due to the use of complan. Nitrogen-balance studies were carried out at intervals and are shown in Fig. 5.

The low level of circulating eosinophils during the first two weeks give an indication of the severe stress response leading to the heavy loss of nitrogen in the urine during this period. The necessary high-level protein intake to combat this was achieved without any difficulty, and it was possible to maintain a positive nitrogen balance almost from the start.

As much as 1½ lb. (680 mg.) of complan daily was easily tolerated in the form of drinks made with water or milk, usually without the addition of flavouring. This alone gave a total of 210 g. of protein and 3,000 calories. It will be seen that serum proteins were up to normal level within four weeks, and weight loss was never severe.

One final point might be mentioned in connexion with this case. Apart from pre-operative medication the only sedative drugs ordered during the entire course of treatment were morphine ¼ gr. (16 mg.) shortly after admission, and quinalbarbitone ("seconal") 1½ gr. (100 mg.) on two subsequent occasions. Occasional doses of aspirin may also have been given, but it is obvious that pain was never severe at any time.

Mortality

The mortality rates in those under 60 years and in those 60 and over are shown in Table III. The poor prognosis in the elderly patient is at once apparent, and is a reminder that a very guarded prognosis must always be given for the

TABLE III.—*Mortality*

Total No. of cases	520
Fatal cases	46
Gross mortality	8·8%

Extent of Burn	Under 60 Years of Age			60 Years and Over		
	Total No.	Fatal Cases	Mortality	Total No.	Fatal Cases	Mortality
0–%	269	Nil	0%	40	5	12·5%
10–%	98	,,	0%	6	5	83·3%
20–%	40	,,	0%	10	8	80%
30–%	21	5	23·8%	4	4	100%
40–%	9	2	22·2%	4	4	100%
50–%	9	4	44·4%	2	2	100%
60% and over	7	6	85·7%	1	1	100%
	453	17	3·6%	67	29	43·3%

TABLE IV

Age	Expected Deaths	Actual No. of Deaths
Under 60 years	25·8	17 (65·9% of expected mortality)
60 and over	36·7	29 (79% ,, ,, ,,)
Total	62·5	46 (73·6% ,, ,, ,,)

patient over 60 who has burns greater than 10%. In contrast it will be seen that in the under-60 group the mortality of burns less than 30% is nil, and that even in the 30 cases with burns of 30–49% the mortality has been kept down to less than 25%.

The excellent statistical analysis carried out at the Birmingham M.R.C. Burns Unit by Bull and Fisher (1954) provides a method of calculating the expected mortality of a series given the age and percentage area of burn in each case treated. Using their "probability chart," it was found that the expected number of deaths in this series was 62.5, whereas the actual number was 46—that is, 73.6% of the expected mortality (Table IV).

Summary

Figures are given concerning the treatment of 520 cases of burns treated at the Basingstoke Unit.

The average in-patient stay of fresh cases (admitted within 72 hours) is 34.5 days, as compared with 65.5 days total stay for cases where admission has been delayed.

Current treatment at the unit is briefly described and an illustrative case presented in detail. A method of treating circumferential burns of the trunk by exposure is described, and the value of "complan" in maintaining a high-protein high-calorie intake is noted.

The mortality of the series is shown to be 73.6% of the mortality expected from M.R.C. statistics.

I thank Mr. E. Ferrill and Mr. R. Burns for the photographs, and Mr. P. Sibson-Drury, clinical artist, who drew the chart.

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PREDICTION OF MITRAL PRESSURE GRADIENT FROM HEART SOUNDS

BY

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The phonocardiogram enables the time intervals between the heart sounds to be measured with accuracy. It has already been shown (Wells, 1954) that the severity of mitral stenosis may be assessed by measuring the interval between the onset of the QRS complex of the electrocardiogram and the first heart sound and the interval between the second heart sound and the opening snap. It was shown that these intervals were approximately related to the size of the mitral orifice as determined at surgical operation. The present report is based on the findings at operation in 100 patients with mitral stenosis who have been assessed pre-operatively by phonocardiogram. At operation the size of the mitral orifice was estimated, the pressure gradient across the mitral valve measured, and the cardiac output calculated. When the size of the mitral orifice was contrasted with the pressure gradient across it considerable differences were found. These differences are due to variations in cardiac output, and also to variations in the pressure gradient necessary to open the rigid valve cusps. The delay of the first sound and opening snap are found to predict the pressure gradient across the mitral valve rather than the size of the mitral orifice.

Material

A total of 106 consecutive patients undergoing mitral valvotomy by Mr. O. S. Tubbs and Mr. I. M. Hill were used for this study. Six of these were excluded because the pre-operative phonocardiograms failed to show an opening snap. This is known to occur when there is much thickening and rigidity of the mitral valve. The remaining 100 patients (85 females, 15 males) were between 18 and 56 years of age. The diagnosis was in each case mitral stenosis, although some of the patients had also slight mitral regurgitation or slight aortic valve disease. Half of the patients were in sinus rhythm and the other half had atrial fibrillation.

Method

Phonocardiograms were taken at rest, using a Sanborn stethocardiette with logarithmic frequency response and a paper speed of 75 mm. a second. Lead II of the electrocardiogram was used as a reference tracing, but lead III was also studied in case there was an initial isoelectric interval of the Q.R.S. in lead II. The precautions necessary to obtain satisfactory phonocardiograms have already been described (Wells *et al.*, 1949).

The delay of the first heart sound (Q–1 interval) was measured from the begining of the QRS complex of the electrocardiogram to the beginning of the maximal vibrations of the first heart sound. These vibrations are of high frequency and are usually quite clearly distinguished from the coarser and smaller vibrations of the diastolic or presystolic murmurs and the first component of the first heart sound. The delay of the opening snap (2–O.S. interval) was measured from the beginning of the second component of the second heart sound (Rappaport and Sprague, 1942) to the beginning of the opening snap. The length of the preceding cardiac cycle was measured from the R–R interval of the electrocardiogram. The intervals were measured in at least 20 cardiac cycles in each patient, and were plotted against the previous cycle length (Fig. 1). From this graph the Q–1

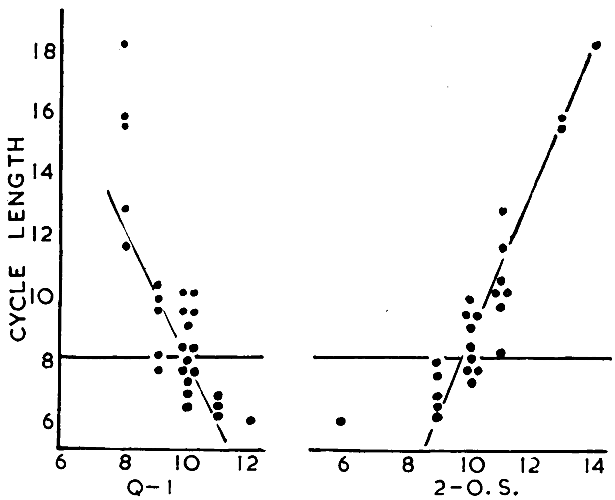

FIG. 1.—Graphs of the interval between the onset of the QRS complex of the electrocardiogram and the onset of the maximal vibrations of the first heart sound (Q–1), the interval between the second sound and the opening snap (2–O.S.), and the length of the preceding cardiac cycle. From such graphs drawn for each patient the values for the Q–1 and 2–O.S. are estimated for a cycle length of 0.8 second. Cycle lengths in tenths of a second, and Q–1 and 2–O.S. in hundredths of a second.

and 2–O.S. intervals were determined for a cycle length of 0.8 second. This cycle length was chosen because it was such that an extrapolation of the graph was rarely necessary. The figures appropriate to this cycle length were called the "corrected Q–1" and "corrected 2–O.S." The other measurements taken from the phonocardiogram were the heart rate, the diastolic filling period, and the duration of systole per minute. The diastolic filling period is the total duration in one minute of the intervals between the opening snap and the next first heart sound. The remainder of the minute was taken as the duration of systole per minute.

The size of the mitral orifice was assessed at operation by the surgeon. The area of the orifice was calculated from its length and breadth by multiplying these by pi over 4. The pressure gradient across the mitral valve has usually been obtained at operation by a Sanborn electromanometer by simultaneous needle puncture of the left atrium and the left ventricle. The mitral gradient has been taken as the mean left atrial pressure during ventricular diastole minus the mean left ventricular pressure in diastole. In a few cases only the mean left atrial pressure by a saline manometer was available, and in these cases the mitral gradient was taken as this figure minus 5 mm. of mercury.

The cardiac output was estimated by means of Gorlin's formula (Gorlin and Gorlin, 1951). This formula uses the pressure gradient across the mitral valve, the size of the mitral orifice, and the diastolic filling period. In the calculation of cardiac output the diastolic filling period was not measured at the time of operation but was obtained from the pre-operative phonocardiogram. This will introduce some error, but it will not be large, as the total variations of the diastolic filling period are small.

Results

There is a definite relationship between the pre-operative "corrected Q–1 minus 2–O.S." and the pressure gradient across the mitral valve at operation. The relationship is shown in Fig. 2. When the "corrected Q–1 minus 2–O.S." lies between $+5\frac{1}{2}$ and $-1\frac{1}{2}$ the mitral pressure gradient is found to be high, while for figures between $-1\frac{1}{2}$ and $-4\frac{1}{2}$ the gradient is found to be low. The pressure gradient may therefore be predicted by the pre-operative phonocardiogram. Such a prediction appears valid despite the modifications of the pressure gradient that are caused by anaesthesia, thoracotomy, and pericardiotomy. These modifications are not well understood, but their presence is indicated by an increase in pulse rate and a reduction in pulse volume and systemic blood pressure. A reduction of cardiac output is probably present, and this would mean that the pressure gradient across the mitral valve would be lower than before operation. For this reason the cases in which the systemic blood pressure fell below 70 mm. Hg at the time the mitral pressure gradient was measured have been indicated in Fig. 2 by a ring.

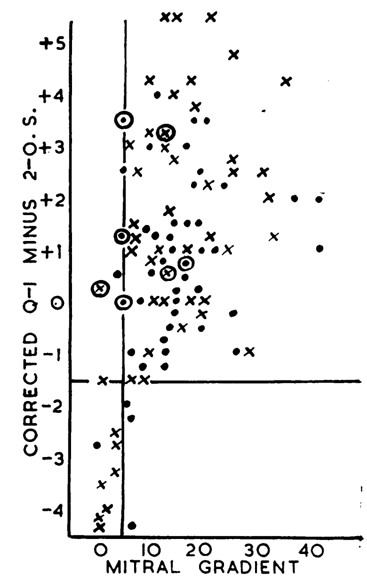

FIG. 2.—Graph showing the relationship between the "corrected Q–1 minus 2–O.S." and the pressure gradient across the mitral valve (in mm. Hg). The crosses denote patients with sinus rhythm and the dots patients with atrial fibrillation. Those cases enclosed in a ring had a systemic blood pressure of below 70 mm. Hg at the time the mitral pressure gradient was measured, rendering the estimation of the gradient misleading.

When the corrected Q–1 and the corrected 2–O.S. are considered separately they do not give as accurate a prediction of the mitral pressure gradient as when they are combined. This could be due to the fact that the combination reduces the error of measurement to a half. Fig. 3 suggests that the corrected Q–1 and the corrected 2–O.S. are too poorly related to each other for this explanation to be satisfactory.

Since the stroke volume in mitral stenosis is reduced (Gorlin *et al.*, 1951) it is possible that the abnormality of the heart sounds might reflect the altered form of the left ven-

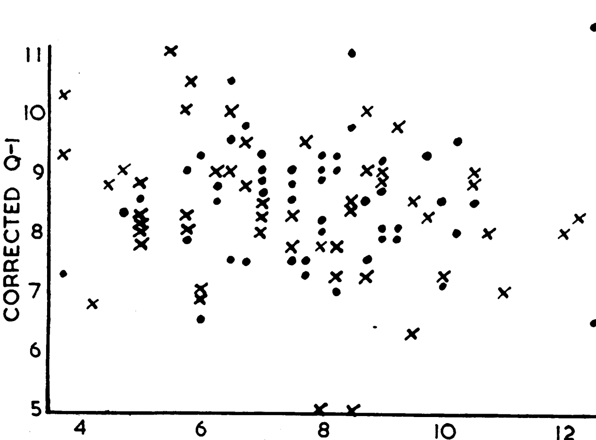

FIG. 3.—Graph showing the corrected Q–1 and corrected 2–O.S. Crosses=sinus rhythm. Dots=atrial fibrillation.

tricular pressure curve. Studies of the left ventricular pressure tracings show that after a brief period of ventricular filling the onset of pressure rise is not delayed but the rise is slower than it is after a long period of filling (Fig. 4). The fall of ventricular pressure is slower and earlier after a short period of filling. Such curves might explain the variations of the Q–1 interval but would not explain the variation of the 2–O.S. interval. Further evidence that the stroke volume is not the important factor in determining the abnormal timing of the heart sounds is provided by Fig. 5. This shows that the abnormal heart sounds are not related to the cardiac output as measured by Gorlin's formula.

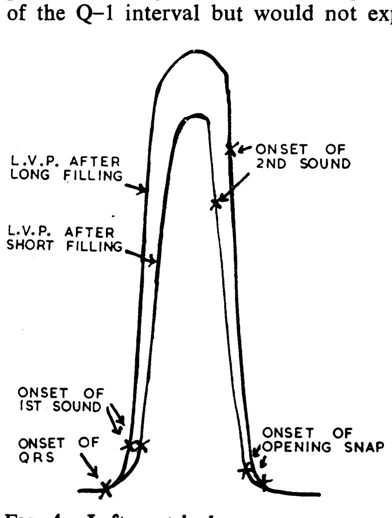

FIG. 4.—Left ventricular pressure curves after long and short diastolic intervals superimposed for contrast. With synchronous onset of QRS the first sounds are separated by 0.04 second, the second sounds by 0.03 second, and the opening snaps by 0.06 second.

Little is known about the mechanism of formation of the first heart sound and opening snap in mitral stenosis. In order to study this problem phonocardiograms have been taken from the exposed heart at operation together with synchronous pressure tracings from the left atrium and the left ventricle. It is difficult to obtain satisfactory sealing of the microphone bell to the surface of the exposed heart without causing ventricular premature beats which confuse the investigation. Such tracings as have been obtained show that the delay of the first heart sound is due to a number of factors. The raised atrial pressure delays the time of crossover of atrial and ventricular pressures; the slow rise of ventricular pressure after a brief period of ventricular filling increases the delay; and, finally, the delay is further increased by an interval between the crossover of pressures and the first heart sound. The last factor is probably due to the difficulty of closure of the deformed mitral valve cusps when there is a small volume of blood in the left ventricle. This is supported by the observations of Smith *et al.* (1950), who showed that in the case of the normal mitral valve it is necessary for blood to flow between the cusps and the ventricular wall before closure of the valves is possible.

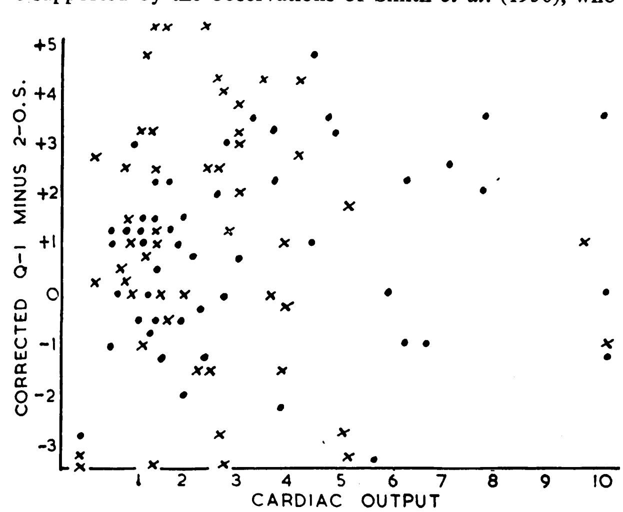

FIG. 5.—Graph showing the "corrected Q-1 minus 2-O.S." and the cardiac output estimated from the mitral orifice size, the mitral pressure gradient, and the diastolic filling period (using Gorlin's formula). Crosses=sinus rhythm. Dots=atrial fibrillation. Cardiac output in litres a minute.

The 2–O.S. interval is not prolonged by the reduced rate of fall of the ventricular pressure in the isometric relaxation period following a short diastolic interval. Indeed, the 2–O.S. interval is actually shorter in these circumstances than after a longer diastolic interval. There are three reasons for this. Firstly, the reduced stroke volume of such a beat causes the second heart sound to occur at a lower ventricular pressure and consequently nearer to the opening snap, as has been pointed out by Bayer *et al.* (1956). Secondly, the raised left atrial pressure causes an earlier crossover of atrial and ventricular pressures. Finally, the higher pressure gradient between atrium and ventricle appears to reduce the delay between the crossover of atrial and ventricular pressures and the occurrence of the opening snap.

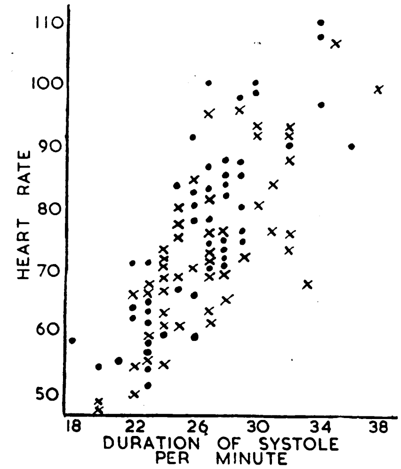

FIG. 6.—Graph showing the heart rate and duration of systole per minute. The latter is expressed in seconds, being the number of seconds in each minute that the mitral valve is closed (first heart sound to opening snap). Crosses=sinus rhythm. Dots=atrial fibrillation.

A further measurement made in this study has been the duration of systole per minute. Normally the duration of systole is measured from the onset of ventricular contraction to the beginning of the second heart sound. In mitral stenosis there is still a pressure gradient and probably a flow of blood between the left atrium and the left ventricle after the onset of ventricular systole. In addition to this the period of isometric relaxation is reduced so that ventricular filling starts earlier than is normal. In view of these features the duration of systole was measured from the beginning of the first heart sound to the beginning of the opening snap. The "duration of systole per minute" was then calculated by finding the number of seconds in each minute occupied by systole. The heart rate was also measured, and the two were recorded on a graph. Fig. 6 shows the findings in the present series, and indicates that there is no difference between the patients with atrial fibrillation and those with normal rhythm. Fig. 7 shows the same patients separated into those with low and those with high mitral pressure

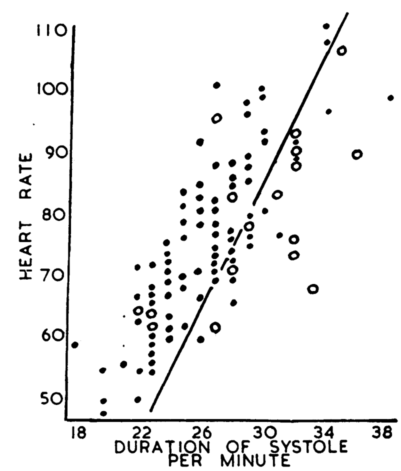

FIG. 7.—Graph showing the heart rate and duration of systole per minute as in Fig. 6. Open circles=cases with low mitral pressure gradient. Small dots=cases with high mitral pressure gradient. The line should separate the cases with a low gradient from those with a high gradient, and might do so more accurately if the duration of systole were measured at the time of measuring the mitral gradient.

gradients. When the duration of systole is long for a given heart rate the pressure gradient across the mitral valve is usually small.

No mention has so far been made of the patients who had mild degrees of mitral regurgitation, aortic valve disease, or hypertension. In none of this series were any of these additional abnormalities considered to be significant from the clinical point of view. The cases have nevertheless been carefully watched throughout the study, and they have shown no feature to distinguish them from the cases of uncomplicated mitral stenosis.

Discussion

The assessment of the severity of mitral stenosis involves the evaluation of a large number of symptoms and signs and special investigations. The precise obstruction at the mitral orifice is indicated by the pressure gradients across the mitral valve considered in conjunction with the cardiac output. The closest approach to this information short of direct puncture of the heart is provided by cardiac catheterization. This test requires an expert team, and even then is not always reliable. Although the present study only shows that the pressure gradient can be predicted by the phonocardiogram it is nevertheless of great practical importance. It also demonstrates that the information hitherto obtainable only by cardiac catheterization may in future be obtained very much more simply.

The 2–O.S. interval has been considered by Bayer *et al.* (1956) to indicate the left atrial pressure. These workers have made no correction for cycle length, which is particularly necessary in the presence of atrial fibrillation. They have demonstrated the changes that occur on exertion, but these are changes that may also occur from increase in the heart rate. In the present study the 2–O.S. interval has not provided as good a correlation with the mean mitral pressure gradient in ventricular diastole as the combination of Q–1 and 2–O.S. One reason for this is that while the 2–O.S. interval may indicate the pressure gradient at the beginning of diastole it will not indicate the gradient at the end of diastole. It does not therefore give an indication of the mean pressure gradient in ventricular diastole. Another reason for subtracting the 2–O.S. from the Q–1 is the theory that the rigidity of the valve material may alter the timing of opening and closing. In the presence of rigid valve cusps a delay of the first heart sound after the crossover of atrial and ventricular pressures could be associated with a delay of the opening snap after the second crossover of pressures. This would explain the wide scatter of Q–1 and 2–O.S. in Fig. 3. When the one interval is subtracted from the other any such factor would be eliminated.

There is much to be learned about the form of atrial pressure curves. When the valve cusps are freely mobile and can be displaced far into the atrial cavity the pressure curve in mitral stenosis may suggest the presence of mitral regurgitation even when this is not present. In these circumstances the tall V wave starts to fall well before the crossover of atrial and ventricular pressures occurs. This pattern is abolished by valvotomy, and the crossover of pressures now occurs near the apex of the V wave. When the mitral valve is rigid there is less rise of left atrial pressure during ventricular systole. When the left atrial cavity is very large the size of the V wave is small even when considerable mitral regurgitation is present.

The pressure gradient across the mitral valve is not constant throughout ventricular diastole but usually increases rapidly to a maximal gradient and then falls at first with moderate speed and then more slowly. When there is sinus rhythm there is usually an increase in gradient during atrial systole. The variations of pressure gradient are indicated by the variations in intensity of the diastolic murmur. The murmur does not, however, indicate the degree of pressure gradient. This information may be provided by the timing of the first heart sound and the opening snap.

Experiments have shown that in the normal subject there is an increase in the duration of mechanical systole if the previous cycle length is long, but that a greater increase occurs if the diastolic volume of the left ventricle is increased (Hafkesbring and Ashman, 1928). Other workers have found that the duration of systole is normally dependent not on the cycle length but on the initial ventricular pressure and stroke volume (Wiggers, 1921 ; Remington *et al.*, 1948). When the duration of systole is reduced by increasing the arterial resistance there is a lengthening of isometric contraction. The changes in the duration of systole in mitral stenosis have received little attention since Lewis (1913) stated that it was practically the same as in normal subjects. The present study shows that the duration of systole is short and the period of isometric contraction is confused by the fact that there is a considerable interval between the onset of systole and the closure of the mitral valve. The period of isometric relaxation is shortened. Other workers have found the stroke volume low (Meakins *et al.*, 1923 ; Gorlin *et al.*, 1951) and this would suggest a shortening of the duration of systole. Although the degree of shortening of systole has not hitherto been used as a measure of the severity of mitral stenosis the present study shows that it may be possible in future to assess the severity of mitral stenosis by this measurement alone.

Summary

A pre-operative phonocardiogram is compared with the operative findings in 100 patients undergoing mitral valvotomy.

The mean pressure gradient across the mitral valve in ventricular diastole may be predicted from a measurement of the time relationships between the electrocardiogram and the heart sounds.

The delay between the QRS and the first heart sound and the interval between the second heart sound and the opening snap are estimated for a cycle length of 0.8 second. The intervals are called " corrected Q–1 " and " corrected 2–O.S."

The corrected Q–1 is not related to the corrected 2–O.S., but the difference between the two (corrected Q–1 minus 2–O.S.) enables a prediction of the mean mitral pressure gradient to be made.

A simpler but less accurate prediction can be made from the duration of systole per minute.

I am indebted to Mr. O. S. Tubbs and Mr. I. M. Hill for their assistance, and for permission to make this study on their patients. I am also indebted to Miss L. Farrar for her technical assistance.

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