The dosage and management of these cases, and the side-effects seen in the course of their treatment, are discussed.

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AN APPRECIATION OF MITRAL STENOSIS*

PART II. INVESTIGATIONS AND RESULTS

BY

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THE ELECTROCARDIOGRAM

P Mitrale

The P mitrale may be defined as a widened P wave of normal or only slightly increased voltage, usually notched, bifid, or flat-topped. It was present in all but four of the surgical cases with normal rhythm. The exceptions included three instances of the P pulmonale (due to extreme pulmonary hypertension in two and to tricuspid stenosis in one); there was only one instance in which the P wave was normal, and this was the mildest in the series. In 10 cases the auricular complex was a mixture of the P mitrale and the P pulmonale: the pulmonary vascular resistance was in the extreme grade in two of these, between 6 and 9 units in three of them, and relatively normal in three; tricuspid stenosis was responsible in the other two. The P mitrale was at least 0.12 second wide in 79% of the whole surgical group.

In the medical series with normal rhythm, the P mitrale was absent in three-quarters of the trivial cases of mitral stenosis and in 10% of the relatively mild cases in the sense that they were not severe enough to warrant valvotomy. It was present in all the cases in which mitral incompetence was associated with stenosis, although usually of only moderate degree; there was no presystolic murmur in 80% of these cases. A P pulmonale was present in the most extreme example of pulmonary hypertension and in two cases of tricuspid stenosis, but in only one other. Excluding the trivial cases, a well-developed P mitrale, at least 0.12 second in duration, occurred in half of all the medical cases with normal rhythm.

In the group with almost pure mitral incompetence the P wave was normal in all trivial and mild cases; it was present in relatively mild degree (0.10 to 0.11 second) in half of those of moderate grade. It was seen, also in relatively mild degree, in 80% of the severe cases (grade 3 or 4).

A conspicuous P mitrale (grade 3 or 4) could not be correlated with a dominant *a* wave in the left atrial pressure tracing: thus only one-third of the cases showing such *a* waves had a grade 3 or 4 P mitrale; conversely, only a similar proportion of cases having a conspicuous P mitrale had an *a* wave higher than *v* in the left atrial tracing. The grade of the P mitrale could not be correlated with the size of the left atrium, this fact being best illustrated by the relatively mild grades found in mitral incompetence, which favours left atrial dilatation. Nor could it be correlated closely with the size of the mitral orifice found at operation, the great majority of those with conspicuous P mitrales having an orifice either in the average grade (1 by 0.5 cm.) or in the slightly tighter grade (0.75 by 0.4 cm.); in only one was the stenosis extreme (0.5 by 0.3 cm.).

It is concluded that the P mitrale is a good sign of well-developed mitral valve disease, and that if it is well marked (grade 3 or 4) it strongly favours stenosis rather than incompetence; also that it should be present in all cases of stenosis that are severe enough to warrant valvotomy.

Right Ventricular Preponderance

The degree of right ventricular preponderance in mitral stenosis based on a conventional interpretation of the six routine V chest leads was closely related to the pulmonary vascular resistance (Fig. 7). An important practical fact noticed in the analysis was that any degree of right ventricular preponderance in mitral stenosis meant that the case was severe enough to warrant valvotomy: the converse, of course, was not true.

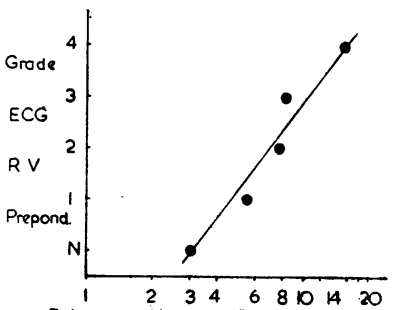

FIG. 7.—Relationship between right ventricular preponderance and pulmonary vascular resistance.

Left Ventricular Preponderance

Left ventricular preponderance was very rare in pure mitral stenosis, and when present was only of slight degree. In the mitral incompetent group, on the other hand, it occurred in 82%, excluding trivial cases, and in degree averaged slightly over grade 2. Grade 3 left ventricular preponderance always meant severe mitral incompetence in the absence of aortic valve disease. In the medical group with significant mitral incompetence, left ventricular preponderance, averaging a little under grade 2, occurred in one-third, ventricular balance being normal in half and

*The second part of a lecture delivered before the San Francisco Heart Association on October 29, 1953, and modified for the Strickland Goodall lecture of the Society of Apothecaries of London, March 24, 1954. Part I appeared in last week's issue (p. 1051).

the right ventricle predominating in the remainder. Amongst the surgical cases with combined mitral stenosis and incompetence, slight left ventricular preponderance (averaging grade 1) occurred in one-third, the ventricular balance being normal in one-third and the right ventricle preponderating in one-third.

It is concluded that left ventricular preponderance is excellent evidence of mitral incompetence in the absence of aortic valve disease. In the whole surgical series there was only one patient with more than slight left ventricular preponderance, and she did not do at all well. Since the results of valvotomy were poor in half the cases of mitral stenosis complicated by more than trivial incompetence, and only fair in another quarter, and since only one-third of this group had left ventricular preponderance at all, and that of only grade 1, it follows that higher grades of left ventricular preponderance are a direct contraindication to mitral valvotomy.

X-RAY APPEARANCES

Small Aorta

Diminution in the size of the aortic knuckle, often to the extent of its being invisible in the antero-posterior view, was noticed in two-thirds of the surgical cases. A normal aorta was attributed to concomitant aortic valve disease, to atherosclerosis associated with age (over 45), to a relatively mild degree of stenosis, or to the maintenance of a normal rather than a low cardiac output at rest (4.5 to 6 litres a minute), each of these factors occurring in 30%, sometimes in varying combination. Their respective incidences in the surgical cases with a small aorta were 7%, 12%, 19%, and 20%, so that aortic valve disease and age were more likely to have been responsible than the degree of stenosis and the measured cardiac output; few of the cases were mild enough for the last two factors to be important. In addition, 6% of those with a normal aorta had a slightly raised blood pressure (about 160/110) against 1% in those with a small aorta. No obvious cause for a normal-sized aorta could be found in 15%.

In the mitral incompetence group, omitting trivial cases and those of grade 1 severity, 50% had a normal aortic shadow, but of these 58% were between 45 and 69 years old. In the cases with a small aorta only 17% were in this age group. If these relatively old patients are also omitted from the analysis, two-thirds of the mitral incompetence group had a small aorta, which is more comparable to the findings in mitral stenosis.

In the medical series two-thirds of those with significant mitral incompetence had a normal aortic shadow. This was attributed to associated aortic valve disease in half of them. On the whole the findings did not implicate mitral incompetence as one of the factors which tend to preserve a normal aortic shadow.

Left Ventricular Enlargement

Radiological evidence of left ventricular enlargement in cases of mitral valve disease proved less reliable than either clinical or electrocardiographic evidence, and deserves no further comment.

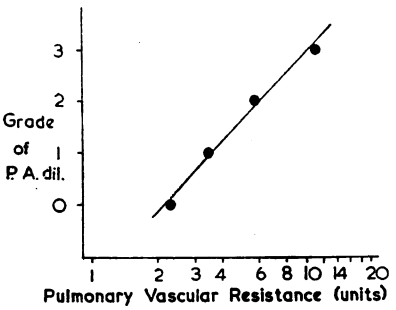

FIG. 8.—Relationship between size of pulmonary artery and pulmonary vascular resistance.

Dilatation of the Pulmonary Artery

There was a close relationship between the size of the pulmonary artery and the pulmonary vascular resistance (Fig. 8). The figures were compiled from the medical and surgical groups, omitting cases of pure mitral incompetence. When the pulmonary artery was normal or only slightly dilated the pulmonary vascular resistance was normal or only slightly increased in 95%, being high in only 5%; on the other hand, when the pulmonary artery was considerably or grossly dilated the resistance was normal or only slightly increased in 17%, whereas it was high or extreme in 83%. No doubt the correlation would have been closer still if there were not so much variation in the radiological appearances of the pulmonary artery in normal individuals.

In the group with pure mitral incompetence considerable dilatation of the pulmonary artery was seen in only one instance; the vessel was normal in 73%, slightly dilated in 21%, and moderately so in 4%. The lack of enlargement was attributed to the relatively low pulmonary vascular resistance found in this group (see below).

Dilatation of the Right Atrium and Ventricle

It was rarely possible to decide which of these chambers was chiefly affected radiologically, either in the antero-posterior or in the oblique positions, and they have therefore been taken together. The clinical and electrocardiographic findings usually make it clear whether or not the ventricle is involved. In any case, isolated dilatation of the right atrium is seen only in tricuspid stenosis.

The presence and degree of right-sided cardiac enlargement was closely related to the size of the pulmonary artery (and therefore to the pulmonary vascular resistance). Thus in the whole series the grading of the two was the same in 55% and within one grade of each other in 35%, being out of harmony in only 10%. In the surgical group, when there was any discrepancy it was usually the pulmonary artery that was relatively larger than the right side of the heart. In the medical group it was the other way round. When the pulmonary artery was conspicuously dilated and the right heart only slightly so, a high pulmonary vascular resistance was present in half the cases; no explanation could be found in the other half. When the shadow of the right side of the heart was conspicuously enlarged and the pulmonary artery normal or only slightly dilated, tricuspid stenosis was present in 44%, pericardial effusion in 12.5%, and "congestive heart failure" without an unduly high pulmonary vascular resistance in 25%; no explanation other than auricular fibrillation could be found for the remainder.

Left Atrial Dilatation

The size of the left atrium was graded so far as possible from the *x*-ray appearances in the antero-posterior view. When it could not be seen at all in this view, but deflected the oesophagus backwards in the first oblique position, enlargement was considered to be slight (grade 1); a similar grading was applied when the right border of the left atrium could be seen through the shadow of the right atrium but did not overlap it in the antero-posterior view. Grade 2 enlargement meant that the left border of the atrium or the appendage itself formed a separate arc between the shadows of the pulmonary artery and left ventricle, or that the right border of the left atrium formed the upper part of the right border of the heart, but did not extend further laterally than the right atrium; in grade 3 dilatation the left atrium bulged conspicuously on both sides of the heart, and extended beyond the shadow of the right atrium on that side; gross enlargement was reserved for aneurysmal dilatation.

The average size of the left atrium in the surgical group worked out at grade 1.62, for the medical 1.92, and for mitral incompetence 2.35; for the whole series it was grade 1.8. These figures confirm the fact that mitral incompetence is a more important cause of left atrial dilatation than mitral stenosis.

In the surgical group no correlation could be found between the size of the left atrium and the degree of stenosis. Omitting the cases complicated by significant

incompetence, grade 1 dilatation was found in 42%, grade 2 in 52%, and grade 3 in 6%; aneurysmal dilatation was not seen. The incidence of each grade of dilatation was much the same in each grade of stenosis. Similarly there was no correlation between the size of the left atrium and the left atrial pressure, provided that a critical degree of stenosis had been reached—as in the surgical group; those with grade 1 dilatation had an average left atrial pressure of 22.9 mm. Hg; those with grade 2 dilatation 21.8 mm. Hg.

In the medical group the size of the left atrium worked out at less than grade 1 for trivial cases, at grade 1.5 for the average case of stenosis not yet severe enough to warrant valvotomy or so severe that death supervened before operation could be undertaken, and grade 2.5 for combined stenosis and incompetence. This confirms the conclusion already drawn.

In the cases in which the pulmonary vascular resistance was extreme (10 units or above) the average size of the left atrium was a little under grade 1.5.

The relationship of the size of the left atrium both to auricular fibrillation and to systemic embolism has been discussed under those headings.

Pulmonary Venous Congestion

Pulmonary venous congestion is of course closely related to dyspnoea, but from time to time intense congestion may be noted radiologically in a patient who is hardly breathless at all, and vice versa. In these unusual cases individual idiosyncrasy in respect of the nervous reflex involved in the mechanism of this type of dyspnoea is inculpated.

As expected, the degree of pulmonary venous congestion judged radiologically was proportional to the left atrial pressure (Fig. 9). This chart shows that the vast majority of cases with radiological signs of pulmonary venous congestion had left atrial pressures between 10 and 30 mm. Hg.

Pulmonary venous congestion was also proportional to the degree of stenosis, provided the pulmonary vascular resistance was not too high. This is shown in Fig. 10, *a* to *d*, which have been compiled from the surgical cases without significant incompetence. When the mitral orifice was less

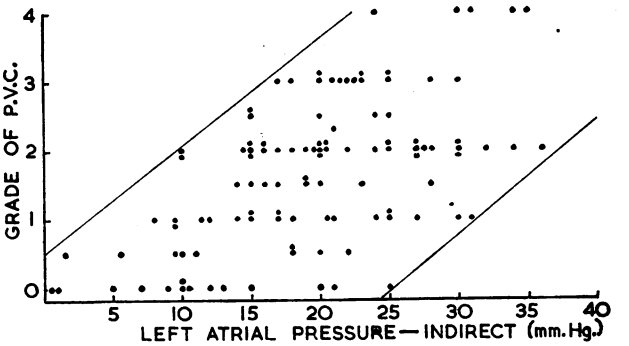

FIG. 9.—Relationship between the radiological signs of pulmonary venous congestion and the left atrial pressure.

stenosed than usual, venous congestion was slight or moderate in degree and was never modified by the pulmonary vascular resistance, for the latter was never raised; in the most common type of case, with an orifice of about 1 by 0.5 cm., congestion was usually moderate or considerable, provided the resistance was not above six units, but fell off sharply when the resistance was higher; when the mitral orifice was tighter than usual, around 0.75 by 0.4 cm., but not yet extreme, the findings were similar; in extreme cases in which the orifice did not exceed 0.5 by 0.3 cm., congestion tended to be considerable or gross and, although modified by resistances between 6 and 10 units, usually required a greater degree of vasoconstriction for its efficient

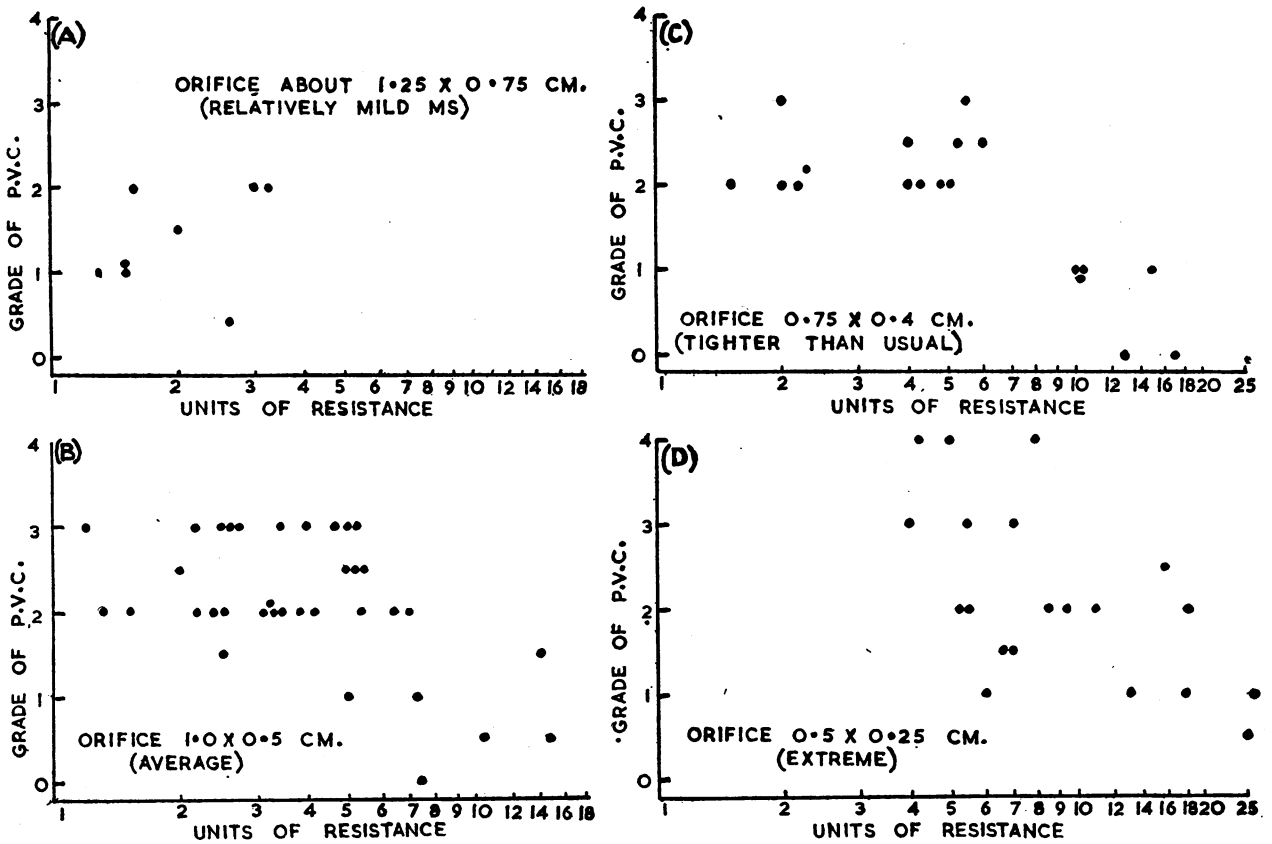

FIG. 10.—Relationship between the intensity of pulmonary venous congestion judged radiologically, the pulmonary vascular resistance, and size of the mitral orifice. In A the orifice was larger than usual, in B it was average, in C it was tighter than usual, and in D it was extreme. In B, C, and D the damping effect of a high resistance is seen.

relief. It may also be noticed from Fig. 10 that there was a higher incidence of cases with a high resistance in the group with extreme stenosis than in the other groups; life may well have depended on it.

Good objective evidence of a functionally successful valvotomy was afforded by relief of pulmonary venous congestion judged by radiological standards.

Haemosiderosis

Incontrovertible haemosiderosis, distinct from pulmonary venous and lymphatic congestion, was observed in 10% of the surgical cases and in 6% of the medical; it did not occur in a single instance of pure mitral incompetence. In the few examples in which serial skiagrams had been taken over a prolonged period haemosiderosis had been present for many years; indeed, the time of its onset was never detected, for it was always present in the first film obtained and did not change subsequently either before or after operation.

Orthopnoea or paroxysmal cardiac dyspnoea occurred in 60% of the cases with haemosiderosis, which is about the same as its incidence in the combined surgical and medical groups as a whole, so that pulmonary venous congestion cannot be the only factor concerned. Normal rhythm and a normal pulmonary vascular resistance were each present in 80% of the cases with haemosiderosis, which is a little higher than in those without. But by far the most important factor correlated with haemosiderosis was *pulmonary apoplexy*, as previously defined, for this had occurred in 55%, which is four to five times higher than its incidence in cases without haemosiderosis (12%). Since haemosiderosis is believed to be due to multiple recurrent haemorrhages from the broncho-pulmonary anastomoses in the mucosa of the terminal bronchioles the relationship was expected (Laubry *et al.*, 1948; Lendrum, 1950).

No correlation could be established between haemosiderosis and mitral incompetence, the left atrial pressure, or the size of the mitral orifice; nor, of course, had it anything to do with pulmonary hypertension.

Calcification of the Mitral Valve

The association between heavy calcification of the mitral valve and a serious degree of mitral incompetence has been emphasized repeatedly, and the point is strongly confirmed in the present series. Thus, 40% of the group with relatively pure well-developed mitral incompetence, 52% of the medical cases of mitral stenosis complicated by serious incompetence, and 62% of similar surgical cases had heavy calcification; in fact, 50% of all cases with a significant degree of mitral incompetence had heavy calcification.

In the surgical group 28% of all cases had some degree of mitral calcification, but it was trivial and in no way influenced the findings, operative technique, or results in over half of them; only 12% of the surgical cases had heavy or moderate mitral calcification, and significant incompetence was present in all but three of them.

Valvotomy was undertaken in these cases because the patients' symptoms were attributed to stenosis despite the leak, or in the hope that the valve could be repaired. The results in this small series were never excellent; they were good in 41%, fair in 12%, and poor in 47%. The chief cause of the bad results was the development of an even greater degree of mitral incompetence. Of three cases in which the pre-operative mitral leak was trivial, two did badly in this way.

In the medical group as a whole 87.5% of those with mitral calcification had moderate or considerable mitral incompetence.

It is concluded that heavy mitral calcification is a serious drawback to valvotomy, not only because it favours too great a degree of mitral incompetence, but because it is likely to result in such incompetence if not already present. It is not merely the calcium which causes the trouble, but the severe destruction of the valve mechanism which leads to its deposition.

Cardio-Thoracic Ratio

Although this was measured and recorded in most cases, it has not been analysed separately, for an increased cardio-thoracic ratio meant little unless the dilated chambers causing the enlargement of the heart shadow were identified. When there appeared to be true general enlargement without a mechanical cause, pericardial effusion proved a more likely explanation than active rheumatic carditis.

CATHETER STUDIES

Cardiac catheterization was carried out in 125 of the surgical cases, 42 of the medical, 17 of those with mitral incompetence, and in 23 awaiting valvotomy—a total of 207 cases. No serious technical difficulty was encountered in any of them; there was no mortality, and no complications other than the occurrence of pulmonary infarction when diodone was injected through a catheter wedged in a distal branch of the pulmonary artery, so that that method of studying the anatomy of the pulmonary circulation had to be abandoned.

Right Atrial Pressure

Tracings obtained from the right atrium confirmed clinical observations on the jugular venous pressure and pulse described under that heading. Little further information was gained by analysing the central tracings themselves. When there was normal rhythm *a* and *v* were usually about equal in amplitude in uncomplicated cases. The *a* wave was usually dominant, measuring 3 to 5 mm. Hg above *v*, in cases with severe pulmonary hypertension, and was occasionally of giant proportions. Giant *a* waves were also recorded in tricuspid stenosis. In advanced heart failure the *v* wave became more prominent and was followed by a steep *y* descent. In tricuspid incompetence the *x* descent was minimal, and in auricular fibrillation it was never seen.

Right Ventricular Pressure

The systolic pressure was of course always the same as the pulmonary artery systolic pressure; this is discussed in the next section. The right ventricular pressure at the end of diastole was raised in 50% of patients with congestive heart failure, lying between 4 and 14 mm. Hg above the sternal angle; that the other 50% with failure did not show high readings was attributed to the fact that patients with heart failure were commonly treated by means of rest, digitalis, a low-sodium diet, and mercurial diuretics, and were not catheterized until they had improved. For this reason few of the figures represent the situation in severe failure.

The right ventricular end diastolic pressure was not raised in tricuspid stenosis. The diagnostic pressure gradient across the tricuspid valve in this condition has already been described and illustrated (Fig. 5, in Part I).

Pulmonary Artery Pressure

In the surgical group the pulmonary artery pressure averaged 64/33, with a mean of 45 mm. Hg. It will be noted that the diastolic level averaged about half the systolic, and that the mean pressure averaged the diastolic plus two-fifths of the pulse pressure. The pulmonary systolic pressure was 100 to 130 mm. Hg in 13%, between 60 and 95 mm. Hg in 40%, between 50 and 59 mm. Hg in 22%, and below 55 mm. Hg in 27%.

The relationship between the pulmonary systolic pressure and the pulmonary vascular resistance in the combined surgical and medical series is shown in Fig. 11. The critical systolic levels were 100 mm. Hg, above which the resistance was always raised, and 50 mm. Hg, below which the resistance was very rarely raised. The resistance varied considerably, however, when the pulmonary systolic pressure lay between 50 and 100 mm. Hg. Nearly all patients with pressures below 100 mg. Hg and an extreme pulmonary vascular resistance had congestive heart failure.

The relationship between the pulmonary pressure gradient (mean P.A.P. – mean L.A.P.) and the pulmonary vascular resistance is shown in Fig. 12. The critical gradient was about 25 mm. Hg, above which practically all cases had a resistance over 6 units. The majority of patients with

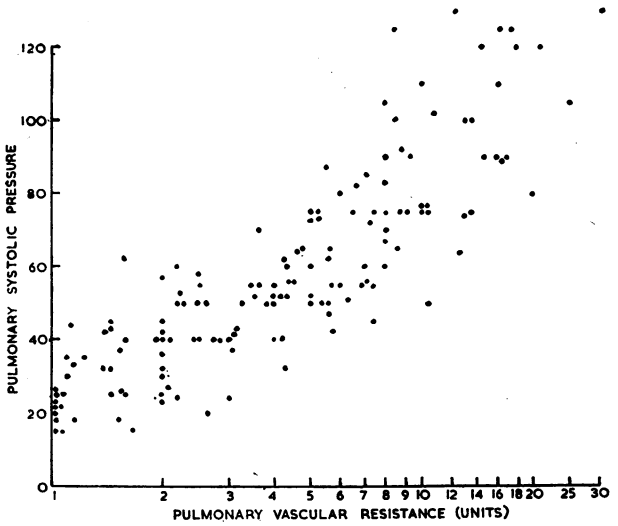

FIG. 11.—Relationship between the pulmonary systolic pressure and the pulmonary vascular resistance.

resistances between 6 and 10 units had gradients between 20 and 30. Practically all cases with an extreme resistance (10 to 30 units) had pressure gradients between 30 and 70 mm. Hg.

The pulmonary artery pressure always rose during effort, often very considerably. When the resistance was relatively normal the rise in pressure tended to run parallel with a rise in left atrial pressure, and in some instances the latter reached unexpectedly high levels, well above 35 mm. Hg. Clinical pulmonary oedema did not develop in these cases, but the effort was maintained for only three minutes. When the resistance was high the pulmonary artery pressure tended to rise disproportionately, often to an extreme degree. Precise figures cannot be given, because neither the work done nor the cardiac output during effort was measured, and unless these factors are known the findings can do no more than indicate the general trend. Since Dexter and his group (Gorlin *et al.*, 1951) showed that the resistance did not in fact change during effort, we have abandoned the test as a

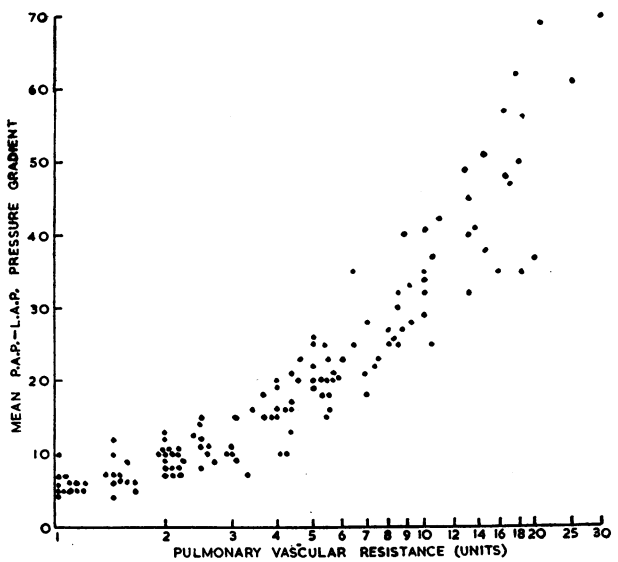

FIG. 12.—Relationship between the pulmonary pressure gradient and the pulmonary vascular resistance.

diagnostic procedure, for it did not seem to provide any information beyond that already obtained in other ways.

Left Atrial Pressure

This was measured indirectly by wedging the catheter in a distal pulmonary artery as described in the introduction under "Method" in Part I. Tracings were considered valid only when venous in form.

The left atrial pressure ranged between 0 and 10 mm. Hg in all the trivial and several of the mild cases in the medical group, but was under 10 mm. Hg in only one of the surgical cases. This man had no effort intolerance, but was operated on for recurrent systemic embolism. The valve orifice was found to be less stenosed than usual.

The average left atrial pressure in the surgical group was 22.5 mm. Hg above the sternal angle, and, as previously mentioned, tended to be only slightly if at all higher in patients with orthopnoea or paroxysmal cardiac dyspnoea than in those without such symptoms; this also applied to patients giving a history of pulmonary oedema (Table IV). The relationship between the left atrial pressure and pulmonary venous congestion judged radiologically has already been discussed and illustrated in Fig. 9.

Pulmonary oedema was a rare complication of cardiac catheterization, and no physiological observations were made during an attack. On two occasions it occurred before the catheter was introduced into the vein. It is clear, however, that left atrial pressures up to 35 mm. Hg with reference to the sternal angle might be tolerated without pulmonary oedema, and that much higher pressures, even up to 50 mm. Hg, were maintained for short periods during the effort test without distress. On the other hand, pulmonary oedema never occurred with a left atrial pressure below 30 mm. Hg at the time, which agrees with the observations of Dexter's group (Gorlin *et al.*, 1951), and with current theory.

The relationship between the left atrial pressure and the pulmonary vascular resistance is shown in Table XVII. It

TABLE XVII.—*Left Atrial Pressure and Resistance*

	Pulmonary Vascular Resistance Units				
	Mild Medical Under 4	Surgical Series			
		Under 4	4–5·9	6–9·9	10–30
Average left atrial pressure (mm. Hg)	9·2	19·6	22·2	23·2	22·4

may be seen that there was some correlation between these two factors up to resistances in the critical range of 6 to 9.9 units, but when the resistance was in the extreme range (10 to 30 units) the left atrial pressure tended to fall off.

The left atrial pressure, as expected, was related both to the size of the mitral orifice and to the cardiac output, as shown in Fig. 13. The ratio C.O./L.A.P. offered a useful index of the degree of mitral stenosis, averaging 45% (range 33 to 66%) when the stenosis was less tight than average, 20% (range 12.5 to 50%) when the stenosis was average or a little tighter than average, and 12.5% (range 10 to 15%) when the stenosis was extreme, as previously defined. Gorlin's formula (Lewis *et al.*, 1952) could not be utilized, because the heart rate was omitted from the analyses.

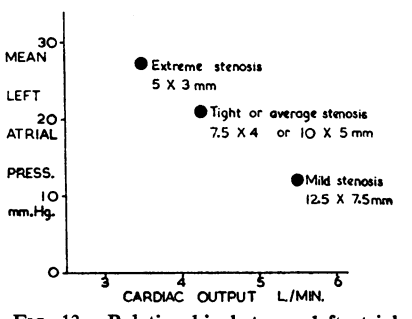

FIG. 13.—Relationship between left atrial pressure, cardiac output, and size of mitral orifice.

Form of the Left Atrial Pressure Tracing

The form of the pulmonary venous pulse has already been discussed in relation to the P mitrale of the electrocardiogram. Only 32% of all cases with reliable indirect left atrial pressure tracings showed *a* waves higher than *v*; *a* and *v* were about equal in amplitude in 39%, and *v* was taller than *a* in 29%.

Giant *a* waves towering more than 5 mm. Hg above *v* were uncommon. In this respect left atrial behaviour is different from right atrial behaviour in tricuspid stenosis. This rather unexpected finding requires further study.

Although *v* was taller than *a* in nearly one-third of the cases of pure mitral stenosis, the difference was usually only a matter of 2 to 4 mm. Hg. In mitral incompetence with normal rhythm, on the other hand, *v* towered above *a*, the average difference in well-developed cases being as much as 14 mm. Hg, the range being 5 to 25. The expression giant *v* wave would not be out of place in these cases. When there was auricular fibrillation the amplitude of the *v* wave in mitral stenosis infrequently exceeded 10 mm. Hg and averaged nearer 5 mm. Hg; in well-developed mitral incompetence, on the other hand, it ranged between 5 and 30 mm. Hg. Thus, although there was considerable overlapping, it is fair to say that a *v* wave over 15 mm. Hg in amplitude nearly always means mitral incompetence, and a *v* wave under 5 mm. Hg nearly always excludes it.

Arterial Oxygen Saturation

The arterial oxygen saturation averaged 91.5% for the whole surgical series, being within the normal range (92 to 96%) for our laboratories in 52%, slightly reduced (88 to 91%) in 34%, and moderately reduced (83 to 87%) in 14%.

An attempt was made to find some factor common to the cases with the lowest range of arterial oxygen saturation. Pulmonary venous congestion could not be inculpated when patients with paroxysmal cardiac dyspnoea were compared with patients without orthopnoea, but appeared to be a significant factor in the group with orthopnoea only (Table XVIII). This suggests that patients with orthopnoea only

TABLE XVIII.—*Relationship Between Arterial O_2 Saturation and Symptoms of Pulmonary Venous Congestion*

	Arterial Oxygen Saturation		
	92–96%	88–91%	83–87%
No orthopnoea or P.C.D. ..	58%	31%	11%
Paroxysmal cardiac dyspnoea ..	52%	36%	12%
Orthopnoea only	38%	35%	27%

may be more advanced than patients with paroxysmal cardiac dyspnoea (a hypothesis which is not as improbable as it might seem), or that the factor chiefly responsible for a low arterial oxygen saturation tends to prevent paroxysmal cardiac dyspnoea: such a factor might well be the pulmonary vascular resistance.

In the small group of cases in which the arterial oxygen saturation ranged between 83 and 87% the pulmonary vascular resistance was extreme in 46%, between 8 and 9 units in 39%, and normal in 15%; in these last instances pulmonary oedema was present at the time. Conversely, 35% of all cases with an extreme resistance had an arterial oxygen saturation under 88%.

In the group with the lowest arterial oxygen saturation the left atrial pressure averaged 22.5 mm. Hg, which is the same as in the rest of the series. The cardiac output averaged 3.3 litres a minute and was below 4 litres a minute in all but one instance. The low cardiac output was probably the result of the high resistance.

Coincidental cor pulmonale, due to emphysema, the result of repeated attacks of winter bronchitis, was a very rare complication of mitral stenosis, as previously mentioned, and certainly played no part in lowering the arterial oxygen saturation in the cases analysed; in the most florid instance, in which independent bronchial asthma was believed to be at least partly responsible for the symptoms, the arterial oxygen saturation was 94%.

Just why a high pulmonary vascular resistance should reduce the arterial oxygen saturation is unknown. The same phenomenon occurs in the later stages of primary pulmonary hypertension. That frank pulmonary oedema lowers the arterial oxygen saturation is well known and requires no explanation; pulmonary venous congestion alone is exonerated.

Arteriovenous Oxygen Difference and Cardiac Output

The relationship between the arteriovenous oxygen difference and the cardiac output in the present series is shown in Table XIX and is illustrated in the shape of a curve in Fig. 14. If for any reason the oxygen consumption cannot be measured at the time the samples are obtained, it may be as accurate or more accurate to estimate the output from the arteriovenous oxygen difference by reference to such a curve than to measure the oxygen consumption subsequently.

TABLE XIX.—*Arteriovenous Oxygen Difference*

A-V Difference (ml./litre)	Incidence	Average Cardiac Output (l./min.)	Range (l./min.)
21– 30	1·5%	9·3	7·3–11·3
31– 40	6·5%	6·2	4·5– 7·8
41– 50	18%	4·8	3·7– 5·7
51– 60	30%	4·0	2·7– 5·5
61– 70	15%	3·4	2·5– 5·25
71– 80	17%	3·2	2·4– 5·0
81– 90	5·5%	3·0	2·2– 4·0
91–100	3·5%	2·9	2·5– 3·7
101–110	3%	2·3	2·0– 3·1

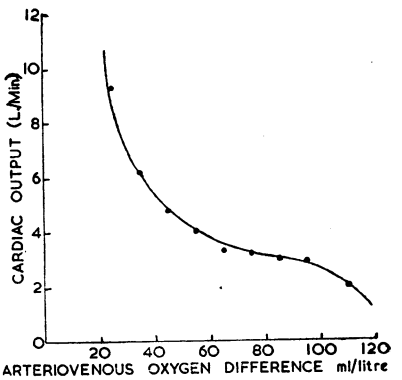

FIG. 14.—Relationship between the cardiac output and the arteriovenous oxygen difference.

The cardiac output averaged 3.8 litres a minute in the surgical cases, being higher in those with normal rhythm (4.1) than in those with auricular fibrillation (3.6), and higher in those with paroxysmal cardiac dyspnoea (4.0) and pulmonary oedema (4.6) than in those without (3.5 in the group also without orthopnoea); it was especially low (3.3) in cases with the typical mitral facies, and was above average (4.2) when there was no peripheral cyanosis at all.

The relationship between the cardiac output and the pulmonary vascular resistance is shown in Fig. 15. The pulmonary resistance is perhaps the most important of all the factors limiting the cardiac output. Certainly the output is restricted by the mitral stenosis itself, but if the resistance did not rise there would be little to prevent the output being maintained at the expense of an extremely high left atrial pressure, which would result in death from pulmonary oedema. This state of affairs has in fact been observed, although death was prevented by prompt treatment. Surges of output in pregnancy, during effort, on excitement, and as the result of other factors in patients with normal resistance may cause paroxysmal cardiac dyspnoea or pulmonary oedema in this way. Such patients may have no orthopnoea under basal conditions; indeed, one of these dramatic attacks may be the first symptom of mitral valve disease in certain circumstances.

The cardiac output was of course low in patients with congestive failure, but this group also had a high pulmonary vascular resistance; nevertheless, it was probably lower in those with failure than in those without, but precise figures are not available because catheterization was usually deferred until congestive failure had responded to treatment.

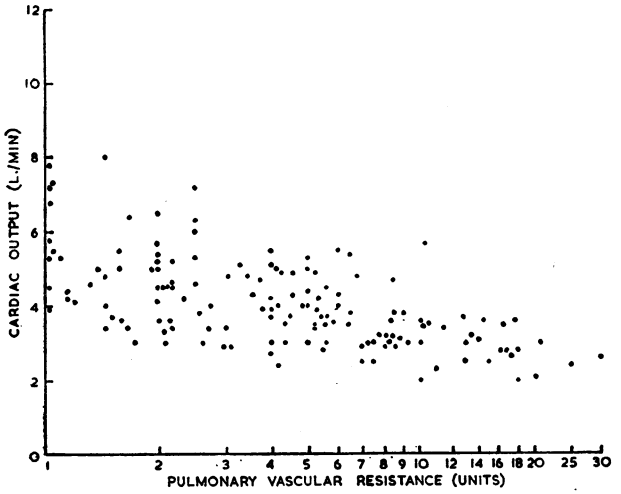

FIG. 15.—Relationship between the cardiac output and the pulmonary vascular resistance.

Pulmonary Vascular Resistance

Adapting the Poiseuille equation—

$$\text{Resistance (R)} = \frac{\text{mean P.A. pressure} - \text{mean L.A. pressure (mm. Hg)}}{\text{pulmonary blood flow (cardiac output in l./min.)}}$$

the result may be expressed in units as in this paper. If it is desired to express resistance in fundamental units of force, as described by Gorlin and Gorlin (1951), pressures in mm. Hg must be converted into dynes/cm.^{2}, and flows expressed in litres a minute must be converted into cm.^{3}/sec. The equation thus becomes—

$$R = U \times \frac{0.1 \times 13.59 \times 981.17 \text{ dynes/cm.}^2}{1{,}000 \text{ cm.}^3/60 \text{ sec.}}$$

where U stands for the simple unit already described. The figure 13.59 is the specific gravity of mercury, and 981.17 cm. per second per second is the g factor—that is, the acceleration force of gravity. The dividend thus becomes 1,333.4 dynes/cm.^{2} The equation may now be rewritten—

$$R = U \times \frac{1{,}333.4 \text{ dynes} \times 60 \text{ sec.}}{1{,}000 \text{ cm.}^5}$$

$$= U \times 80.004 \text{ dynes sec./cm.}^5$$

Thus it is only necessary to multiply the unit by 80 to express the resistance in dynes sec./cm.^{5}

In the 200 cases in which it was measured the pulmonary vascular resistance averaged 6 units for the surgical group, 4.2 units for the medical, and 3.5 for those with mitral incompetence, or 5.4 for the whole series. Further details are given in Tables XX and XXI. The estimates for the whole series were contrived by including the 100 cases that were not catheterized, arbitrarily giving to each the average resistance of the group to which it belonged on clinical and other grounds. This was desirable because high-resistance cases were more likely to have been selected for physiological investigation than the others.

TABLE XX.—*Pulmonary Vascular Resistance*

	Average Resistance (Units)	Incidence of Each Grade of Resistance			
		Normal 1–3·9 Units	Transitional 4–5·9 Units	High 6–9·9 Units	Extreme 10–30 Units
Surgical	6·0	38·4%	26%	23%	12·6%
Medical	4·2	63%	15%	12%	10%
Mitral incompetence	3·5	56%	31%	6·5%	6·5%
Total catheterized	5·4	45%	24%	19·5%	11·5%
Estimate for whole series	4·2	60%	20%	12%	8%

TABLE XXI

	Pulmonary Resistance		
	"Normal" 1–5·9 Units	High 6–9·9 Units	Extreme 10–30 Units
M.S. serious	64%	19%	17%
,, all cases	73%	14%	13%
,, *M.I.* serious	74%	26%	—
,, all cases	79%	21%	—
M.I. serious	84%	13%	3%
,, all cases	90%	8%	2%

It may be added that predictions concerning resistances were rarely far wrong once the principles outlined in this paper were understood.

Although high resistances were rare in pure mitral incompetence they were not uncommon in combined lesions; extreme resistances, however, were very rare in anything but pure stenosis (Table XXI).

The behaviour of the pulmonary vascular resistance is perhaps the most important physiological event in mitral stenosis, and to a large extent determines the course and pattern of the disease. Thus a high resistance puts a considerable strain on the right ventricle and causes that chamber to enlarge with or without functional tricuspid incompetence; it prevents the pulmonary venous system and left atrium from developing unduly high pressures and so diminishes orthopnoea and abolishes paroxysmal cardiac dyspnoea and pulmonary oedema; it limits the cardiac output directly and also indirectly by tending to reduce the pressure gradient across the mitral orifice. In other words, a high pulmonary vascular resistance saves the patient from drowning at the expense of a low cardiac output; a high venous pressure, hepatic distension, oedema, and fatigue replace haemoptysis, severe breathlessness, paroxysmal cardiac dyspnoea, and pulmonary oedema. Most of the evidence upon which these conclusions are based has already been presented in previous sections. It remains to be shown that congestive heart failure itself occurs only as a result of a high pulmonary resistance. That this was so in mitral stenosis is clear from Fig. 16. This omits

FIG. 16.—Relationship between congestive heart failure and the pulmonary vascular resistance. •=Mitral valve disease without failure. ●=Congestive failure in mitral stenosis. O=Congestive failure in mitral incompetence. *=Failure due to thyrotoxicosis.

transient congestive failure provoked by auricular fibrillation with uncontrolled ventricular tachycardia. There was no single instance in which a primary myocardial fault was responsible for failure. In mitral incompetence, on the other hand, there were as many cases of heart failure with relatively normal resistances as with high, and either a myocardial fault or some other factor must have operated. This question needs further study.

It might be thought that a high resistance developed in mitral stenosis gradually over the years in all well-established cases and that it depended on structural changes in the pulmonary arteries resulting from passive pulmonary hypertension secondary to a rise in left atrial pressure; that it was an inevitable end-result which must occur sooner or later if the patient did not die prematurely from pulmonary oedema, systemic embolism, or other complication of mitral stenosis. This hypothesis was not supported

by the facts. On the contrary, the average age of the group with an extremely high pulmonary vascular resistance was the same as in the rest of the series, as already mentioned; indeed, in the whole series the three most florid examples of extreme pulmonary hypertension were aged 27, 23, and 27. Again, no case of irreversible pulmonary hypertension has yet been encountered, and there is good reason to believe that the pulmonary vascular resistance falls after technically successful mitral valvotomy in practically all these cases, even if the operation is undertaken only in the very last stages and in the presence of gross heart failure. Finally, only 20% of the really high-resistance cases gave a previous history of pulmonary congestive symptoms, the great majority presenting the clinical picture of active pulmonary hypertension from the start. Just what determines this vasoconstrictive response is unknown. Much the same problem is encountered in cor pulmonale and the Eisenmenger syndrome (Wood, 1952).

Operative Findings

These have already been correlated with the pre-operative findings, and will therefore be reviewed here only briefly.

1. *Atrial Thrombosis.*—A clot was found in the left atrial appendage or sometimes in the left atrium itself in 23% of cases, as described in the section on systemic embolism, to which its relationship has been fully discussed. Brock has stressed the importance of allowing blood to gush momentarily from the incised auricle when a clot is detected or suspected, with the object of washing it out, and this manœuvre has been successful in a number of cases (Baker *et al.*, 1952). Even so, systemic embolism complicated valvotomy in 10%.

2. *Mitral Incompetence.*—A regurgitant jet was appreciated by the surgeon in 24%, being slight in just over half of them, moderate in nearly a quarter, and considerable in nearly a quarter. Some degree of incompetence was predicted in 90% of these cases, as a rule with reasonable accuracy in respect of degree. Thus the prediction was correct in all but one of those with considerable regurgitation; in fact, half of them had been put up for surgical repair rather than valvotomy. Some were put up for valvotomy at a time when an attempt was being made to see what could be done for combined stenosis and incompetence, usually at the repeated request of the patient. The results were uniformly poor or fair; the degree of mitral incompetence was never less after the operation, and as a rule it was worse. Nevertheless, one-third of these patients improved enough to have made valvotomy worth while, and from being totally incapacitated they were comfortable and able to get about, though scarcely well enough to work.

Of the cases in which a moderate regurgitant jet was found, one had been predicted to have considerable incompetence and two mild incompetence—the rest were accurately assessed. Of those with a small jet, a trivial degree of incompetence had been predicted in 72%, the leak had been overlooked in 17%, and a moderate leak had been diagnosed in 11%.

Mitral incompetence of trivial degree was diagnosed clinically in 9% of the series, apparently in error. In one-third of this small group—that is, in 3% of the whole series—it was expected to be moderate in degree; but no instance of serious mitral incompetence was predicted erroneously. The final results in those with trivial or moderate leaks were not quite as good as in the rest of the series, there being fewer graded as excellent, and in over one-third of them mitral incompetence became considerable in degree.

Calcium.—Mitral-valve calcification has already been discussed in the radiological section. Only trivial calcification was sometimes overlooked on screening, important calcification practically never.

Size of Orifice

The orifice was commonly described as a small oval 1 by 0.5 cm. (Brock, 1952); it was about this size in 46% of the surgical cases, but was tighter (0.75 by 0.4 cm. approximately) in 18%, and extremely stenosed (0.5 by 0.3 cm. approximately) in 21%; in only 5% was the orifice a little larger, and it never exceeded 1.5 cm. in length in cases of simple stenosis. When there was a serious degree of associated mitral incompetence the orifice usually measured from 1.25 to 2 cm. by 0.75 to 1 cm. in length. In these cases the valve was severely disorganized and commonly heavily calcified, as described by Brock (1952). There were too few cases of pure incompetence examined to form any opinion about those.

The relationship between the size of the orifice and the symptoms, physical signs, and physiological findings has been discussed in other sections. It need only be said here that extreme stenosis tended to have more dire consequences than an average-sized opening, and that the grade of stricture should not be considered less important than the physiological reaction to the obstruction. Certainly pulmonary oedema was just as likely to occur in a patient with an average or relatively large orifice (provided it was within the critical range) as with extreme stenosis; auricular fibrillation, haemoptysis, and systemic embolism were also indifferent to the size of the orifice; but the pulmonary vascular resistance was undoubtedly influenced by the degree of stenosis, never being raised with a relatively large orifice, and never being normal with extreme stenosis (Fig. 10, *a–d*); angina pectoris, the left atrial pressure, the degree of pulmonary venous congestion, and the cardiac output all bore an inverse relationship to the size of the orifice. The matter may be summed up by stating that the degree of stenosis was the fundamental factor which determined the severity of the disease, and pulmonary vasoconstriction was the most important physiological reaction which modified its course and behaviour; auricular fibrillation and embolism were in the nature of accidents.

Post-operative Course

Shock from the operation, intrathoracic haemorrhage, pleural effusion, collapse of the lung, and left chest pain, having no bearing on the present thesis and being purely surgical matters, are not discussed.

Post-operative Auricular Fibrillation.—Auricular fibrillation occurred post-operatively in 24% of the surgical cases, usually during the first week. It tended to last about ten days in those cases in which normal rhythm was resumed spontaneously, but if left to nature it was often permanent. At first we attempted to prevent the rhythm change by means of quinidine, but this failed; it was found much better to prepare the patient with digitalis, so that the ventricular rate was controlled when auricular fibrillation developed. We also learned that it was a mistake to try to restore normal rhythm too soon, the reversion being more easily accomplished towards the end of the second week. Since it is now believed that only fresh clots are responsible for embolism, anticoagulants are begun on the seventh day, so that no clot is likely to form in the left atrium during the five days before quinidine is given. Normal rhythm was restored in this manner and without embolic complications in 95% of the cases in which quinidine was used (Table XXII). Post-operative auricular fibrillation was left alone when the surgeon had found clots in

TABLE XXII

	Incidence (%)		Functional Results (%)			
	Total	In Each Group	Excellent	Good	Fair	Poor
Normal rhythm throughout	31·3		56	33	9	2
Post-op. A. Fib.	24					
Spontaneous reversion		21	100		0	0
Quinidine "		59	40	55	0	5
" failed "		3	100		0	0
Permanent A.F., no quinidine		17	50			50
Pre-op. A.Fib.	38					
Spontaneous reversion		0				
Quinidine "		10	80		20	0
" failed "		10	80		20	0
Permanent A.F., no quinidine		80	12	37	33	18
Died	6·6					

the left atrium, or when valvotomy was not technically satisfactory. Quinidine was also given to a limited number of patients whose auricular fibrillation had been present before the operation if conditions for restoring normal rhythm seemed favourable. The results in this small group were far less satisfactory, however; for normal rhythm was restored in only half of them, and of these two-fifths relapsed.

Fever and Left Chest Pain.—Recurrent attacks of fever, usually associated with pain in the left chest, lasting about one week and with intervals up to a month, occurred in 10%. For a long time the cause of these attacks was by no means clear. The course of each was uninfluenced by antibiotics and salicylates, and it was soon realized that both fever and pain abated just as quickly when no special treatment was given. No rheumatic manifestations accompanied the fever. Reference of pain to the left neck and flank, occasional pericardial friction or effusion, and certain electrocardiographic changes suggested pericarditis, and it is now believed that this is the usual explanation. The attacks closely resembled those seen in association with pericardial foreign body (Wood, 1950). No serious consequences have ever been observed, and in the end they have always subsided permanently.

SUMMARY

All cases of mitral valve disease may be grouped according to the anatomical lesion or the physiological state; in certain circumstances the former is more useful, in others the latter. In practice, a combination of the two has been found best. In respect of anatomy one is concerned whether mitral stenosis or mitral incompetence is dominant and with the degree of obstruction or leak; also with the presence and degree of associated aortic valve disease or tricuspid stenosis. Physiologically, the most important factor is the pulmonary vascular resistance. In the present series the cases have been grouped according to the anatomical lesion and its severity when the resistance was normal or borderline; but when the resistance was high or extreme the cases were grouped separately and subdivided into those with dominant stenosis and those with dominant incompetence, for the degree of valve damage was never trivial or mild in these cases. The incidence of each group and subgroup is set out in Table XXIII.

TABLE XXIII.—*Chief Groups*

	Pure M.S.			M.S. Trivial M.I.			M.S. Serious M.I.			Pure M.I.			High Pul. Resistance		Gross Pul. Resistance		Mitral and Aortic	Mitral and Tricuspid
	Trivial	Rel. Mild	Serious	Trivial	Rel. Mild	Serious	Trivial	Rel. Mild	Serious	Trivial	Rel. Mild	Serious	Dom. M.S.	Dom. M.I.	Dom. M.S.	Dom. M.I.		
Surgical	—	—	70	—	—	10	—	—	12	—	—	2	22	6	18	—	5	5
Medical	6	27	2	2	8	—	2	7	16	—	—	—	2	4	4	—	12	5
Mitral incompetence	—	—	—	—	—	—	—	—	—	7	14	24	—	4	—	1	—	—
Total	6	27	72	2	8	10	2	7	28	7	14	26	24	14	22	1	17	10
Incidence %	2	9	24	0·6̇	2·6̇	3·3̇	0·6̇	2·3̇	9·3̇	2·3̇	4·6̇	8·6̇	8	4·6̇	7·3̇	0·3̇	5·6̇	3·3̇
Incidence % discounting severity	35			6·6̇			12·3̇			15·6̇			12·6̇		7·6̇		5·6̇	3·3̇
Chief groups	41·6̇						28						20·3̇				Others 10	

Psychosis.—Confusional psychiatric states, usually with delusions, during the immediate post-operative course occurred in 5% of cases. The disturbance was always temporary, however, and normal mental function was restored within a matter of weeks. There was no evidence of cerebral embolism in these cases, but the exact mechanism is unknown.

Results

Results were assessed in terms of function and were excellent in 30%, good in 40%, fair in 15%, poor in 9%, and fatal in 6%. *Excellent* meant that effort intolerance became normal or improved by three grades. For example, the result was classed as excellent if a patient who was totally incapacitated before the operation had only slight effort intolerance three months afterwards. A good result meant that effort intolerance improved by two grades and a fair result by one grade. Good results were also characterized by abolition of paroxysmal dyspnoea, orthopnoea, haemoptysis, angina pectoris, peripheral embolism, and serious winter bronchitis in all cases.

The chief causes of indifferent or bad results were inadequate splitting of the commissures or mitral incompetence (either pre-operative or as a direct consequence of the valvotomy). The chief surgical complication which sometimes spoiled an otherwise good result was systemic embolism.

During the three-year period under review 5% of the cases have re-stenosed, including 3 out of the first 20. Since mitral stenosis takes from three to fifteen years to develop after active rheumatic valvulitis, a similar time interval must elapse before the true incidence of re-stenosis is known.

1. Pure Mitral Stenosis (35%)

The clinical features of pure mitral stenosis may now be described as follows.

The patient is usually a woman in the mid-thirties. The chief symptom is breathlessness rapidly progressing to paroxysmal cardiac dyspnoea, orthopnoea, and sometimes death from acute pulmonary oedema. Blood-spitting is frequently associated with congestive attacks, and these are often complicated by winter bronchitis. Pulmonary apoplexy may be an early symptom. Pregnancy aggravates the symptoms and usually causes some permanent deterioration.

On examination she looks well, and although the hands may be cold there is little peripheral cyanosis and the mitral facies is commonly absent. The peripheral pulse is small and firm, the jugular venous pressure and pulse are normal. The left ventricle cannot be felt at the apex of the heart; there is only a slight lift, if any, over the right ventricle in the left parasternal line, and none over the pulmonary artery. In the mildest cases a presystolic murmur and an accentuated first heart sound are the only auscultatory signs, but an opening snap soon develops. In better-developed cases which are still free from symptoms all the classical auscultatory signs are invariably present. At the apex of the heart these consist of a presystolic murmur, a loud slapping first sound, no systolic murmur, a soft aortic second sound, a loud opening snap, no third heart sound, and a long mitral diastolic murmur of moderate intensity, often accompanied by a thrill. The tap imparted to the palpating hand represents the first heart sound. At the base the second heart sound is normally split, and the second or pulmonary element is only slightly if at all accentuated. There is no pulmonary incompetence. In the third left space it is often possible to hear the pulmonary component of the

second sound separating out on inspiration, and the opening snap increasing in intensity during expiration.

The electrocardiogram shows a normal P wave in trivial cases and a P mitrale in better-developed cases, certainly in all those requiring valvotomy. The QRS–T complexes are normal.

X-ray films show a small aorta, a normal or only slightly dilated pulmonary artery, slight or sometimes moderate dilatation of the left atrium, normal ventricles and right atrium, and a varying degree of pulmonary venous congestion, according to the severity of the case, being absent in mild cases and gross in the most severe. Haemosiderosis may be present in cases giving a history of pulmonary apoplexy. No calcification can be seen in the mitral valve, or if present it is only slight. The cardiothoracic ratio is under 50%.

On cardiac catheterization the right atrial pressure and wave form are normal. The right ventricular diastolic pressure is normal. The mean pulmonary artery pressure is commonly 10 to 15 mm. Hg above the left atrial pressure, which is normal in trivial cases, still under 10 in mild cases, and between 15 and 30 in the great majority requiring valvotomy. On exertion the left atrial pressure rises considerably, sometimes well above 35 mm. Hg, and the pulmonary artery pressure rises passively. Whether or not pulmonary vasoconstriction develops during an attack of pulmonary oedema is still uncertain. Such a reflex would certainly be expected as a result of the anoxia and would be a physiological life-saving event. The arterial oxygen saturation is normal unless there is pulmonary oedema. The arteriovenous oxygen difference is well below 50 ml. per litre in mild cases and commonly between 50 and 60 in those requiring valvotomy. The cardiac output is normal or only slightly reduced at rest; it rises normally in mild cases, but is strictly limited in the more severe; nevertheless, it is by no means fixed. The pulmonary vascular resistance is normal or near normal. At operation in cases severe enough to warrant it, the left atrium is usually free from clot, there is no calcium in the mitral valve and there is no mitral incompetence. The mitral orifice commonly measures 10 by 5 mm., but may be a little tighter (8 by 4 mm.) or even extreme (5 by 3 mm.); it is occasionally less stenosed, but is never more than 15 by 5 mm. as estimated by R. C. Brock (1952). Necropsy figures are usually higher. The cusps themselves are usually mobile, but the margins of the orifice may be fibrous and tough.

Mitral valvotomy is advised in all cases of pure stenosis with grade 2B to grade 4 effort intolerance, the results of a technically successful operation being excellent. Premature valvotomy should be avoided in view of the operative risks and the chance of re-stenosis (probably greater than at present envisaged).

2. Mitral Stenosis with Trivial Incompetence (6.6%)

This small group differs in no way from that just described except for the presence of a slight-to-moderate mitral systolic murmur, and a small regurgitant jet appreciated at operation.

3. Mitral Stenosis with Serious Incompetence (12.3%)

The patient is as likely to be a man as a woman. The symptoms are similar to those described for group 1, but pulmonary apoplexy is more likely to have occurred. The physical signs are very different. The peripheral pulse is small, but slightly water-hammer in quality. Auricular fibrillation is highly probable. The cardiac impulse is left ventricular in type and hyperdynamic. On auscultation there is no presystolic murmur even in those with normal rhythm, the first heart sound is soft, normal, or only slightly accentuated, there is a loud mitral systolic murmur usually associated with a thrill, no opening snap, a loud third heart sound, and a mitral diastolic murmur of moderate intensity and duration. The electrocardiogram usually shows left ventricular preponderance. The *x*-ray appearances are characterized by considerable or gross dilatation of the left atrium, enlargement of the left ventricle, and conspicuous calcification of the mitral valve; haemosiderosis may be seen in cases giving a past history of pulmonary apoplexy. The cardio-thoracic ratio is usually much increased owing to the dilated left heart.

The physiological findings are similar to those of pure stenosis except that the left atrial pressure tends to swing more and the arterial tracing may show systolic collapse.

At operation a powerful regurgitant jet can nearly always be felt. The valve is heavily calcified and disorganized, and usually measures about 15 to 20 by 5 to 10 mm. If it is sufficiently stenosed to encourage the surgeon to undertake simple valvotomy the degree of incompetence usually increases, and, although the patient is occasionally improved, he is usually no better off. Partial valvotomy may be more rewarding than a radical bilateral split. Combined stenosis and incompetence really requires a repair operation, but the techniques employed to date are none too satisfactory, and the results are indifferent. At the time of writing, therefore, it is wise to defer such cases, if not too advanced, in the belief that surgical techniques will continue to improve. If life is already threatened, however, conservative or partial valvotomy may be the best solution.

4. Pure Mitral Incompetence (15.6%)

The patient is usually a man. The symptoms are similar to those of pure mitral stenosis except that the downhill course is more rapid once breathlessness has developed. There is often, however, a longer latent interval which may compensate for the more rapid course. On examination the physical signs are similar to those of the combined lesion described in group 3, except that the mitral diastolic murmur is very short or absent altogether, and the gap between the systolic murmur and the third sound may be partly closed. The electrocardiographic and *x*-ray appearances are also similar to those in the combined lesion, but occasionally the left ventricle dominates the whole picture in a manner never seen when stenosis is present. Conspicuous systolic expansion of the left atrium, particularly in the antero-posterior view, is a valuable sign of organic mitral incompetence. The physiological findings are similar to those of the combined lesion, and in some the swing of the *v* wave in the left atrial pressure pulse is gross.

A repair operation is required. This may be undertaken at the present time if it is too dangerous to wait (Logan and Turner, 1952), but should be deferred in the majority of cases until the surgical technique is more satisfactory.

5. Mitral Valve Disease Complicated by a High Pulmonary Vascular Resistance (12.6%)

In this group the symptoms are much the same as in simple stenosis, the degree of pulmonary vasoconstriction being insufficient to prevent the development of high pulmonary venous pressures, but in some of the cases the symptoms of pulmonary venous congestion are damped. In a sense it is a transitional group between those with relatively normal resistances and those in the extreme grade.

There is more obvious peripheral cyanosis and the mitral facies may be present. The peripheral pulse is very small, and the jugular venous pressure may be a little raised; in some cases there is frank congestive heart failure or functional tricuspid incompetence, which are not seen in cases of stenosis with normal resistance. The left ventricle cannot be felt at the apex of the heart unless there is marked mitral incompetence as well; but there is nearly always a strong lift over the right ventricle. The auscultatory signs may be slightly damped, but as a rule are scarcely changed, except that the pulmonary element of the second sound is clearly accentuated. The electrocardiogram shows right ventricular preponderance, but the P wave is still mitrale in type. *X*-ray films show enlargement of the pulmonary artery and right side of the heart in addition to the appearances already described in the other groups.

Cardiac catheterization reveals a higher mean pulmonary artery pressure and a pressure gradient between 20 and 30 mm. Hg; the cardiac output tends to be lower and more fixed, the arterio-venous difference between 60 and 70 ml. per litre, and the pulmonary vascular resistance between 6 and 10 units. At operation the pulmonary artery is seen to be bulging and tense and the right-sided enlargement is confirmed. After technically successful valvotomy there is nothing to prevent an excellent result, and the pulmonary resistance is expected to return to normal.

6. Mitral Stenosis Complicated by an Extreme Pulmonary Vascular Resistance (7.6%)

It is very unusual for gross resistance to develop in cases of mitral incompetence or combined stenosis and incompetence. The patient is more likely to be a woman than in any other group. Although there is still breathlessness on exertion, and even slight orthopnoea in some cases, paroxysmal cardiac dyspnoea and pulmonary oedema do not occur and breathlessness is overshadowed by fatigue and oedema; ascites and angina pectoris are relatively common. Symptoms from pulmonary venous congestion are replaced by those related to a low cardiac output. It is this group, above all, that develops functional tricuspid incompetence and congestive heart failure. Haemoptysis due to pulmonary infarction occurs late in the course; indeed, death from pulmonary embolism secondary to phlebothrombosis in the legs is a constant danger.

The patient has either a conspicuous mitral facies and intense peripheral vasoconstriction, or, rarely, the palmar flush and vasodilatation of hepatic dysfunction. The peripheral pulse is exceptionally small. The jugular venous pressure is usually raised and the venous pulse may show a giant *a* wave in cases with normal rhythm. The left ventricle is always impalpable, but the heaving thrust over the right ventricle may extend as far across as the anterior axillary line. There may be pulsation over the pulmonary artery, but it is uncommon. The auscultatory signs are thoroughly damped. A presystolic murmur, if present, is difficult to hear. The first heart sound, however, is still accentuated. A loud systolic murmur may sometimes be heard at the apex of the heart, but it is tricuspid in origin and can be heard equally well at the left sternal edge. The opening snap may be inaudible, but in such cases may sometimes be demonstrated by means of phonocardiography. There may be a right ventricular third heart sound, which in association with the systolic murmur already mentioned may encourage a mistaken diagnosis of mitral incompetence. The mitral diastolic murmur may be abolished altogether or it may be heard only very occasionally and then only with great difficulty. In other cases the auscultatory signs of mitral stenosis are still obvious, but they are never florid. At the left sternal edge in addition to the tricuspid systolic murmur there may be a loud pulmonary systolic click synchronous with the opening of the pulmonary valve, as described by Leatham (1954). At the base the pulmonary component of the second sound is short, sharp, high-pitched, and loud, but may be difficult to separate from the aortic element even on inspiration. When there is pulmonary incompetence, which is common, the pulmonary second sound loses its characteristic quality.

The electrocardiogram shows either a P pulmonale or a combination of this and the P mitrale. There is usually gross right ventricular preponderance, high-voltage R waves and inverted T waves extending across from V_1 to V_3 or V_4, and no Q waves can be seen in V_6, for the right ventricle usually forms the apex beat.

X-ray films reveal a very small aortic knuckle, considerable or gross dilatation of the pulmonary artery, and marked enlargement of the right ventricle and atrium. The left atrium may not be obviously dilated in the antero-posterior view, but can usually be distinguished in the first oblique position. Pulmonary venous congestion may be absent altogether, the pulmonary vascular markings being chiefly arterial proximally, and very light distally, as described by Goodwin *et al.* (1952). The cardio-thoracic ratio is much increased owing to the right-sided enlargement.

The physiological findings are characterized by a prominent *a* wave in the right atrial tracing when there is normal rhythm, a raised right atrial and right ventricular end diastolic pressure, a pulmonary artery pressure in the region of 100/50 mm. Hg or above, a pulmonary pressure gradient well over 30 mm. Hg, and only an average rise in left atrial pressure. The arterial oxygen saturation is a little reduced in about one-third of the cases, the arteriovenous oxygen difference very high, and the cardiac output low and fixed. The pulmonary vascular resistance is between 10 and 30 units.

After a technically successful valvotomy the right ventricle may remain in difficulties for many weeks or months, and convalescence must be slow. There is good reason to believe, however, that the resistance falls gradually over the months and the whole situation may be very much improved a year afterwards.

7. Associated Aortic Valve Disease (5.6%)

When this is trivial it does not alter any of the clinical syndromes described. When it is severe it dominates the picture and need not be considered here. The cases which make up the group under discussion are those in which it is often difficult to decide whether the aortic or the mitral lesion is the more important.

The symptomatology and course are like that of mitral valve disease. The physical signs are thoroughly complicated, particularly when there is both aortic and mitral stenosis and incompetence, which is as likely as not. The mitral lesion tends to damp the signs of the aortic. When the pulmonary vascular resistance is raised in addition, the confusion is even greater and it becomes almost impossible to know which lesion is mainly responsible for the physiological changes in the circulation. It must suffice here to say that if aortic valve disease is not obviously the chief lesion, either it is of no importance or mitral disease is more advanced than suspected.

When aortic valvotomy or aortic valve repair can be more successfully undertaken these cases will have to be worked out with greater precision. At the moment the results of mitral valvotomy and attempted aortic valvotomy are indifferent, although sometimes good enough to have made the operation worth while.

8. Tricuspid Stenosis (3.3%)

Just as mitral stenosis damps the features of aortic valve disease, so does tricuspid stenosis damp those of mitral valve disease. These cases present with clinical features resembling those of the extreme pulmonary hypertensive group, but on examination, although the giant *a* is present in the neck, there is no lift over the right ventricle and no accentuation of the pulmonary second sound; similarly, the electrocardiogram reveals a tall P pulmonale, but little right ventricular preponderance, and radiologically, although the right side of the heart is distended, the pulmonary artery is not. Careful auscultation usually reveals separate tricuspid murmurs which are louder during inspiration. The diagnosis is made with certainty by demonstrating a pressure gradient of several mm. Hg across the tricuspid valve during diastole.

When tricuspid stenosis is severe mitral valvotomy cannot be recommended. But in relatively mild cases, in which the symptoms are due to mitral stenosis, the operation has been very successful. Tricuspid valvotomy is in its infancy.

Conclusion

Three hundred cases of mitral valve disease have been studied in detail. It is hoped that the facts revealed may be of some value to those interested in this fascinating subject.

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HORMONE TREATMENT OF DISSEMINATED BREAST CANCER

BY

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In the endeavour to control malignant disease, clinical and experimental work is being carried out to find substances which will inactivate cancer or reverse the cancerous changes back to normal. There is evidence that by alterations brought about in the hormonal status of the body by various methods the cancerous process in certain patients can be checked, thus enabling them to live on for a number of years in excellent health. By this means a form of treatment is being developed which may enable us to attain our object, and ultimately it seems likely that hormone therapy will play an important part in those cancers which are hormonal-dependent. At present new methods are required for biological assays of hormones to provide us with scientific measurements of the changes which are brought about by various stages of cancer and the effects of hormonal treatment. We could thus measure the hormonal balance of the body and abnormal amounts of particular hormones, and determine the constitution of abnormal hormones which may be present. Treatment to-day is largely empirical, based upon clinical observations, and further advances will be made in our search for the truth when the laboratory comes to our aid in this way.

The presence of disseminated breast cancer creates a serious situation for the patient and a difficult problem for the surgeon. Until recent years the prospect was gloomy, but now a little gleam of light is showing. A number of workers have demonstrated that some of these patients are sensitive to variations of their sex hormones; for regression in the disease has occurred with oophorectomy, adrenalectomy, and the administration of either androgens or oestrogens. This important therapeutic progress is not reviewed here; the object of this paper is to record the effects in a group of patients and especially to call attention to those patients who are living in excellent health more than four years later. The case record of the first patient has already been published (Raven, 1950); her subsequent history is now reported.

Case 1

A married woman aged 50 was seen on April 13, 1948, with disseminated carcinoma of the left breast. She stated that the various lumps became bigger just before her menstrual periods. A carcinoma 3.5 cm. in diameter was present in the upper inner quadrant of the left breast, with enlarged cervical and left axillary lymph nodes, the latter being fixed. Numerous skin deposits were present in the region of the left shoulder, left arm, chest wall, and right loin. A nodular lump 3.4 by 2.2 cm. was present in the right pre-auricular region. Histological examination of a cervical lymph node and a skin nodule showed spheroidal-cell carcinoma.

I performed a bilateral oophorectomy on July 7, 1948. The disease gradually disappeared, and on February 22, 1949, I found no evidence of cancer. The 17-ketosteroids in the urine were normal in January, 1950. In January, 1951, I excised a group of enlarged right axillary lymph nodes. Histological examination showed nodes replaced by sheets and cords of closely packed anaplastic polyhedral carcinoma cells. On January 8, 1952, an enlarged right supraclavicular lymph node and two small skin nodules in the posterior aspect of the chest were found; the patient was given methyltestosterone, 50 mg. daily, and these lumps regressed. The testosterone was withdrawn on July 28, 1953. Radiological examination of the chest and cervical, dorsal, and lumbar parts of the spine and pelvis was always negative for metastases. On December 22 I found a cyst 4 cm. in diameter in the left breast, and there was no clinical evidence of cancer anywhere. The patient is well, lives a normal life, and I think she looks younger than before, with colour in her cheeks: she volunteered the information that the latter was new for her, as she was always pale before the treatment. The amount of hair on her face has now decreased markedly, but her voice remains at a lower pitch than normal.

Case 2

A married woman aged 42, without children, noticed a lump in the right breast in November, 1946. This was removed elsewhere in February, 1948, and histological examination showed a carcinoma. A week later I performed a right radical mastectomy. In May, 1949, radiological examination showed metastases in the ribs, pelvic bones, right femur, and probably in the neck of the left femur. Palliative high-voltage *x*-irradiation was given to relieve the pain they were causing, and she was also given methyltestosterone, 50 mg. daily, until September, 1950. There was marked reduction in the pain in the right hip and improvement in the pain in her back. In March, 1951, she looked and felt very well; hot flushes occurred after the testosterone was withdrawn. Flexion was slightly limited at the right hip, otherwise movements in both hips were full. Testosterone therapy was recommenced and the dose increased to 75 mg. daily by April, 1952; it was withdrawn in May, 1952. At this time palliative *x*-irradiation was given to the right hip. In June, 1952, pain occurred in the right shoulder and there was radiological evidence of a metastasis in the upper part of the shaft of the right humerus; palliative *x*-irradiation was given to this region.

On October 20, 1953, methyltestosterone, 25 mg. daily, was given because radiological examination of the pelvic bones showed that the affected areas were bigger and an increase had occurred in the area of rarefaction in the right