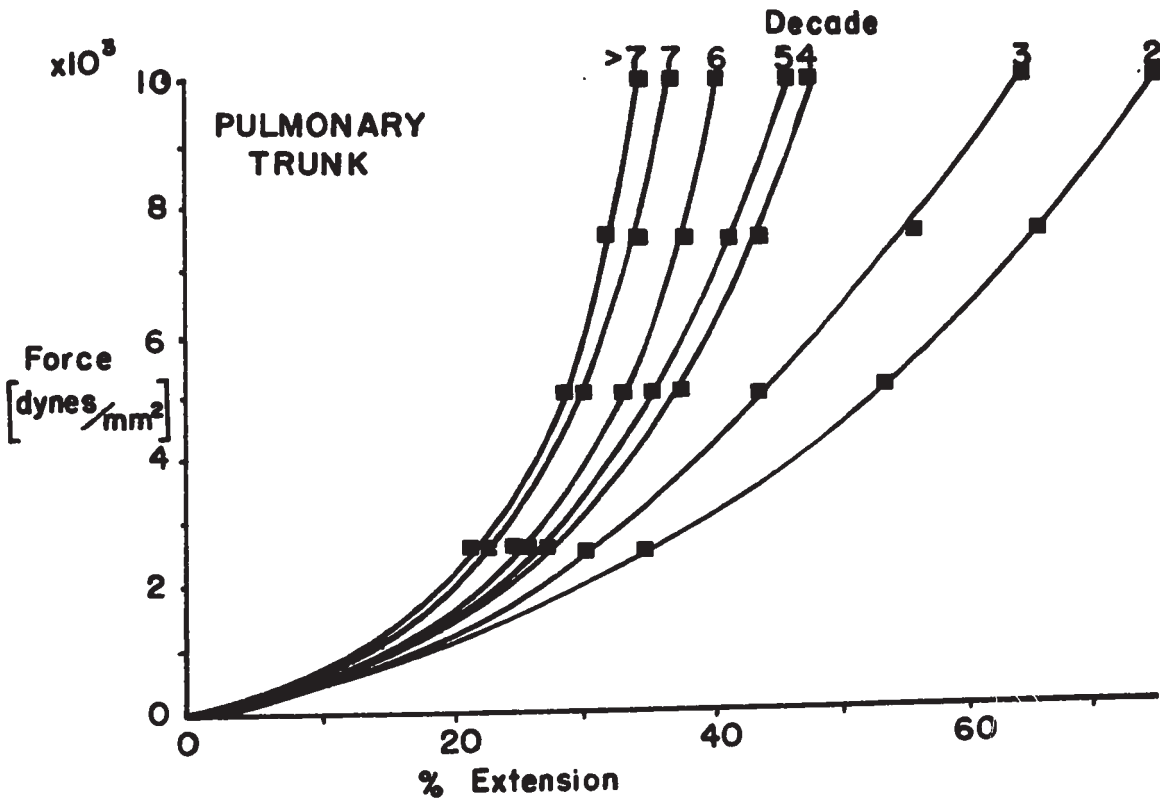
Secondly, we might expect the "hilar dance" to decrease or even eventually disappear in older age groups since the tension-radius curve shifts to the left with age<sup>(70,142)</sup> (Fig. 47). The initial slope gradually increases as changes occur in the elastin<sup>(75,76,113)</sup>. More collagen is laid down and increased collagen crosslinking occurs with age<sup>(63,70)</sup>. The increased slope means a decreased radius change between systole and diastole and thus less chance of movement being seen on fluoroscopy.

The one case of Marfan's syndrome warrants further discussion. This patient had an hereditary disorder of elastin which is characterized histologically by gradual elastin disintegration and disruption and clinically by aortic dilatation and dissection. Involvement of the pulmonary artery is not usually looked for in these patients since it rarely gives rise to findings of clinical significance<sup>(118)</sup>. In two patients examined at autopsy by Baer *et al*<sup>(8)</sup> the same histologic lesions were observed in the pulmonary artery as in the aorta, although the aortic lesions alone had been considered significant clinically.

Figure 47

With advancing age arteries become stiffer. The elastic diagram shifts to the left as collagen crosslinking increases and elastin content decreases. Such changes have been shown to occur in both the human pulmonary trunk (top) and the human external iliac artery (bottom).

[from Harris, Heath and Apostolopoulos (70)  
and Roach and Burton (142)]



Enlargement of the pulmonary conus had been noted on the chest X-ray of one patient. Rarely does involvement of the pulmonary artery dominate the picture<sup>(5,8,166)</sup> although pulmonary dissection is described<sup>(120)</sup>.

The patient reported here was considered to have a normal cardiac catheter study and angiograms. However, measurement of the elastic properties of his pulmonary vessels showed them to be distinctly abnormal since the values of wall tension versus strain fell within the range measured for vessels exhibiting dilatation due to intravascular turbulence and murmurs. The changes postulated to explain the altered tension-length diagram in poststenotic dilatation have been related to changes in elastin<sup>(52,143,144,146)</sup>. This patient, with a congenital disorder of elastin, presents with a picture similar to the acquired dilatation due to a murmur and turbulence and confirms that the etiology of dilatation in the latter group is due to changes in the elastin network.

It is also worth noting that the vessels of patients with Marfan's syndrome do not dilate progressively and rupture. The collagen in the wall, which is apparently not affected<sup>(120)</sup>, prevents this from occurring just as it does in poststenotic dilatation. But what can we expect if a murmur and turbulence coexist with the congenital disorder? McKusick<sup>(118)</sup> states: "One would expect that the combination of interatrial septal defect and inherent weakness of the pulmonary arterial wall might result in even more dilatation of the pulmonary artery than is usually seen with either lesion alone. This has not been demonstrated with certainty however". Actually the final sentence

should not be surprising since if the changes normally produced by a murmur are already present on a congenital basis, no further dilatation should be expected as long as the collagen is not altered.

In summary, I have demonstrated that the elastic properties of the pulmonary artery in atrial septal defect are altered in the same manner as they are in poststenotic dilatation. The changes are in the elastin portion of the curve and are the same as those seen in Marfan's syndrome, a congenital disorder of elastin. The factors which produce or modify hilar dance have been discussed and are illustrated in Fig. 48.

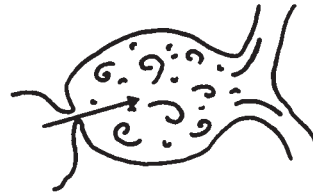
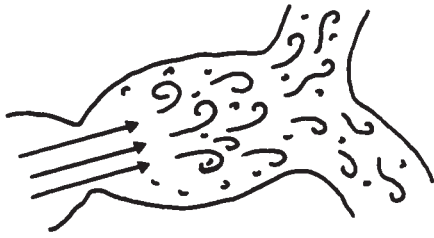
### Figure 48

The factors affecting the presence or absence of 'hilar dance' as seen on fluoroscopy: If the intravascular turbulence is localized to an area just beyond the pulmonary valve (B) then the hilar vessels will not be affected. Any abnormality that produces widespread pulmonary artery turbulence (A) (e.g., atrial septal defect, ventricular septal defect, anomalous pulmonary venous drainage as long as the left to right shunt is large enough) will show 'hilar dance' by decreasing the initial slope of the elastic diagram (C). The presence of 'hilar dance' in these conditions will be modified by age, which causes the elastic diagram to shift to the left (D), and by elevation of the pulmonary artery pressure, which puts systole (s) and diastole (d) on the steeper slope of the elastic diagram (F). 'Hilar dance' will also be seen in complete heart block and in pulmonary insufficiency, where the diastolic pressure has been lowered and a wide pulse pressure is present (E).



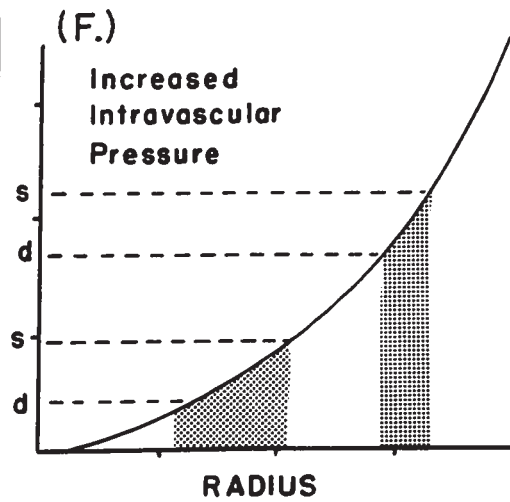
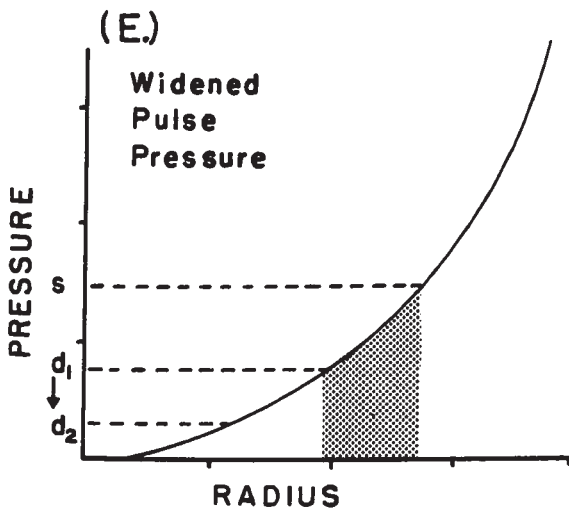
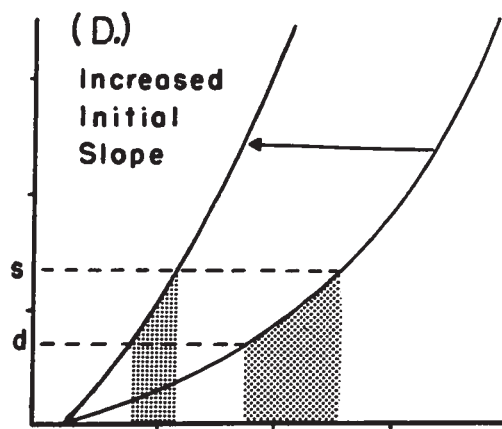
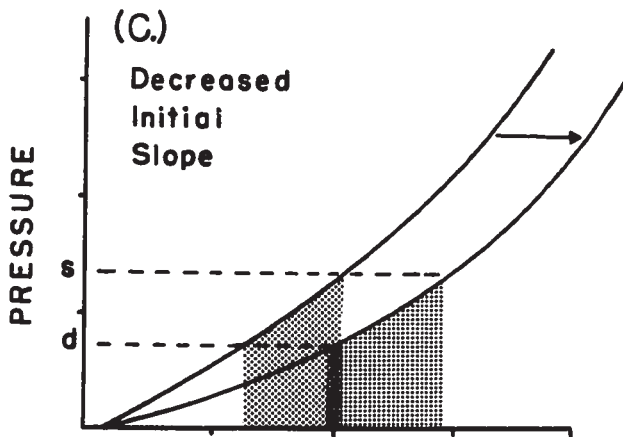
"HILAR DANCE"  
PRESENT

"HILAR DANCE"  
ABSENT



(A) Widespread  
Turbulence

(B) Localized  
Turbulence



Discussion (ii)Vibration of Arteries

I have shown that human external iliac arteries, *in vitro*, will dilate when exposed to the frequencies contained in murmurs. The changes that occur in the elastic properties of the vessel wall are the same as those shown for poststenotic dilatation and, in any given artery, age appears to alter the frequencies required to produce dilatation. Even though fixed at various intraluminal pressures, histologic examination by light microscopy did not show any consistent changes after vibration.

The functional structure of the arterial wall was first elucidated by Wolinsky and Glagov<sup>(59,177)</sup> in 1965, and their results are outlined in the Historical Review (ii). Their work with rabbit aortae showed the gross changes which occur in the orientation of collagen and elastin with increasing pressure. On electron microscopy they showed the presence of fine elastin nets joining the lamellae, apparently serving to evenly distribute the wall tension for the elastin network.

Their histological findings correlated well with the two component tension-radius diagram for the arterial wall, with elastin providing the tension at low pressures and collagen at high pressures (141). Since the effects of vibration did not alter the final slope of the elastic diagram it is unlikely that any change in the collagen has occurred. The damage appears to be to the elastin network. If this is the case, the damage is not likely to be found in the elastin lamellae for two reasons. First, changes here should be readily

visible on light microscopy and second, if the lamellae were broken up the elastic diagram would no longer be a two component curve. The collagen alone would be left to produce the wall tension and since it has a high elastic modulus the curve would turn upward rapidly (i.e., be shifted to the left). This was not the case.

The most likely explanation for the findings observed is that changes were produced within the elastin nets joining the lamellae. Disruption of small portions of the crosslinks within these nets, or the entire net, would result in failure of the overall elastin network to resist stress normally and a general decrease in the elastic modulus for the arterial elastin. These changes would produce only minimal changes in the unstressed radius but when the intraluminal pressure is increased, the greater extensibility of elastin would result in a larger vessel radius before sufficient wall tension occurred to stress the collagen. Thus for any given intraluminal pressure, the vascular diameter would be greater than normal.

Such changes in the elastin network would also explain why the vessel does not progressively dilate and rupture. First, the failure to significantly alter the elastin lamellae means that the elastin network as a whole would still function but with a decreased elastic modulus. Secondly, if the elastin network is finally destroyed by vibration, the collagen would remain to prevent vessel rupture. The collagen is unaltered by the frequencies contained in murmurs.

Although the alterations must remain speculative, we can from present knowledge, suggest how the disruption of these nets might occur. The elastin lamellae are arranged in a helical fashion within the arterial wall<sup>(177)</sup>. They can be pictured as a collection of springs

(58 for the human aorta<sup>(178)</sup>), lying one inside the other, each with unknown length and pitch but interconnected by the fine elastin nets. This 'model' should be visualized for the following discussion.

When a force is applied to a vessel it can be resolved into the planes perpendicular to and parallel to the vessel wall<sup>(131)</sup>. A small amplitude pressure wave applied to a particular point on a vessel will produce displacement perpendicular to the wall and will also be transmitted horizontally along the vessel. As shown by our second set-up (Fig. 18) the amplitude of the vertical displacement on passage through the wall will not be attenuated to any significant degree regardless of frequency. Resonance peaks do not occur with the frequencies used.

However, the same small pressure wave will be transmitted horizontally along the vessel wall<sup>(47,49)</sup> and will be attenuated to varying degrees depending on the frequency<sup>(6,47)</sup> and the intraluminal pressure<sup>(47)</sup>. This attenuation could not be assessed by our methods since the mounted vessel was stimulated serially by a train of waves moving along within it. Any site of vibration on the surface corresponded to a site of stimulus within the vessel.

The longitudinal transmission of vibration will be the motion most likely to result in tissue disruption. Vibrations are transmitted along the vessel at a rate of approximately 5 meters/sec<sup>(6,47,88,95)</sup> and the general arrangement of the wall is in the form of helices (especially the elastin lamellae) as already noted. As a vibration passes along an elastin fiber or lamella each adjacent portion will have a motion consisting of two vectors:

(i) perpendicular to the vessel wall and (ii) parallel to the fibre direction (rather than longitudinal, conduction would be described as "helical"). The latter results in the attenuation of the wave. Resonance phenomena could quite conceivably be set up within the lamellae by the range of wavelengths involved in murmurs (e.g., for 100 Hz at 5 meters/sec velocity the wavelength is 5 cm). The resonance peaks would not be easily detectable on the vessel surface and are not essential to the argument.

The longitudinal movements of the lamellae set up by vibration would not likely be in unison. Even simple differences in lamellar length would alter their response to a particular vibration. In addition the lengths and properties of the interconnecting elastin nets would affect their motion and it is therefore conceivable that adjacent lamellae could be as much as  $180^\circ$  out of phase. Under such conditions the elastin nets between them might be subjected to large stress and shear forces which could cause their disruption. This explanation would allow for a band of frequencies being able to produce the changes observed rather than requiring a single "resonance" frequency.

The apparent change of this important band of frequencies with age can also be explained by this theory. Roach and Burton<sup>(142)</sup> have shown that the elastic diagram for the arterial wall shifts to the left with increasing age. These results have been confirmed by others<sup>(31,70,126)</sup> and the changes that occur in the wall appear to influence mainly the initial portion of the curve where a decreased distensibility is seen. With increasing age the relative amount of

arterial collagen and elastin (expressed as a percent of the dry weight) may change with a relative decrease in elastin and increase in collagen<sup>(43,127,157)</sup>. However, some authors claim no relation between the age of the human aorta and the percent elastin<sup>(74,96)</sup> and it is apparent that the real quantitative changes have not been properly assessed<sup>(113)</sup>.

Changes in the nature of the elastin "springs" could account for the increased stiffness of the arterial wall. For any spring the stiffness can be doubled without changing the number of coils by (i) increasing the wire diameter by 19%, (ii) decreasing the coil diameter by 26%, or (iii) decreasing the number of coils by one half<sup>(72)</sup>. Hass extracted elastin from the human aorta by heating at 45°C after immersion in formic acid<sup>(74)</sup>. The elastin networks so isolated retained their normal properties of extensibility, retractibility and tensile strength, and showed a decreasing distensibility with age<sup>(75,76)</sup>. The fine coiled fibrous elements of elastin<sup>(64)</sup> have an alteration in their fluorescent spectra with age suggesting an increased elastin crosslinking<sup>(15,113)</sup>. Thus an increased "wire" diameter and a decreased number of coils are possible. Such changes could account for the alteration of the frequencies necessary for elastin disruption.

The elastin nets may also be responsible for the "creep" phenomenon observed and used as a baseline. A material which normally obeys Hooke's Law as a single fibre can display viscoelastic properties when woven into the form of a net. Not only will a hysteresis loop be produced but "creep" can be demonstrated<sup>(138)</sup>. Remington<sup>(137)</sup> has demonstrated that the hysteresis loop is not a specific characteristic

of muscle alone but can be seen with elastin, e.g., ligamentum nuchae. Creep and stress relaxation were also demonstrated for the ligamentum nuchae but were not present for tendon (collagen).

The possibility that disruption of muscle fibres was responsible for the changes observed following vibration seems unlikely. Prevention of smooth muscle contraction with sodium amytal did not alter the viscous properties observed and exposure of another vessel to norepinephrine produced no evidence of smooth muscle activity. Early studies on the effects of smooth muscle on the elastic properties of the arterial wall gave conflicting results. Lawton<sup>(99)</sup> and Torrance and Schwartz<sup>(165)</sup> found that vascular smooth muscle excitation decreased arterial distensibility but others found increased distensibility<sup>(172,173)</sup> or decreased distensibility at low pressures and increased at high pressures<sup>(4,94)</sup>. The arterial wall is less distensible *in vivo* than *in vitro*<sup>(61)</sup>, probably due to smooth muscle activity, and recently Dobrin and Rovick<sup>(38)</sup> have clearly shown that smooth muscle contraction produces an increased elastic modulus at all but the highest stresses. By exposing vessels first to norepinephrine to produce muscle contraction, then to potassium cyanide (KCN) to remove all muscular activity, they illustrated the differences in the elastic diagram produced by smooth muscle. From their results we would expect the break-down of muscle fibres in spasm to make the vessel more distensible at both high and low stress. Such was not the case. The increased distensibility we found after vibration was limited to the lower values of wall stress and our tension-length diagrams most closely resembled the vessels exposed to KCN. Also, epinephrine

does not appear to alter the size of poststenotic dilatation<sup>(82)</sup>.

The question of resonance of the arterial wall in response to vibration remains unanswered. We found no evidence of resonance peaks of the type reported by Foreman and Hutchison<sup>(53)</sup> for the *in vitro* arterial wall and there was no apparent attenuation of any frequency over the range tested. It is possible that we may have missed such peaks if they were small or of a narrow frequency band but Lees and Dewey<sup>(102)</sup> found no evidence of resonance peaks in four murmurs recorded from human carotid and femoral vessels *in vivo*.

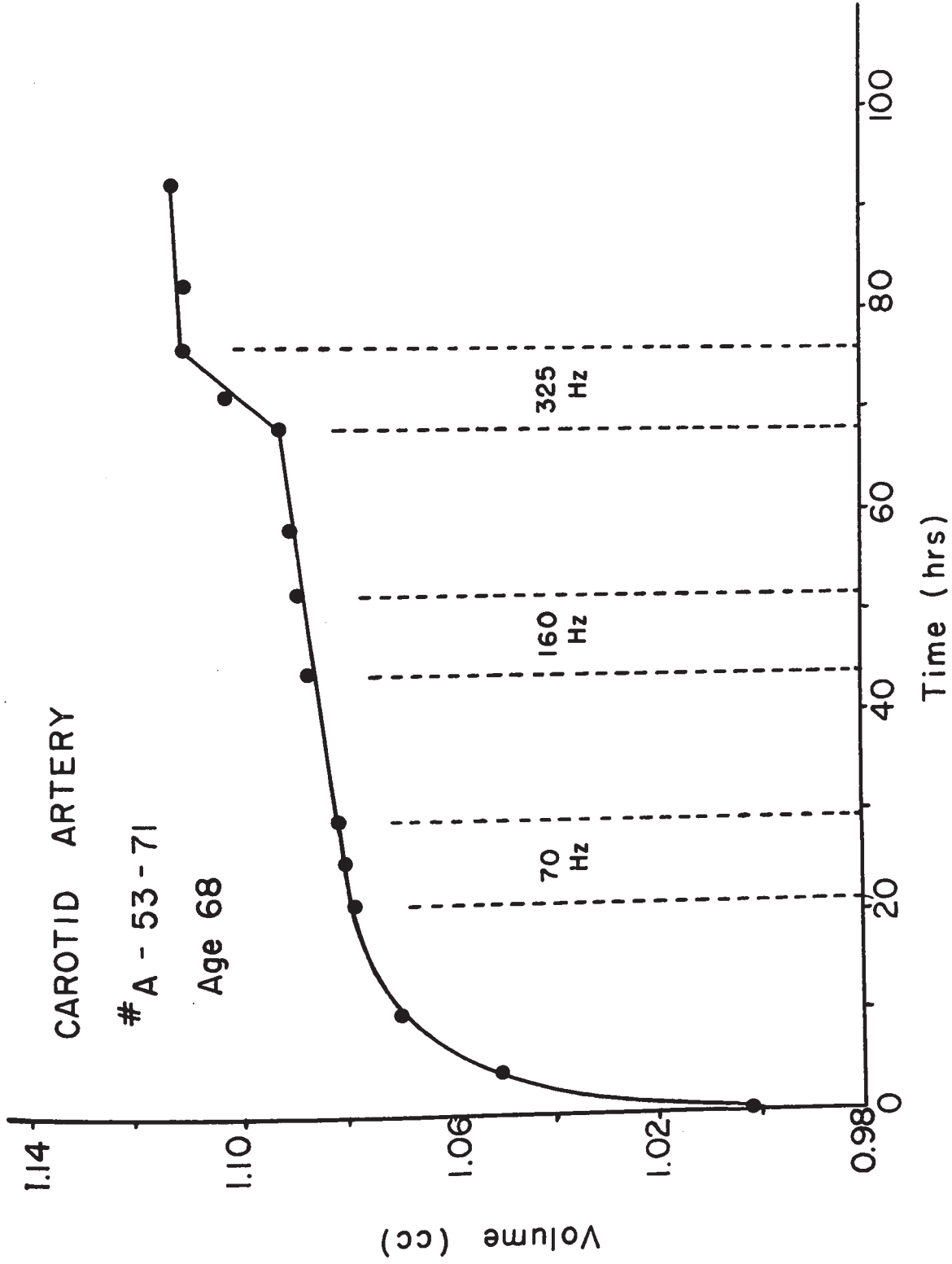
Since Bergel<sup>(13)</sup> showed, in dogs, that the static mechanical properties of femoral and carotid arteries, as well as abdominal and thoracic arteries, were similar, we feel that our findings in human external iliac arteries can be projected to other large vessels in the body. To verify this assumption, one carotid artery, age 68, was obtained and exposed to various frequencies. The vessel failed to dilate to the low (70 Hz) and middle range (160 Hz) frequencies but did dilate to a vibration of 325 Hz (Fig. 49).

In summary, vibration produces changes in the elastic diagram similar to those seen in poststenotic dilatation. The change appears to be in the elastin network and is likely due to a disruption of the interlamellar elastin nets. The variability of the frequency required to produce dilatation is probably due to the changes that occur in arterial elastin with age.



Figure 49

A segment of common carotid artery from a 68 year old male was exposed to vibrations of 70 Hz, 160 Hz and 325 Hz. Only with 325 Hz did dilatation occur over that expected from 'creep'.



Discussion (iii)Frequency Content of Murmurs

Frequencies recorded within a tube using a microphone pickup correspond to the turbulent frequencies measured by particle tracer studies<sup>(52,125)</sup> and the walls of an elastic tube will respond to those vibrations<sup>(125)</sup>. Using a phonocatheter placed distal to a stenotic aortic valve the intravascular turbulence recorded had a predominant frequency content lying between 50 and 190 Hz in all seven cases. Components up to 800 Hz were common and a few frequencies even higher were occasionally recorded. This range of frequencies agrees with the findings reported by Wallace *et al*<sup>(170)</sup> for a seven year old boy with aortic stenosis. They used McKusick's sound spectrograph<sup>(114)</sup> to analyze the murmur recorded from a phonocatheter within the boy's aorta. The murmur showed, in addition to the frequencies up to 240 Hz, considerable frequency content up to 500 Hz. No comparison was made with a recording from the chest surface.

Some degree of poststenotic dilatation was present in all of our cases and all had frequency components falling within the range used for our *in vitro* studies, section (ii). Six of these patients, aged 33-64 years, had mild to severe poststenotic dilatation. All of these six had relatively high amplitude frequency components falling within the range predicted by our *in vitro* studies to produce poststenotic dilatation for their age group.

One 63 year old patient showed minimal poststenotic dilatation on angiography. His murmur contained relatively few components in the

"high" frequency range above 200 Hz, which is the range used to produce dilatation in this age group and supports our *in vitro* predictions.

The diameter of a vessel in an area of poststenotic dilatation does not correlate with the degree of stenosis for either the aortic<sup>(85,152)</sup> or pulmonary<sup>(22)</sup> valves. Absence of poststenotic dilatation is unusual but does occasionally occur<sup>(152)</sup>. More recently Roach<sup>(148)</sup> has demonstrated that for renal artery stenosis the length of the poststenotic dilatation, rather than the diameter of the dilated vessel, correlates with the degree of stenosis. Since vibration apparently produces the dilatation, the extent of the intravascular turbulence is therefore the important factor. Although our results *in vivo* cannot be considered conclusive they support the findings in section (ii). It appears that the degree of poststenotic dilatation is probably related to the presence or absence of intravascular turbulence with the correct frequency content for that age group.

On comparing our matching internal and external murmur recordings we noted a definite change in configuration of the amplitude-frequency spectrum on the chest surface with apparent broad resonance peaks between 100 and 200 Hz appearing. Two variables could have produced these changes during transmission of the intravascular vibrations to the external microphone: (i) the aortic wall and (ii) the "thorax".

*In vitro* studies have shown that an elastic tube responds to the frequencies to which it is exposed at high flow rates<sup>(125)</sup>.

Our results from section (ii) demonstrated that the arterial wall responds to each individual frequency and transmits it by transverse motion without evidence of attenuation or resonance peaks. This agrees with the *in vivo* studies on carotid and femoral arteries by Lees and Dewey<sup>(102)</sup> but contradicts the *in vitro* studies of Foreman and Hutchison who found resonance peaks between 100 and 200 Hz plus attenuation of higher frequencies.

It has been clearly shown by several authors that the thorax attenuates frequencies below 100 Hz moderately and above 300 Hz considerably<sup>(48,50,181)</sup> and does not attenuate frequencies from 100-200 Hz. Normal respirations do not alter the transmission characteristics<sup>(50)</sup>. By percussing the chest and analyzing the frequency of the resultant sound, McKusick<sup>(117)</sup> claimed that the resonant frequency of the chest was about 140 Hz. Also, by producing sounds within the heart and great vessels in three dogs Zalter *et al*<sup>(181)</sup> noted resonance peaks between 100 and 200 Hz for two dogs when the sounds were recorded on the chest surface.

Thus the evidence suggests that the wall 'transduces' the intravascular pressure fluctuations into sound and the changes in the frequency spectrum occur on the passage of these vibrations through the chest tissues. Therefore the external recordings cannot be used to assess the frequency spectrum of intraaortic turbulence. The external frequency spectrum recordings do bring up an interesting point, however. Stethoscopes, which are simply mechanical amplifiers, have an individual frequency response depending on their design.

The frequency responses of a variety of stethoscopes have been studied by Ertel *et al*<sup>(44,45)</sup> and the differences documented. The amplification of frequencies below 100 Hz is easily accomplished by any modern stethoscope using the "bell" position. The problems arise in amplifying the frequencies above 100 Hz. The function of the diaphragm is to attenuate the low frequencies and thus unmask the higher ones. Since the thorax transmits the 100-200 Hz frequencies best, it is essential that the diaphragm side of the stethoscope be most efficient over this range. A number of the most modern stethoscopes produce marked attenuation over the entire high frequency range. In others the diaphragm attenuates all frequencies up to nearly 200 Hz rather than just to 100 Hz. A more scientific approach to the construction or to the selection of a stethoscope appears to be warranted.

In summary, the results of our frequency analyses demonstrate that the frequencies used to vibrate arteries in section (ii) are realistic and associated with poststenotic dilatation *in vivo*. The degree of poststenotic dilatation may be related to the presence or absence of appropriate frequency components for that age group. The vibrations are altered by passage through the thorax and therefore any analysis of the frequencies to which a vessel is being exposed must be done either from recordings within the vessel or on the vessel wall.

CHAPTER VI

CONCLUSIONSConclusions (i)Turbulence without Stenosis

- (i) The dilatation of pulmonary arteries in patients with atrial septal defects is due to a decrease in the slope of the initial portion of the elastic diagram.
- (ii) The change in the elastic properties of these vessels corresponds to the changes seen distal to pulmonary valve stenosis. The enlargement of vessels observed in A.S.D. is on the same basis as poststenotic dilatation and, therefore, a stenosis is not necessary for dilatation to occur. The presence of intravascular turbulence and a murmur is all that is necessary.
- (iii) Our *in vivo* measurement of pulmonary artery elastic properties shows that the previous *in vitro* measurements, which demonstrated a decreased elastic modulus for the elastin portion of the tension-length diagram in poststenotic dilatation, applies to the *in vivo* situation.
- (iv) The altered elastic properties seen with turbulence and vibration are, as previously suggested, due to changes in the elastin network of the vessel wall since we found that the pulmonary artery from a patient with a congenital disorder of elastin (Marfan's syndrome) showed similar alterations.
- (v) The abnormally great pulsation of the hilar pulmonary vessels ("hilar dance"), visualized clinically on fluoroscopy of



patients with atrial septal defect, is due to the altered elastic properties of the vessel walls. The decreased slope of the elastic diagram, on which normal systole and diastole fall for these vessels, gives a greater than normal change in radius for normal changes in wall tension.

(vi) Disappearance of "hilar dance" with the onset of marked pulmonary hypertension or with advancing age is explained by changes in position or shape of the elastic diagram. In both cases the change in radius decreases for a given change in wall tension.

(vii) "Hilar dance" is seen with atrial septal defect and not with pulmonary stenosis because in A.S.D. the altered elastic properties extend more peripherally.

Conclusions (ii)Vibration of Arteries

- (i) When held at a constant intraluminal pressure, the human external iliac artery displays a viscous property known as "creep". This is a slow extension under constant tension.
- (ii) Arteries dilate when vibrated with frequencies contained in murmurs. These are low frequencies ranging from 30 Hz to 600 Hz.
- (iii) The age of a given artery determines the frequency range necessary to produce dilatation. The elastic properties of younger vessels are altered by lower frequencies than are the older vessels.
- (iv) The changes produced by vibration appear to cause a decrease in the elastic modulus of the elastin portion of the arterial tension-length curve. The collagen portion is unaffected. These changes correspond to the alterations found in an area of poststenotic dilatation and also found in the pulmonary arteries of patients with atrial septal defects.
- (v) No gross histologic changes were visible on light microscopy. The changes are likely due to disruption of the elastin nets attached to adjacent elastin lamellae and visible only on electron microscopy. This results in an increased distensibility of the elastin network and thus an overall increased radius of the wall for any given wall tension.
- (vi) These alterations have been discussed in relation to changes that could occur as a result of the helical arrangement of the arterial wall elastin lamellae and the interconnecting elastin nets.

(vii) The propagation of vibration through the arterial wall does not appear to produce attenuation or resonance peaks in the range of frequencies tested (10-1000 Hz).

Conclusions (iii)Frequency Content of Murmurs

- (i) The frequencies used to vibrate arteries were contained in the murmurs from seven patients with aortic stenosis and are associated with poststenotic dilatation.
- (ii) The absence of frequency components contained in a murmur which are necessary to produce alterations in a specific age group (< 45 years requires < 100 Hz; 45-60 years requires 100-200 Hz; >60 years requires > 200 Hz) may be responsible for the minimal poststenotic dilatation seen in one patient.
- (iii) Damping of various frequency components of a murmur occurs during passage from the blood to the chest surface.

CHAPTER VII



GENERAL CONCLUSIONS

Turbulence arises in arteries when the critical Reynolds' number is exceeded. This turbulence causes the vessel wall to vibrate and this vibration is heard as a murmur and felt as a thrill. The frequency content of these vibrations is variable and is often of a broad spectrum lying between 30 and 600 Hz. Frequencies of this range produce dilatation of vessels, probably due to changes in the interlamellar elastin nets. The age of the vessel determines the frequency required to produce dilatation and if the correct frequencies are not present dilatation does not occur. This could be due to changes in the properties of elastin with age. Such vascular enlargement develops when turbulence appears either due to a high flow rate alone or due to an increased flow rate produced by a stenosis.

Thus any pathological process that causes turbulence containing sounds of the right frequency should cause arterial dilatation.

CHAPTER VIII



SUGGESTIONS FOR FUTURE RESEARCH

A number of possibilities are suggested for future research by the results of this work.

Turbulence without Stenosis

(i) Abnormal pulsations of the hilar vessels are occasionally noted in patients with ventricular septal defects (V.S.D.). Measurement of the elastic properties of pulmonary arteries in a variety of cases of V.S.D. could be made and correlated with the degree of shunt. This could be a useful clinical sign in this defect.

(ii) Construction of the entire elastic diagram for the pulmonary arteries in atrial septal defect could be attempted by obtaining patients with increased intraluminal pressures due to increased pulmonary vascular resistance.

(iii) An attempt to answer how quickly the changes produced by vibration are repaired could be made by following patients after surgical correction of an atrial septal defect. Disappearance of the dilated vessels would be a measure of this repair.

(iv) Do all patients with Marfan's syndrome have involvement of the pulmonary arteries? Can involvement here be used as a prognostic sign? Study of further cases is indicated.

(v) At what age do the changes in the elastic diagram become sufficient to decrease hilar dance? How long can such a decrease in abnormal pulsations alone be attributed to elevation of the



pulmonary artery pressure?

Vibration of Arteries

- (i) Do lower or higher pressures alter the frequency required to produce dilatation? If so, different frequencies could be expected to produce dilatation in the pulmonary arteries than on the systemic side.
- (ii) Since low frequency vibrations alter elastin in arteries, could they not alter elastin elsewhere, such as within the bronchial tree?
- (iii) Can other frequencies alter other components of the arterial wall?
- (iv) Viscous properties of the arterial wall were observed separate from those related to smooth muscle activity. Although they appear to be small, quantitation of these properties would be valuable in the development of arterial wall models.
- (v) Little consideration has been given previously to the helical structure of the arterial wall. Measurement histologically of the pitch of the elastin lamellae and possibly their length would be useful.
- (vi) The damping of frequencies by the arterial wall is due to the longitudinal transmission of vibration. Evidence of resonance phenomena in the lamellae should be looked for in the lack of such attenuation of particular frequencies.

Frequency Analysis

(i) A knowledge of the frequency content of a variety of murmurs is lacking yet statements that specific murmurs are usually low pitched or high pitched are frequently made. At the present time there is no foundation for such comments and a frequency analysis of a variety of murmurs would be useful.

(ii) Comparison of the frequency content of a variety of murmurs recorded intravascularly with that recorded on the chest surface would be useful to determine the response of the arterial wall to vibration and the amount of attenuation of different frequencies on passage to the body surface. Production of specific frequencies intravascularly and recording the response on the chest wall and in nearby vessels would be useful.

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**Appendix 1**



Appendix 1

Murmurs are graded clinically<sup>(105)</sup> according to their "loudness" or amplitude when heard on the chest surface.

- grade 1 - the faintest bruit that can be definitely heard, probably easily overlooked by the casual examiner
- grade 2 - a slight or faint murmur
- grade 3 - a murmur of moderate intensity
- grade 4 - a loud murmur
- grade 5 - a very loud murmur usually accompanied by a palpable thrill
- grade 6 - the loudest possible murmur, audible without a stethoscope