DISABILITY AND CIRCULATORY CHANGES IN MITRAL STENOSIS

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Investigations associated with the surgical treatment of mitral stenosis have led to an increase in our understanding of the cause of disability in that condition. There are three reasons for this. First, the selection of cases for operation requires the separation of patients in whom operable mitral stenosis is the chief cause of disability, and this requirement has resulted in more exact diagnosis than was previously necessary. Secondly, judgment of the value of mitral valvotomy has led to a careful assessment of the degree of the patient's disability before and after the widening of the stenosed valve. Thirdly, the use of cardiac catheterization as a method of investigation has permitted measurement of the circulatory changes associated with the different degrees of disability.

These developments led to an investigation of the circulatory changes associated with different degrees of disability in patients with uncomplicated mitral stenosis. By showing the sequence of circulatory changes with increasing disability, and the degree of their reversal after successful mitral valvotomy, the investigation suggests which changes are more important in the causation of symptoms. The study also has a practical aspect, for it defines the pattern of circulatory changes to be expected with each grade of disability due to uncomplicated mitral stenosis. These patterns have been compared with those in patients in whom causes of disability in addition to mitral stenosis were present. The results of this comparison may be of assistance in determining whether mitral stenosis is the chief cause of disability when the exact assessment of a case is difficult.

Circulatory changes that might be the cause of symptoms in mitral stenosis have been demonstrated by many investigators. In 1923 Meakins *et al.* showed that the circulation rate is reduced and its increase on exercise is limited. Cournand (1947) found a marked increase in pulmonary artery pressure in some patients. Hellems *et al.* (1949) showed how to measure the increased pressure in the pulmonary capillaries. Gorlin and Gorlin (1951) suggested a method using hydrodynamic principles by which the decrease in the "area of the mitral valve opening" might be calculated. Epps and Adler (1953) measured the increase of pressure in the left atrium.

The relation of the degree of these changes in the circulation to the disability from which the patients suffered has also been the subject of considerable study. Borden *et al.* (1949) related disability to the elevation of the pulmonary arterial pressure and the reduction of cardiac output. Eliasch (1952) included measurement of the pulmonary capillary pressure in his comparison, and Dexter *et al.* (1952) calculated the "mitral valve area." The relief of disability following mitral valvotomy has been compared in individual patients with the corresponding change of circulatory measurements by Draper *et al.* (1951) and Donald *et al.* (1954). The findings in general were that with increased disability there was a greater departure from normal of circulatory measurements. However, it was not established which changes are more closely associated with disability. There are two reasons for this. The number of patients studied was not large enough to take individual differences into account, and the significance of the findings was reduced by the inclusion of patients showing evidence of lesions in addition to the mitral stenosis.

During the past six years we have made a study of the relationship between disability and circulatory changes in an experiment designed to define it as precisely as possible. A careful investigation of each patient enabled us to exclude those in whom causes of disability other than mitral

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stenosis might exist, and to assign the selected patients to one of four groups according to the degree of their disability. The number of patients had to be large in order to take into account the individual variations to be expected in any group of patients. Statistical analysis of the findings ascertained which measurements showed the more significant differences between the groups of patients.

MATERIAL

Since 1948 more than a thousand patients with rheumatic heart disease have been referred to this hospital for mitral valvotomy, and cardiac catheterization has been carried out on more than 200 of these as an aid to determining their suitability for operation. In only 81 of these did we consider that mitral stenosis was the sole cause of their disability, though sometimes it was accompanied by atrial fibrillation. As will be shown later the inclusion of the latter patients had an insignificant effect on the conclusions reached. All the 81 patients had the long rumbling diastolic murmur typical of mitral stenosis. All came to operation, with the exception of four whose disability was judged too slight to justify mitral valvotomy, and at operation the clinical diagnosis was confirmed by direct observation. The following complications have been considered and excluded as factors contributing to their disability.

Aortic Valve Disease. No patient had a systolic murmur in the aortic area. In twelve patients a less than Grade II early diastolic murmur to the left of the sternum had been heard on occasions, but in none was there any alteration of the peripheral pulse, unusual pulsation in the left ventricle on fluoroscopy, or clinical, radiological, or electrocardiographic evidence of left ventricular hypertrophy to indicate that the murmur was due to aortic valve disease.

Mitral Incompetence. Four patients had a soft systolic murmur at the cardiac apex, but at valvotomy none of these patients had a valve orifice greater than 1.0×0.5 cm., and no regurgitant stream was felt. None of these patients had clinical, electrocardiographic, or radiological evidence of left ventricular hypertrophy.

Tricuspid Valve Disease. Nine patients had a soft systolic murmur medial to the apex or in the tricuspid area, but in none of these were there any other signs of tricuspid incompetence. Tricuspid stenosis was excluded because no patient had, at catheterization, a measurable pressure gradient across the tricuspid valve during diastole.

Hypertension. No patient had a systolic blood pressure higher than 140 mm. Hg, nor a diastolic pressure higher than 90 mm. Hg.

Respiratory Disease. No patient had clinical or radiological signs of emphysema, nor recurrent bronchitis antedating cardiac dyspnoea.

Active Rheumatism. No patient had pyrexia, a raised sedimentation rate, or recent arthralgia.

Anæmia. No patient had a hæmoglobin of less than 11 g. per 100 ml.

Cardiac Neurosis. We have excluded all patients in whom the possibility of the complication of cardiac neurosis was suspected.

There were 27 men and 54 women; 22 patients were in the third decade, 42 in the fourth decade, and 17 in the fifth decade. Twenty-five of the patients included had established atrial fibrillation with ventricular rate controlled by digitalis. At the time of catheterization no patient had clinical signs of congestive heart failure; in none was the right atrial mean pressure higher than 10 mm. Hg. Twenty-seven of these patients were studied again after mitral valvotomy, from which operation 23 had derived much relief and four less relief. The findings provide the opportunity to observe which changes in measurement accompany the relief of symptoms.

METHODS

The patient's degree of disability in his everyday life was determined from a detailed history, according to the following scheme.

Grade A No disability. 0 patients.

Grade B Unduly breathless on walking quickly on the level or walking at normal pace up an incline. 7 patients.

Grade C Breathless on moderate exertion and unable to hurry, though able to walk some miles on the level at their own speed. 18 patients.

Grade D Unable to walk more than a few hundred yards because of dyspnoea and fatigue, and forced to take frequent rests on inclines or stairs. Seriously incapacitated in day to day activity, and unable to do more than light work. 37 patients.

Grade E Breathless and fatigued on very light activity and usually confined to their homes. 19 patients.

For the assessment of disability we had the advantage of consultation with the physicians under whose care the patients were, Dr. Maurice Campbell and Dr. Charles Baker. Either Dr. Campbell or Dr. Baker first saw the patient and made an assessment of disability. Our independent assessment usually agreed with theirs, and never differed by more than one grade of disability; agreement was reached by discussion of the case. Each assessment of disability therefore is the agreed view of two or three physicians.

Cardiac catheterization was done a day or two after the clinical examination. To minimize emotional disturbance at catheterization this interval was used to gain the confidence of the patient. The day before catheterization he was taken to the room in which the catheterization was to be performed and given practice in breathing through the spirometer. The procedure to be adopted was explained to him as clearly as possible, taking care not to frighten him. During actual catheterization care was taken to keep physical discomfort to a minimum. The patient lay supine on the couch which was inclined at 15 degrees to the horizontal so that his head was slightly raised. When necessary, an orthopaedic patient was supported by additional pillows.

Pressures were measured by electronic capacitance manometers (Peterson *et al.*, 1949). All pressures were referred to the intersection of the mid-sagittal and mid-coronal sections at the level of the fourth costal cartilage.

The precautions taken in recording "pulmonary capillary pressure" have been described elsewhere (Venner and Holling, 1953). A double lumen catheter was used to measure pulmonary artery and capillary pressures simultaneously. When necessary mean pressures were determined by planimetry from the records.

Oxygen consumption was measured by a spirometer fitted with thin rubber flap valves to reduce resistance. In the earlier observations oxygen was breathed from the spirometer; later the apparatus was modified so that air or oxygen could be breathed (Donald and Christie, 1949). Breathing oxygen has the effect of raising the oxygen saturation of arterial and venous blood an average of 5 per cent, without altering the arterio-venous oxygen difference. In a few early cases observations on the mixed venous blood were obtained only whilst the patient was breathing oxygen; when necessary for comparative purposes these were corrected by the subtraction of 5 per cent. Brachial artery and pulmonary arterial samples were taken for the estimation of the A-V oxygen difference. The samples were kept in iced water and analysed as soon as possible, that is within 2 to 3 hours. The Haldane blood gas apparatus was used to determine the oxygen saturation of the samples (Douglas and Priestley, 1948). The accuracy of this method has been considered fully elsewhere (Holling *et al.*, 1955). The total oxygen combining power was determined indirectly by colorimetric estimation of the haemoglobin content (Reeve, 1944). The cardiac output was calculated using the Fick principle. To enable comparisons to be made between patients of different physique, the cardiac output is expressed as the cardiac index in litres per minute per square metre of body surface area.

At catheterization the response to exercise was observed as the patient pedalled against a spring resistance at the rate of one leg extension per second, timed by a metronome. The rate of working was 1/70 H.P. and was maintained at a steady rate for at least five minutes. The rate of oxygen consumption was at least doubled. Blood samples were taken and pressures measured during the last minute of exercise. Severely disabled patients were not exercised.

At valvotomy the pressure in the left atrium, right and left ventricles, pulmonary artery, and aorta was measured through a 21-gauge needle connected with a manometer by a metre of hardened plastic tubing of 1.4 mm. diameter bore.

Because patients continued to improve for some months after valvotomy and changes in the circulatory state take place over this time (Baker *et al.*, 1952), at least six months were allowed to elapse between operation and recatheterization. In the majority of patients this interval was about a year, the longest interval being four years.

The size of the mitral valve orifice was estimated by the surgeon at operation and was also calculated from a formula (Gorlin and Gorlin, 1951).

The ratio

$$\frac{\text{mean pulmonary artery pressure} - \text{mean pulmonary capillary pressure (mm. Hg)}}{\text{cardiac output (litres per minute)}}$$

which has been claimed to measure the pulmonary vascular resistance, was calculated for rest and exercise in each patient where this was possible. The results are expressed in arbitrary units of resistance. The vital capacity was measured in most patients before and after valvotomy.

In the statistical analysis of results the patients have been treated as groups according to the degree of their disability. For each circulatory measurement the mean value for each group of patients was calculated. All measurements showed a greater departure from normal in the more seriously affected patients, but the significance of the differences found between groups differed according to the measurement. In order to estimate the significance of these differences due allowance must be made for the variation of

findings in each group, and for the fact that, for various reasons, all measurements could not be made on all patients. "Student's" *t* test was applied to the results.*

RESULTS

The results obtained in the 81 patients with mitral stenosis are given in Tables I—V.

TABLE I
DISABILITY AND CIRCULATORY CHANGES IN MITRAL STENOSIS AT REST (R) AND ON EXERCISE (E)
(81 PATIENTS)

		Grade B disability (7 patients)		Grade C disability (18 patients)		Grade D disability (37 patients)		Grade E disability (19 patients)	
		No. of cases	Mean and S.D.	No. of cases	Mean and S.D.	No. of cases	Mean and S.D.	No. of cases	Mean and S.D.
Mitral valve area, sq. cm.	R.	6	1.97 ± 0.72	16	0.94 ± 0.28	26	0.85 ± 0.34	6	0.52 ± 0.10
	E.	5	1.87 ± 1.0	9	1.10 ± 0.19	10	0.76 ± 0.25	1	0.45 ± —
Cardiac index, litres/sq.m./min.	R.	6	2.77 ± 0.5	18	2.31 ± 0.5	37	2.28 ± 0.5	19	1.98 ± 0.7
	E.	5	3.76 ± 1.3	17	3.02 ± 0.8	29	2.83 ± 0.9	11	2.31 ± 0.7
Stroke index, ml.	R.	4	34.0 ± 10.3	15	29.6 ± 8.0	30	27.0 ± 7.2	9	22.0 ± 7.3
	E.	3	30.3 ± 7.3	14	29.6 ± 13.5	23	23.0 ± 8.4	7	17.5 ± 5.5
Oxygen saturation of mixed venous blood (%)	R.	7	69.0 ± 3.0	18	65.0 ± 7.0	37	58.0 ± 7.9	19	49.0 ± 9.0
	E.	5	55.0 ± 6.0	17	52.0 ± 9.0	31	42.0 ± 10.0	13	32.0 ± 10.0
Left atrial mean pressure (at opera- tion), mm. Hg	R.	2	12.5 —	12	23.0 ± 5.0	32	28.0 ± 8.0	9	26.0 ± 6.0
	E.	—	—	—	—	—	—	—	—
Pulmonary capillary mean pressure, mm. Hg	R.	7	11.0 ± 4.0	17	22.0 ± 6.1	26	23.0 ± 7.9	7	25.0 ± 12.3
	E.	5	20.0 ± 8.0	9	25.0 ± 9.7	9	35.0 ± 7.7	1	35.0 ± —
Pulmonary arterial mean pressure, mm. Hg	R.	7	18.0 ± 5.0	18	33.0 ± 10.0	34	51.0 ± 17.0	18	65.0 ± 19.0
	E.	5	26.0 ± 9.0	16	46.0 ± 18.0	27	74.0 ± 26.0	13	91.0 ± 19.0
Pulmonary arterial resistance, units	R.	7	1.5 ± 0.76	17	3.0 ± 2.44	27	7.6 ± 5.27	6	13.3 ± 9.02
	E.	3	1.2 ± 0.61	9	3.8 ± 2.6	10	11.4 ± 7.7	2	31.0 ± 7.9
Vital capacity, litres/sq. m.	R.	7	1.4 ± 0.3	14	1.4 ± 0.2	36	1.3 ± 0.2	15	1.2 ± 0.3

DISCUSSION

Reliability of Findings. Before making any comparison of disability and objective measurement it is important to consider the reliability of both. In the final assessment of a patient's condition it is possible to be more impressed by the seeming accuracy of a laboratory measurement than by comparatively indefinite clinical judgment.

It is recognized that various factors affect the disability caused by a cardiac lesion. For example, one patient will be brought to a stop by a degree of dyspnoea that another will ignore.

* The significance of any difference found is shown by the value "p" which expresses the probability that the observed difference was due to chance. The smaller the value of p, the less likely is the difference due to chance. A p value of 0.05 or less has been accepted as significant, and indicates that the probability of the difference being due to chance is less than 1 in 20; a p value of 0.005 or less has been accepted as highly significant, and indicates that the probability is less than 1 in 200. Obviously, any measurement that shows significant differences between adjacent pairs of groups B and C, C and D, D and E, will be of more value as an objective measure of the patient's condition than one that shows less significant differences.

TABLE II
COMPARISON OF FINDINGS IN
PATIENTS WITH NORMAL RHYTHM AND THOSE WITH ATRIAL FIBRILLATION

Disability group	At rest				During exercise			
	Normal rhythm		Atrial fibrillation		Normal rhythm		Atrial fibrillation	
	No. of patients	Mean	No. of patients	Mean	No. of patients	Mean	No. of patients	Mean
<i>Pulmonary artery mean pressure in mm. Hg</i>								
B	6	17	1	22	5	26	1	45
C	11	32	6	33	10	53	6	57
D	25	51	8	48	21	76	6	71
E	11	59	7	63	9	95	4	83
<i>Pulmonary capillary mean pressure in mm. Hg</i>								
B	6	11	1	16	4	17	—	—
C	11	22	6	21	6	27	3	28
D	20	24	7	24	9	38	1	27
E	4	28	3	31	1	42	1	35
<i>Cardiac Index in litres/sq.m./min.</i>								
B	5	2.9	1	2.2	4	4.0	1	3.0
C	12	2.6	6	1.9	11	3.3	6	2.5
D	26	2.3	11	2.2	22	3.0	7	2.5
E	12	1.9	7	1.8	8	2.5	3	1.7
<i>Mixed venous blood in % saturation</i>								
B	6	68.6	1	71	5	55	—	—
C	12	67.7	6	58.7	11	54	6	48
D	26	59.2	11	49.3	22	43	8	37
E	12	45.6	6	49.8	10	33	3	31

TABLE III
P VALUE OF DIFFERENCE OF MEAN FINDINGS, GROUP BY GROUP

	Grades B and C		Grades C and D		Grades D and E	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Mitral valve area	0.63	<u>0.04</u>	0.40	<u>0.005</u>	0.45	—
Cardiac index	0.08	0.12	0.80	0.55	0.07	0.08
„ „ (patients in sinus rhythm) ..	0.2	0.3	0.2	0.3	<u>0.05</u>	0.3
Stroke index	0.40	1.00	0.30	0.08	<u>0.02</u>	0.10
Oxygen saturation (percentage) of mixed venous blood	0.15	0.27	<u>0.001</u>	<u>0.005</u>	<u>0.001</u>	<u>0.005</u>
Left atrial mean pressure	<u>0.02</u>	—	<u>0.05</u>	—	0.70	—
Pulmonary capillary mean pressure ..	<u>0.02</u>	0.35	0.65	0.08	0.60	—
Pulmonary arterial mean pressure	<u>0.001</u>	<u>0.03</u>	<u>0.001</u>	<u>0.001</u>	<u>0.01</u>	<u>0.02</u>
Pulmonary arterial resistance	0.15	0.10	0.10	<u>0.01</u>	0.10	<u>0.01</u>

Significant differences underlined. Highly significant differences doubly underlined.

TABLE IV
FINDINGS BEFORE AND AFTER MITRAL VALVOTOMY
PATIENTS GROUPED ACCORDING TO DEGREE OF CLINICAL IMPROVEMENT AFTER OPERATION

Case No.	Improvement in clinical grading	Blood oxygen combining power (ml./100 ml.)	Arterial blood (O ₂ % satn.)	Mixed venous blood (O ₂ % satn.)		Vital capacity (litres/sq.m.)	Pulmonary artery mean pressure (mm. Hg)		Pulmonary capillary mean pressure (mm. Hg)		Cardiac output (litres/min.)		Stroke volume (ml./beat)	
				Rest	Exercise		Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
G 6 G 43 G 42 G 31 G 9 G 10 G 55 G 52 G 35 G 38 G 22 G 32 G 46 G 73 G 84 Mean change S.D.	B.	17.0	91	44	58	Normal rhythm.	100	116	—	—	2.7	3.8	—	37
	A.	18.0	96	47	58	1.2	80	116	—	—	2.4	4.0	—	73
	B	18.7	95	47	56	1.2	80	116	—	—	2.4	4.0	—	73
	E	19.0	96	48	56	1.2	80	116	—	—	2.4	4.0	—	73
	B	20.4	95	47	56	1.5	84	116	—	—	2.4	4.0	—	73
	E	20.5	95	48	56	1.5	84	116	—	—	2.4	4.0	—	73
	B	20.1	93	42	56	1.1	53	116	—	—	2.6	3.5	—	40
	E	20.8	96	42	56	1.1	53	116	—	—	2.6	3.5	—	40
	B	14.4	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	21.5	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	B	15.8	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	17.0	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	B	17.7	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	18.4	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
G 5 G 29 G 27 G 23 G 44 G 49 G 59 Mean change S.D.	B.	17.0	91	44	58	Normal rhythm.	100	116	—	—	2.7	3.8	—	37
	A.	18.0	96	47	58	1.2	80	116	—	—	2.4	4.0	—	73
	B	18.7	95	47	56	1.2	80	116	—	—	2.4	4.0	—	73
	E	19.0	96	48	56	1.2	80	116	—	—	2.4	4.0	—	73
	B	20.4	95	47	56	1.5	84	116	—	—	2.4	4.0	—	73
	E	20.5	95	48	56	1.5	84	116	—	—	2.4	4.0	—	73
	B	20.1	93	42	56	1.1	53	116	—	—	2.6	3.5	—	40
	E	20.8	96	42	56	1.1	53	116	—	—	2.6	3.5	—	40
	B	14.4	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	21.5	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	B	15.8	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	17.0	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	B	17.7	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	18.4	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
G 39 G 4 G 24 G 58 Mean change S.D.	B.	17.0	91	44	58	Normal rhythm.	100	116	—	—	2.7	3.8	—	37
	A.	18.0	96	47	58	1.2	80	116	—	—	2.4	4.0	—	73
	B	18.7	95	47	56	1.2	80	116	—	—	2.4	4.0	—	73
	E	19.0	96	48	56	1.2	80	116	—	—	2.4	4.0	—	73
	B	20.4	95	47	56	1.5	84	116	—	—	2.4	4.0	—	73
	E	20.5	95	48	56	1.5	84	116	—	—	2.4	4.0	—	73
	B	20.1	93	42	56	1.1	53	116	—	—	2.6	3.5	—	40
	E	20.8	96	42	56	1.1	53	116	—	—	2.6	3.5	—	40
	B	14.4	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	21.5	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	B	15.8	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	17.0	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	B	17.7	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40
	E	18.4	96	42	56	1.5	53	116	—	—	2.6	3.5	—	40

Columns headed B show observations made before mitral valvotomy, columns headed A contain observations made after valvotomy.

TABLE V
CALCULATED MITRAL VALVE AREA (SQ. CM.) BEFORE AND AFTER OPERATION

Case	Before operation		After operation	
	Rest	Exercise	Rest	Exercise
<i>Mitral stenosis.</i>	<i>Good result.</i>	<i>Normal rhythm</i>		
G 42	0.6	—	1.9	—
G 31	0.5	—	1.7	1.2
G 55	0.5	0.5	1.7	1.7
G 35	0.8	—	1.1	1.1
G 38	0.8	—	1.2	1.3
G 22	1.0	—	1.5	1.6
G 32	0.7	—	1.1	—
G 46	0.4	—	2.4	1.7
G 73	0.8	0.8	1.2	1.6
G 84	0.7	—	2.3	1.4
<i>Mitral stenosis.</i>	<i>Good result.</i>	<i>Atrial fibrillation</i>		
G 29	0.5	0.5	0.9	0.7
G 27	1.1	—	1.0	—
G 44	0.6	—	0.8	0.7
<i>Mitral stenosis.</i>	<i>Moderate result</i>			
G 39	0.5	—	0.8	0.8
G 58	0.7	1.1	1.0	—

The history is influenced by the patient's memory and intelligence, and by his desire to have, or to avoid, an operation ; after operation his symptoms may be affected by factors other than the physical improvement due to valvotomy. These considerations indicate the care with which a patient's statements must be judged. Further, although it is expedient to classify the patients into five groups, disability shows continuous graduation, so that some of the patients might have been put into an adjacent group. For these reasons it had been questioned whether a patient's disability can be assessed accurately from his symptoms ; but with the care we took over this, we believe that the grading was reasonably accurate. Moreover, since the object of treatment is to relieve disability rather than to alter laboratory findings, unless it can be shown that the two are related it is more practical to use disability as a measure of the patient's general condition than to use the result of a laboratory observation.

The reliability of laboratory findings is also difficult to assess. The technique of the actual measurement may be accurate, but the findings may be unreliable because we might have failed to achieve a basal or steady state in the patient during observations. Cardiac catheterization is likely to be a disturbing procedure for the patient and in spite of all precautions it may not be possible to observe him in a basal state. The degree of emotional disturbance may be difficult to assess, for we have observed some elevation of the pulse rate and oxygen consumption in an apparently tranquil patient. Patients in whom the degree of disturbance was such that the pulse rate was over 100 a minute have been excluded from this series. In early observations it was found that the supine position during catheterization sometimes caused distress, with a rise of the pressure in the pulmonary vessels and a reduction in arterial oxygen content : the results obtained from these patients have also been discarded. Furthermore, painful or emotional stimuli may cause a rise of pulmonary vascular pressures. Thus, while we acknowledge that the possibility exists that observations were made in some patients who were not basal, we made every effort to recognize and minimize abnormal conditions. If we had any grounds for doubt in this respect we have not included the results in this series.

The technical error of a single measurement may or may not be great, but when a number of measurements are combined, as in calculation of the cardiac output or of the mitral valve area, the error of the final figure is a function of all the measurements used in its calculation. For this reason,

direct measurements are more to be relied on, for example the oxygen saturation of the mixed venous blood as an indication of the adequacy of the blood flow to the needs of the body, rather than the calculated figure for the cardiac output. Originally we mistrusted the figures obtained when the "area of the mitral valve" is calculated, because the calculation is based on five measurements and three assumed figures. We compared the figures obtained in the resting patients with that in the same patients when exercising, and if the calculated area is related to the true area the two results should correspond. Our mistrust of the values obtained lessened when it was found that the two series of results corresponded well, though exceptions occurred; i.e. G 58, 46, and 84 (Table V). These findings are in agreement with those of Gorlin and Gorlin (1951) and also of Rodrigo (1953) who, on theoretical grounds, assessed the likely error in the calculation of the mitral valve area to be about 20 per cent.

As will be seen later, we were able to show a significant, sometimes highly significant, relationship between our assessment of the degree of disability of a group of patients and certain of the laboratory findings. We conclude therefore that clinical assessment of disability and certain laboratory findings support and justify each other as measurements of the severity of the disease.

RELATIONSHIP OF DISABILITY TO THE MEASUREMENTS MADE

Mitral Valve Area. If the symptoms in patients with mitral stenosis are either the direct or indirect result of obstruction caused by the stenosed valve, the degree of stenosis should be related to the degree of disability. We find that once symptoms become noticeable (Grade B disability) the calculated mitral valve area is already reduced to less than half the area of the healthy valve. A large difference in valve area occurs between patients with only slight disability (Grade B), and those with more, though still only mild symptoms (Grade C), the mean valve area of the former being twice that of the latter (Table I). With increase in disability the mean value of the mitral valve area calculated for each group is successively smaller. Statistical analysis of the differences found shows (Table III) that those between disability grades B and C, and C and D are significant if the figures obtained during exercise are used, but since so few patients of Grade E disability were allowed to exercise it was not possible to obtain sufficient data to discriminate between Grades D and E.

Though the mean calculated mitral valve area does show a change between the grades, it is to be noted that the changes are slight, and it seems to us unlikely that the surgeon at operation could appreciate such fine differences. Indeed the valve areas in these patients were reported by the surgeon as relatively constant from patient to patient (Brock, 1952).

In 15 of the patients it was possible to compare the calculated mitral valve area before and after mitral valvotomy (Table V). In general the results are consistent with the clinical state of the patient. Ten patients in normal rhythm who derived great benefit from operation showed an increase in mitral valve area to more than a square centimetre. In three patients in atrial fibrillation who also derived great benefit from operation, the increase in calculated mitral valve area was less. It was also less in two patients who derived only moderate benefit from operation.

The calculated valve area of groups of patients with different degrees of disability can therefore discriminate between them. This suggests that the calculated mitral valve area is related to the actual mitral valve area, and that disability may be related to the degree of stenosis.

Anomalous results of this calculation, however, are sometimes obtained, and since small differences in mitral valve area appear to have a large effect on disability, greater precision in its measurement should be sought. More reliable figures for its calculation might be obtained if the pressure gradient across the valve during the filling time of the left ventricle could be measured directly. This could be done at operation or by puncture of the left atrium (Epps and Adler, 1953) and passing a fine catheter from left atrium through the mitral valve so that the pressure on each side of it could be measured. A simultaneous measurement of the mitral valve flow would have to be made to calculate the mitral valve area. These measurements are possible and would be of considerable theoretical interest as providing a measure of the degree of narrowing of the mitral

valve, and would be of practical use to the surgeon as a measure of the technical success of his operation.

Cardiac Output. The calculated mitral valve area provides an index of the anatomical severity of mitral stenosis. A functional measure of the stenosis is given by the reduced blood flow through it. This is the cardiac output and, on theoretical grounds, the measurement is to be preferred to the calculation of the mitral valve area because it involves fewer assumptions.

Uncomplicated mitral stenosis of sufficient degree to give rise to symptoms always has the effect of reducing the cardiac output. Even in the group with least symptoms the mean cardiac output is less than normal (3.2 litres per sq. metre of body surface per minute). In groups of patients with greater disability, a slight further reduction of cardiac output is found with increasing disability (Table I). Whatever the disability, the increase of cardiac output on exercise is small. It is progressively smaller from Grade B to Grade E.

Though these changes occur, relationship between the degree of disability and the degree of reduction of cardiac output is not a close one. Neither cardiac output nor the lessened ability to increase the cardiac output on exercise affords a sensitive means of distinguishing between disability groups (Table III). The changes in cardiac output after valvotomy also indicate that the level of cardiac output is not closely related to the degree of disability. Thus a group of 17 patients in sinus rhythm showed an insignificant increase in cardiac output after operation, whereas a group of six with atrial fibrillation showed an insignificant decrease. The ability to increase cardiac output on exercise showed no alteration in the group of patients with normal rhythm; and a greater increase in the three patients with atrial fibrillation than before operation. Yet all these patients had derived similar and great improvement as a result of the operation.

The poor relation of disability to our measurements of restriction of cardiac output is surprising. It may be because expression of the cardiac output in terms of flow per minute is an inadequate measure of restriction of the circulation. To express the results in terms of stroke volume might be more satisfactory, especially when dealing with the effects of exercise, because shortening of the ventricular filling time during the tachycardia of exercise (Wiggers, 1923) exaggerates the obstructive effect of mitral stenosis. The results in Table I show that the stroke volume usually falls during the tachycardia of exercise, even in the most mildly affected groups. Often the reduction in stroke volume is sufficiently great to account for a reduction of cardiac output measured over a minute, particularly in the more severely affected patients. This confirms the opinion that tachycardia is an inefficient method of increasing cardiac output in the presence of mitral stenosis. A decided increase in stroke volume is often, but not invariably, seen following a successful valvotomy. The measurements of stroke volume as a whole, however, are too variable (Table III) to serve as a method of discrimination between groups of patients with different degrees of disability.

Oxygen Saturation of the Mixed Venous Blood. This indicates the effectiveness of the blood stream in supplying the needs of the body for oxygen. We have found it to discriminate between the groups of patients with different degrees of disability more decisively than the cardiac output (Table III). In the group with least symptoms the level is slightly less than in normal subjects, and decreases with increasing disability of the group (Fig. 1). After operation good clinical results are associated with a large increase in the oxygen saturation of the mixed venous blood though the patients with moderate improvement show a similar change (Table IV).

The effect of exercise on the oxygen saturation of the mixed venous blood of a normal subject has been reported to be only slightly altered by mild exercise (Hickman and Cargill, 1948), and Donald *et al.* (1955) found it to be reduced from a level of 79 to 69 per cent in four normal subjects performing exercise comparable in severity to that performed by our patients. When our patients with mitral stenosis exercised, the greater the degree of disability, the lower was the oxygen saturation of the mixed venous blood (Fig. 1 and Table I). The discrimination between the two groups of patients with mild symptoms was not significant (Grades B and C), but highly significant differences were found between disability grades C and D, and D and E (Table III). After operation the increase in oxygen saturation of the mixed venous blood on exercise was related to the degree of

improvement (Table IV), it even rose in some patients in the absence of an increase in cardiac output.

Oxygen saturation of the mixed venous blood discriminates better between the different degrees of disability than the cardiac output because cardiac output is but one of the factors affecting the carriage of oxygen to the tissues. Williams (1953) has shown that the oxygenation of the blood in the lungs may be impaired in mitral stenosis, and a reversal of this process is indicated by the increase in arterial oxygen saturation seen in many of our patients following operation (Table IV). We have also observed a rise in blood hæmoglobin content after a successful valvotomy (Table IV) showing that a diminished oxygen-carrying capacity of the blood was adding to the circulatory difficulties of these patients before operation.

The lowered oxygen content of the mixed venous blood seen in disabled patients is evidence of a threefold difficulty of oxygen supply, (1) reduced cardiac output, (2) reduced arterial oxygen content, (3) reduced oxygen-carrying capacity of the blood. The difficulty in oxygen supply is compensated for by an increased uptake of oxygen from each volume of blood passing through the tissues. Measurements of the oxygen saturation of the mixed venous blood can therefore be regarded as a comprehensive measure of the factors impeding the supply of oxygen to the tissues. As an objective measure of disability it is superior to, and has an additional advantage over, the cardiac output because it is a direct measurement and not derived from a calculation involving two other estimations—arterial oxygen content and the rate of oxygen consumption.

Left Atrial Pressure and Pulmonary Capillary Pressure. Another method that might gauge the severity of mitral stenosis is measurement of the rise of pressure behind it in the left atrium. This pressure has been measured directly at operation and also studied indirectly, but under more physiological conditions, as the pulmonary capillary pressure at catheterization. Epps and Adler (1953) showed that the pulmonary capillary pressure corresponded to the left atrial pressure, and our results agree with this in that the mean left atrial pressure of each group of patients is similar to the mean pulmonary capillary pressure (Table I).

In patients with Grade B disability the pulmonary capillary pressure is slightly higher than in normal subjects. The greatest and only significant (Table III) difference in pressure occurs between the mean pressure of this group with minimal symptoms and patients with definite, though still slight, symptoms (Grade C) (Fig. 2 and Table I). This corresponds to our finding of a difference in the calculated mitral valve area between the two mildly affected groups of patients and shows that, as the mitral valve narrows, a marked rise of pressure takes place behind it. In the absence of this increase of pressure gradient across the valve the difference in cardiac output between the groups of patients with Grade B and Grade C disability would be greater than that observed. The level of cardiac output therefore may be maintained by the increase of the pressure gradient. In the other groups of patients the increase in disability appears to be disproportionate to the small additional increases of pulmonary capillary and left atrial pressures. The mean pulmonary capillary pressure of the group of patients who are breathless on only moderate exertion (Grade C) being 22 to 23 mm. Hg, that of patients who are so disabled as to be confined to their homes being 25 to 26 mm. Hg. It is unlikely that our methods of measurement can discriminate between such fine differences, nor are the differences found significant (Table III).

Following valvotomy a fall in pulmonary capillary pressure from the range of 20 to 30 mm. Hg to the range of 10 to 20 mm. Hg is often observed in patients who are much improved, but over the whole series the fall after operation did not correspond well with the relief from disability. In a few patients in whom a low pulmonary capillary pressure was associated with severe symptoms before operation, considerable relief from symptoms was associated with only a small fall of pressure. The fall in two patients who derived only moderate benefit from operation was as much as in those who derived great benefit.

All patients showed a rise of pulmonary capillary pressure on exercise, and particularly high levels were reached in the patients who were more disabled (Table I and Fig. 2). However, the level of the pulmonary capillary pressure on exercise failed to provide a satisfactory means of discriminating between the groups of patients with different disability (Table III).

Pulmonary Artery Pressure. Previous work has established that slight increase of pulmonary capillary pressure in patients with mitral stenosis is associated with a comparable rise in pulmonary artery pressure, but that when the pulmonary capillary pressure is increased to about 25 mm. Hg a disproportionate rise of pulmonary artery pressure occurs (Gorlin *et al.*, 1951). Our observations show that the rise of pulmonary artery pressure is associated with an increase in disability. In the group of patients with minimal symptoms the pulmonary pressure at rest was slightly above normal (Table I and Fig. 2) and with greater disability a further rise of pressure occurs. Through all degrees of disability the mean pulmonary artery pressure of the group is found to bear a significant relationship to the degree of disability (Table III). This is apparent both in the observations made on the patients at rest and when they are exercising.

After valvotomy clinical improvement is associated with reduction of the pulmonary artery pressure both at rest and on exercise (Table IV). A large reduction in pulmonary artery pressure is always associated with much clinical improvement. Obviously in patients, in whom the pulmonary artery pressure is not greatly increased before operation, the fall in pressure is limited, though clinical improvement may be considerable. The degree of reduction of pulmonary artery pressure is less in patients who derive only moderate benefit from operation. Our finding that the elevation of the pulmonary artery pressure at rest and during exercise is more closely related to the patient's disability than the reduction in cardiac output does not agree with the opinion of Wade *et al.* (1954). It is questionable whether their material is sufficient on which to base an opinion, for findings in individual patients may differ from those of a more representative group: in seven only of the patients they investigated before and after mitral valvotomy was the lesion of mitral stenosis uncomplicated by other conditions, and according to our standards, marked clinical improvement occurred in only three of them after valvotomy. These three patients showed a fall in pulmonary artery pressure and a rise in cardiac output consistent with the observations in certain of our patients, e.g. G 55, G 6, and G 42 in Table IV, but the changes observed in these cases taken alone, show a different trend from the findings in the larger group of which they are a part.

Pulmonary Arteriolar Resistance and Disability. Since the rise in pulmonary artery pressure that occurs with increasing disability is not associated with an equal rise in pulmonary capillary pressure, it must be caused by an increase in the resistance of the pulmonary arterioles to the flow of blood through them. An indication of this resistance is given by the ratio,

$$\frac{\text{mean pulmonary artery pressure} - \text{mean pulmonary capillary pressure}}{\text{cardiac output}}$$

This was found to increase with increased disability (Table I). During exercise in the less severely affected patients it was unaltered, but in the more severely affected it rose. We find, however, that the calculated ratio gives a less close correspondence with the degree of disability than the simple pulmonary artery pressure (Table III). This is because the ratio includes the figures for the cardiac output and the pulmonary capillary pressure which are not closely related to the degree of disability. Moreover, for reasons we have stated in the analysis of results, a simple measurement is likely to be more reliable than a combination of readings.

Vital Capacity. In the observations made before operation there was little relation between the vital capacity and disability, and this measurement showed no significant change after mitral valvotomy, the mean increase in patients with a good clinical result being 0.07 litres per sq. metre of body surface area. It was our impression that the vital capacity was more related to the physique and previous mode of life of the patient than his disability.

Effect of Atrial Fibrillation. In this investigation, patients in normal rhythm have been considered together with patients with atrial fibrillation whose ventricular rate was controlled by digitalis. Since the relation between disability and circulatory measurements in patients with mitral stenosis might be altered by the onset of atrial fibrillation, it is necessary to enquire whether separation of the findings in patients with atrial fibrillation would have resulted in the relationship between

disability and circulatory measurements being more clearly defined. Whether the presence of atrial fibrillation causes an increase in disability is not relevant to this discussion.

In Table II, dealing with the observations made before operation, the patients with sinus rhythm have been separated from those with atrial fibrillation. From the results before and after operation shown in Table IV further comparisons between the two categories of patients may be made.

It is clear that atrial fibrillation does not affect the relation between disability and pulmonary vascular pressures. In the observations made before operation (Table II) no difference of pulmonary arterial and capillary pressures was found between the two categories of patients. The fall in pulmonary artery and pulmonary capillary pressure after a successful operation was similar, and the degree of improvement of symptoms was the same (Table IV).

The relation between disability and cardiac output is, however, affected when there is atrial fibrillation. Patients with fibrillation have a low and fixed cardiac output whether they are mildly or severely disabled; those in normal rhythm show a reduction of cardiac output with increase of disability. Nevertheless, if patients with atrial fibrillation are separated, the measurements of cardiac output in those in normal rhythm still fail to show significant differences between groups of patients with different degrees of disability (Table III). After a successful operation there is an insignificant increase in the mean cardiac output of the patients with normal rhythm, and an insignificant decrease in those patients with atrial fibrillation.

No difference is found between the oxygen saturation of the mixed venous blood at rest in patients with normal rhythm and those with atrial fibrillation. On exercise the oxygen saturation of the mixed venous blood falls lower in the patients with fibrillation with Grades C and D disability, but no difference is found in the most severely affected patients. None of the differences were statistically significant.

These findings indicate that the relationship between disability and circulatory measurements is essentially the same in patients with normal rhythm and patients with controlled atrial fibrillation; only in the case of the cardiac output can minor differences be shown. It is therefore unlikely that consideration of the two categories of patients together has obscured the relationship between disability and circulatory measurements.

CIRCULATORY CHANGES AND THE DEVELOPMENT OF DISABILITY IN MITRAL STENOSIS

If we assume that the calculated mitral valve area does in fact provide an approximate index to the size of the mitral opening then we can trace the sequence of circulatory changes in the average patient with mitral stenosis, as his disability increases with the progress of his disease (Fig. 1 and 2).

Stage I. Reduction of calculated size of "mitral orifice" from 4 to 6 sq. cm. to 2 sq. cm., producing no disability (Grade A). The orifice of the mitral valve may be reduced to half its normal size without the appearance of symptoms in a person who does not subject himself to unusual physical stress. Reduction of the cardiac output occurs, together with a limitation of the capacity to increase cardiac output on exercise. No rise of the pulmonary vascular pressures occurs.

Stage II. "Mitral orifice" 2 to 1.5 sq. cm. Grade B disability. Reduction in the size of the mitral orifice to this degree is associated with no symptoms in a sedentary life, but undue breathlessness may occur on much exertion. The cardiac index is reduced from 3.8 to 2.8 litres per sq. metre per minute, and a slight increase in pressure in the pulmonary circulation occurs, and this increases on exercise.

Stage III. "Mitral orifice" 1 sq. cm. Grade C disability. Further reduction in the size of the mitral orifice is associated with an inability to undertake moderate exertion. Little further decrease in cardiac output occurs, this being maintained by an increase in the left atrial pressure, with an equal increase in the pulmonary capillary pressure and pulmonary arterial pressure. An appreciable rise of pulmonary vascular pressures occurs on exercise.

FIG. 1.—The normal value of “mitral valve area,” cardiac index, and oxygen saturation of mixed venous blood, at rest and on exercise, compared with the mean of the same measurement at the four grades of disability.

FIG. 2.—The normal value of the pulmonary capillary and pulmonary arterial pressures at rest and on exercise compared with the mean of the same measurements at the four grades of disability.

Stage IV. “Mitral orifice” 1 to 0.5 sq. cm. Grade D disability. With more contraction of the mitral orifice a serious limitation of activity develops. The further reduction in cardiac output is slight, though impairment of the oxygen supply to the body is shown by the large fall in oxygen saturation of the mixed venous blood, especially during exercise. At this stage there is a slight further rise of the pulmonary capillary pressure and a greater rise in the pulmonary artery pressure both at rest and on exercise, indicating the development of pulmonary arteriolar resistance.

Stage V. “Mitral orifice” 0.5 sq. cm. or less. Grade E disability. With such severe reduction of the orifice of the mitral valve the patient becomes confined to a life of chronic invalidism. The further reduction in cardiac output and rise of pulmonary capillary pressure is slight but the pulmonary artery pressure both at rest and on exercise is much increased. Further impairment of the oxygenation of the tissues is shown by a fall in the oxygen saturation of the mixed venous blood.

Effect of Atrial Fibrillation. This may supervene at any time during the progress of the disease and clinical experience shows that even if the heart rate is controlled, atrial fibrillation is likely to be associated with an increase in disability. Our observations show that the cardiac output is reduced when the atria fibrillate. There is a limitation of the ability to increase cardiac output on exercise, and this is associated with a reduction in stroke volume. If disability increases there is an associated rise in the pulmonary vascular pressures.

Effect of Myocarditis. The selection of patients for this study excluded those who had lesions of cardiac valves other than the mitral. As in the case of a similar group of patients described by Walsh *et al.* (1940) the attacks of rheumatic fever in most of our 81 patients had been mild and without frequent recurrences. We therefore believe that the incidence of myocarditis in them was not severe. Lesions resembling Aschoff bodies were seen in the endocardium in some of them, but the significance of these lesions is uncertain and reasons have been given for believing that they do not indicate active rheumatism (Enticknap, 1953). Atrial fibrillation, which occurred more commonly in the more seriously disabled patients, may be regarded as evidence of failure of the muscle of the atria, but it seems less likely to be due to myocarditis than to failure to contract against an increased atrial pressure. If atrial fibrillation should be due to active myocarditis it is difficult to explain why after operation patients with atrial fibrillation do as well, and perhaps better than, patients in sinus rhythm (Baker, Brock, and Campbell, 1955). The more seriously affected patients had pulmonary hypertension, and showed evidence of a hypertrophied and strongly acting right ventricle; it seems unlikely, therefore, that the right ventricular muscle was weakened by rheumatic myocarditis. The cause of the disability remaining after a successful valvotomy is usually attributed to an incomplete opening of the valve but it may be due to myocardial disease. Even if this is so it must be admitted that myocarditis plays a minor role in the causation of symptoms in patients with uncomplicated mitral stenosis.

BREATHLESSNESS IN MITRAL STENOSIS

The observations recorded here are relevant to the factors involved in the causation of exertional dyspnoea in patients who are not in congestive cardiac failure. Pulmonary congestion is regarded as an important factor in the breathlessness of heart failure and heart disease generally. This term implies engorgement of the alveolar capillaries and increased transudation from them when the filtration pressure exceeds the colloid osmotic pressure of the plasma proteins. The degree of pulmonary congestion is therefore to be related to the pulmonary capillary pressure and to the amount of fluid in the lungs, and if it plays an important role in the dyspnoea we should expect to observe a parallelism between the degree of breathlessness, the rise of pressure in the lung capillaries, and the evidence of increased fluid in the lungs.

With minor degrees of disability (Grades B and C) our findings correspond with the theory that pulmonary congestion plays a role in the causation of dyspnoea. But in the more severe grades of disability (Table I), pulmonary capillary pressure, both at rest and on exercise, shows little difference as the disability increases.

Though the pulmonary capillary pressure at rest is seldom higher than 30 mm. Hg it is recognized that the pulmonary arterial pressure may continue to increase in the pulmonary artery-pulmonary capillary pressure gradient (Gorlin, 1951). The increased pulmonary arteriolar resistance that this implies has been thought to protect the pulmonary capillaries from an undue increase in pressure. We find, as do other workers (Davies *et al.*, 1954) that, if such protection exists, it fails under the strain of very mild exercise (Tables I and IV), when the pulmonary capillary pressure rises sharply. After exercise we did not find clinical evidence of increased fluid in the lungs of more severely affected patients, though the pressure in the lung capillaries might have exceeded that of the colloid osmotic pressure of the plasma proteins. The patients quickly recovered and no basal râles were heard. These observations support Drinker's (1954) opinion that "heightened capillary pressure and stretching of the (alveolar) vessels does cause increase in the tissue fluid of the lungs, but this fluid enters the lymphatics rapidly and until they are filled with lymph and the restricted

entrance into the blood offered by the right lymphatic duct causes lymph stasis, obvious pulmonary oedema of conventional character is not seen. Something more than increased capillary pressure is necessary to cause oedema." We believe therefore that pulmonary congestion, as measured by the level of pulmonary capillary pressure, or clinical evidence of increased fluid in the lungs, does not play a primary role in the dyspnoea of patients with mitral stenosis, severely affected but not in cardiac failure.

The level of pulmonary capillary pressure at rest and on exercise is not closely related to the degree of dyspnoea on exertion, but the closer relation between pulmonary arterial pressure and dyspnoea requires further consideration. A possible mechanism by which pulmonary hypertension may contribute to the dyspnoea of mitral stenosis is suggested by the observations of Marshall *et al.* (1954). In respiratory studies on patients with mitral stenosis, not in cardiac failure, they found that the lungs are more rigid than normal, especially on exercise, so that an increased amount of work was necessary to ventilate them. Pulmonary vascular pressures were not measured, but they suggest the changes are due to pulmonary congestion; our findings suggest that the changes are due to pulmonary arterial hypertension. That pulmonary hypertension is a factor in the causation of lung rigidity is also supported by observations we have made on patients with "primary pulmonary hypertension" in whom dyspnoea on exertion is associated with an increased pulmonary artery pressure, but with no marked increase in pulmonary capillary pressure or disease of the lung parenchyma.

The level of oxygen saturation of the mixed venous blood is a measure of the general level of oxygenation of the tissues, so that the value observed at the end of exercise is a measure of the oxygen debt incurred. In our studies on the level of oxygen saturation of mixed venous blood and the degree of disability we have in effect observed that the greater the ease with which exertional dyspnoea is evoked, the greater is the oxygen debt incurred in the performance of a standard exercise. This corresponds with the observations of Campbell and Sale (1927) and Stock and Kennedy (1953), who found that when a patient with mitral stenosis performs a standard exercise, more ventilation of the lungs takes place than in a normal subject, and the degree of disability can be related to the margin between ventilatory cost of exercise and the maximum ventilatory capacity of the patient. They suggest that the excess ventilation may be attributed to a large oxygen debt which arises because the blood flow to the tissues is inadequate to supply their need for oxygen.

Because the oxygen saturation of the mixed venous blood and the rise of the pulmonary artery pressure are both closely related to the degree of disability, we enquired whether the two changes were related to each other. This was found to be so, both at rest and on exercise (Fig. 3). This relationship may occur because the reduced oxygen tension of the mixed venous blood acts as a stimulus to pulmonary vasoconstriction, either by direct action on the vessels or through a reflex mechanism. Supporting the hypothesis of a causal relationship is the association of a reduction in venous oxygen tension and a rise in pulmonary artery pressure when a low concentration of oxygen is breathed by patients with mitral stenosis (McGregor *et al.*, 1953), and changes in the opposite direction when a high oxygen concentration is breathed. It is not proved, however, that the lowered oxygen saturation of the mixed venous blood in those observations is the stimulus that is responsible for the increase in pulmonary arterial pressure. The investigations of Duke and Killick (1952) indicate that the stimulus to elevation of the pulmonary artery pressure in animals breathing low oxygen concentration is most likely the oxygen tension in the alveoli. Therefore the occurrence of low venous oxygen saturation and high pulmonary artery pressure in a patient with severe mitral stenosis may be independent indications of the severity of his condition and show that a number of factors must be taken into account before we can fully understand the mechanism of dyspnoea in this condition.

DIAGNOSTIC USE OF CARDIAC CATHETERIZATION

Clinical Estimation of Pulmonary Arterial Pressure. We have shown that if patients are taken together in groups, the pulmonary artery pressure is closely related to the degree of disability. It is

FIG. 3.—The relation of mean pulmonary artery pressure to oxygen saturation of the mixed venous blood in 81 cases of mitral stenosis.

therefore of interest to find whether the degree of pulmonary hypertension can be estimated from the physical signs and electrocardiographic and radiological features without the aid of cardiac catheterization. Our experience on this point is in substantial agreement with that of Whitaker (1954), who found that more frequently than by chance, a reasonable clinical estimate of the pulmonary artery pressure can be made. However, we find that our clinical assessment of

pulmonary artery pressure often shows a marked difference from the pulmonary artery pressure measured at cardiac catheterization, so that it cannot be relied on.

Investigation of Complicated Cases of Mitral Stenosis. Though cardiac catheterization was originally carried out in all patients being prepared for mitral valvotomy, it is now clear that most of the results did little more than support clinical judgment (Baker *et al.*, 1952). The investigation remains of considerable value in the diagnosis in such conditions as atrial septal defects, which may complicate mitral stenosis, but in general it is carried out only when the exact diagnosis is uncertain, or the significance of the signs of the complications not apparent.

The results obtained in patients with no cause for disability other than mitral stenosis serve as useful criteria for comparison with the findings in patients who have evidence of other causes of disability as well. Such patients have made up the majority of those referred to hospital for mitral valvotomy, the most frequently encountered complications being mitral incompetence, cardiac neurosis, aortic lesions, or chronic respiratory disease. In such patients it is necessary to decide whether the stenosis of the mitral valve is itself the cause of sufficient disability to justify the operation of mitral valvotomy. To help in this decision the results of the catheterization may be compared to the measurements (Tables I and III), that we have found to give an objective assessment of the degree of disability due to mitral stenosis. Unfortunately the findings at catheterization in patients in whom considerable mitral incompetence has been demonstrated at operation have not served to distinguish them with any reliability from patients with uncomplicated mitral stenosis. Moreover, experience with methods recently suggested as valuable in the differentiation of patients with mitral incompetence has not altered our opinion (Venner and Holling, 1953) that there is as yet no satisfactory method by which this can be done. In patients in whom cardiac neurosis was contributing considerably to their symptoms, we have found that the measurements made at catheterization indicated a degree of disability much less than that from which the patient was complaining.

Differences have also been found in patients in whom we have considered that aortic valve disease, of which there were definite signs, contributed considerably to their disability. In such patients a technically successful valvotomy has been followed by a disappointing clinical result, and the remaining disability has been ascribed to the disease of the aortic valves. Before operation these patients were found to have a lower pulmonary artery pressure and a higher degree of oxygen saturation of the mixed venous blood than the group of patients with the same degree of disability due to uncomplicated mitral stenosis.

In patients in whom it was considered that chronic respiratory disease contributed considerably to their symptoms and in whom the result of mitral valvotomy proved disappointing, we have also observed that the catheterization before operation showed a pattern of pulmonary pressures different from that shown by patients with uncomplicated mitral stenosis. In them the rise of pulmonary artery pressure was as high as in corresponding patients with uncomplicated mitral stenosis, but the pulmonary capillary pressure was lower. This corresponds with the findings of Yu *et al.* (1953) that chronic respiratory disease is associated with a high pulmonary artery pressure and a low pulmonary capillary pressure.

These comparisons are likely to be of assistance in the assessment of complicated cases of mitral stenosis before operation. Thus an opinion that either cardiac neurosis or aortic disease is contributing considerably to the disability of a patient with mitral stenosis is supported if the oxygen saturation of the mixed venous blood and the pulmonary artery and pulmonary capillary pressure are found to be less abnormal than corresponds to the degree of disability. An unexpectedly low pulmonary capillary pressure in a patient with mitral stenosis and chronic respiratory disease suggests that the respiratory disease is contributing considerably to the disability. In these patients a guarded prognosis of the results of operation is to be given.

Studies after Valvotomy: Evidence of Persistence of Changes in the Pulmonary Vessels. The observations made on patients after a successful mitral valvotomy have been examined for evidence of difference in the pulmonary circulation from unoperated patients suffering from the same mild

degree of disability. The problem was whether an alleviation of disability from Grade D or E before operation to Grade B after operation was accompanied by a restoration of the pulmonary circulation to that of unoperated patients with Grade B disability. To investigate this the findings in the 24 patients shown in Table IV who were improved from Grade D or E disability by operation have been compared with findings of unoperated patients of Grade B and C disability. In Table VI the relevant results have been abstracted from Tables I and IV. The patients who were of Grade B disability after operation were in some respects more abnormal than unoperated patients of Grade B disability, but always less abnormal than those of unoperated patients of Grade C disability.

TABLE VI
PULMONARY VASCULAR PRESSURES IN OPERATED AND UNOPERATED PATIENTS

Measurement	Mean pressure of group		
	7 Unoperated patients, Grade B disability	24 Operated patients, Grade B disability	18 Unoperated patients, Grade C disability
Pulmonary artery pressure, mm. Hg			
At rest	18.0	26.0	33.0
Exercising	26.0	44.4	46.0
Pulmonary capillary pressure, mm. Hg			
At rest	12.4	13.0	22.0
Exercising	20.0	23.3	25.0

The pulmonary artery pressure at rest in the patients after operation is higher than in patients of the same disability group who have not been operated on, the difference being highly significant, but the pulmonary artery pressure is significantly lower than that of unoperated patients of Grade C disability. On exercise the pulmonary artery pressure of operated patients corresponds to that of unoperated patients of Grade C disability. An obvious explanation of these findings is that some of the patients after operation had more disability than had been thought, the judgment of the patient and perhaps of his doctor having been biased by enthusiasm for the results of the operation. The obvious explanation, however, does not explain the pulmonary capillary pressures. These in the operated patients are the same as in unoperated patients of the same degree of disability, and the difference from that of patients of Grade C disability is highly significant. On exercise the pulmonary capillary pressure rises slightly more in the operated patients than in unoperated patients of Grade B disability. This shows that an increase in pulmonary artery-pulmonary capillary pressure gradient persists after operation and indicates that all the effects of severe mitral stenosis on the pulmonary circulation were not reversed at the time of the post-operative catheterization. This abnormality might be ascribed to the persistence of structural changes in the pulmonary vessels (Parker and Weiss, 1936) after operation.

SUMMARY AND CONCLUSIONS

From a large number of patients being considered for mitral valvotomy 81 were selected as examples of mitral stenosis with no evidence of mitral incompetence, chronic respiratory disease, cardiac neurosis, or disease of other heart valves. Twenty-five of the patients had atrial fibrillation. The disability from which each patient suffered was judged by enquiry into capacity for effort in everyday life. According to the degree of their disability the patients were divided into four groups.

Cardiac catheterization was used to make circulatory measurements on them at rest and during

a standard exercise. In 27 patients the circulatory measurements were repeated six months to four years after mitral valvotomy had been performed. The degree of disability of the patient during this interval was assessed.

The circulatory measurements of each group of patients were compared in order to determine which measurements most clearly discriminated between groups of patients of different degrees of disability, with the following results. The pulmonary artery pressure measurement affords a good means of discriminating between all groups of patients. The oxygen saturation of the mixed venous blood discriminates clearly between the three more severe grades of disability. Though cardiac output shows some reduction with increasing disability the relationship is not close enough to afford a satisfactory means of discrimination. "Pulmonary arterial resistance," pulmonary capillary pressure, left atrial pressure (at operation), and the calculated "mitral valve area" discriminate between some groups of disability.

The relationship between disability and circulatory measurements in patients in sinus rhythm and with controlled atrial fibrillation was investigated. With the same degree of disability the cardiac output at rest was lower when there was atrial fibrillation, and the increase on exercise was less; the differences, however, were not significant. With the same degree of disability, there was no significant difference between the two categories of patients in the pulmonary vascular pressures or in the oxygen saturation of the mixed venous blood.

The results obtained indicate the circulatory changes that are associated with increasing disability in the average case of mitral stenosis. With the first appearance of symptoms the mitral orifice is calculated to be reduced to half its normal area and the cardiac output reduced by a quarter: there is little rise of the pulmonary vascular pressure. With further increase in disability the greatest changes occur in the pulmonary arterial pressure and the oxygen saturation of the mixed venous blood, the least in the cardiac output.

A rise of the pulmonary arterial pressure may be a more important cause of severe dyspnoea than a rise of pulmonary capillary pressure, because the height of the latter is similar in the three groups of more disabled patients, while the former shows a significant difference from group to group. The increased tendency to dyspnoea could be explained by the lungs being made more rigid by the increase in pressure within their arterial network. The association between disability and oxygen saturation of the mixed venous blood has been found to be closer than that between disability and cardiac output. The reason for this is that the reduction of cardiac output is but one of the factors affecting the carriage of oxygen to the tissues, other factors being a reduced arterial oxygen blood saturation and a reduction in oxygen carrying capacity of the blood in severe mitral stenosis. The measurement of the oxygen saturation of the mixed venous blood provides a comprehensive measure of the effect of these factors.

The degree of depression of the oxygen saturation of the mixed venous blood and of elevation of the pulmonary arterial pressure are related to each other. No cause for this relationship is suggested except that the two changes are independent indications of the severity of the patient's condition.

When the findings at cardiac catheterization in patients with mitral stenosis complicated by other conditions are compared with the findings in the 81 patients here described, differences can be shown that may be of assistance in deciding to what degree the disability of a complicated case is to be attributed to the existing mitral stenosis. No satisfactory method of distinguishing the effects of mitral regurgitation has been found. When mitral stenosis is complicated by cardiac neurosis the measurements indicate a degree of disability less than that from which the patient is complaining. The patients in whom aortic valve disease contributes considerably to their disability show a lower pulmonary artery pressure and a higher degree of oxygen saturation of the mixed venous blood than the group of patients with the same degree of disability due to uncomplicated mitral stenosis. The association of mitral stenosis and chronic respiratory disease results in the pulmonary artery pressure being as high as in uncomplicated cases of mitral stenosis of the same degree of disability, but the pulmonary capillary pressure is lower.

Evidence of the persistence of pulmonary vascular changes in patients whose severe mitral stenosis has been relieved by mitral valvotomy has been found. This is suggested by the finding of a higher pulmonary artery-pulmonary capillary pressure gradient in patients after operation than in patients with the same degree of disability who have not been operated on.

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