Late Systolic Murmurs and Non-Ejection ("Mid-Late") Systolic Clicks

An Analysis of 90 Patients

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Evidence has previously been produced from this laboratory (Barlow and Pocock, 1963; Barlow et al., 1963; Barlow, 1965) that apical late systolic murmurs denote mitral regurgitation, and that the commonly associated non-ejection systolic clicks also have an intracardiac, and probably chordal, origin. It has also been suggested that the association of these auscultatory features with a distinctive electrocardiographic pattern and a billowing posterior leaflet of the mitral valve constitutes a specific syndrome (Barlow, 1965; Barlow and Bosman, 1966).

In this paper we present an analysis of 90 subjects with either a late systolic murmur, a non-ejection click, or both. The intracardiac origin of these murmurs and clicks is reaffirmed and their possible mode of production is considered. The abnormal electrocardiogram, the probable structural abnormality of the mitral valve mechanism, the various underlying aetiological factors, and the prognosis are discussed.

Subjects and Methods

Of the 90 subjects, 65 were referred to the Cardiac Clinic for assessment of their auscultatory signs. Seven were found during hospital admission for a non-cardiac illness; 6 were detected after closed mitral valvotomy, and 5 others after other forms of mitral valve surgery. One 30-year-old woman complaining of palpitations, who regularly attended the Clinic, developed a late systolic murmur and click a year after observation began. Examination of relatives of patients with late systolic murmurs or non-ejection clicks produced a further 6 cases.

The 90 subjects ranged in age from 4 to 63 years; 45 of them, including 13 children, were under the age of 30; 33 were male and 57 female. All were White with the exception of 2 Bantu girls.

Classification. The patients were divided into 5 groups (Fig. 1). Group 1 comprised 11 patients with isolated systolic murmurs; Group 2, 21 patients with isolated non-ejection clicks; Group 3, 34 patients with both late systolic murmurs and non-ejection clicks, and Group 4, 18 patients with either a late systolic murmur or a non-ejection click, or both, together with a "pathological" murmur (Table 1). For purposes of this study, a "pathological" murmur is a diastolic murmur of mitral or aortic origin, an apical pansystolic murmur, or an aortic ejection murmur in young normotensive subjects (Barlow and Pocock, 1962). Such associated "pathological" murmurs, which clearly arise at either the mitral or aortic valves, provide supportive evidence for the intracardiac origin of the late systolic murmurs and the non-ejection clicks. Coincidental congenital heart disease in patients with late systolic murmurs or non-ejection clicks is not regarded in the same light and these patients were not included in Group 4. The 7 patients with congenital heart disease were therefore placed in Groups 1, 2, or 3. Group 5 comprised 6 patients who developed non-ejection clicks after closed mitral commissurotomy. These patients, though they had "pathological" murmurs, were grouped separately because the clicks which appeared after mitral valvotomy differed in timing, behaviour, and character from other non-ejection clicks.

There were 3 patients in Group 1, 2 in Group 3, and 1 in Group 4, who had diastolic pressures over 100 mm. Hg. The remainder were normotensive.

Investigations. All subjects were examined by at least two of us. A phonocardiogram, an electrocardiogram, and chest x-ray films were routinely done.

Phonocardiography was performed with a New Electronic Products (N.E.P.) multichannel apparatus. Sixteen patients (3 in Group 2, 12 in Group 3, and 1 in
Group 4) had phonocardiograms immediately after standing as well as in the supine position. The effects of the erect posture on murmurs and clicks were assessed clinically in a further 7 (1 in Group 1, 2 in Group 2, 3 in Group 3, and 1 in Group 4). Alterations in the auscultatory signs produced by the Valsalva manoeuvre (58 patients), amyl nitrite inhalation (55 patients), and phenoxyphenine injection (43 patients) were studied. Changes in timing of murmurs and clicks were assessed in relation to the altered length of mechanical systole which invariably accompanies these manoeuvres.

Twenty-eight patients (4 in Group 1, 1 in Group 2, 14 in Group 3, 7 in Group 4, and 2 in Group 5), of whom 20 had late systolic murmurs, were subjected to retrograde left ventricular cine-angiography. Direct coronary arteriograms were obtained in 2 patients in Group 3. Intracardiac phonocardiograms were recorded in the left ventricle in 5 patients in Group 3 and in 1, with a pansystolic murmur and non-ejection click, in Group 4.

Symptoms. Tiredness, palpitations, breathlessness, or chest pain were present in 39 of the 63 patients in Groups 1, 3, and 4. Fourteen of these had associated pathology, such as a congenital heart lesion, significant valvar disease, hypertension, or ischaemic heart disease. Nevertheless, of the 25 subjects in these 3 groups without any associated significant heart disease (all but 1 of whom had late systolic murmurs), 20 complained of tiredness, palpitations, or exertional dyspnoea, and 14 had experienced praeordial pain. This was ill defined and fleeting except in 2 women, aged 22 and 56 years respectively, in whom the pains were suggestive of angina pectoris.

Only 10 of the 21 patients in Group 2 complained of symptoms and 6 of these had other significant pathology. One of the remaining 4 suffered from palpitations and the other 3 from tiredness. The 6 patients in Group 5 had been considerably disabled and the post-operative symptomatic improvement was variable.

AUSCULTATORY AND PHONOCARDIOGRAPHIC FEATURES

Late Systolic Murmurs. A total of 53 subjects had late systolic murmurs, 11 in Group 1, 34 in Group 3, and 8 in Group 4. Of the 8 patients in Group 4, with late systolic murmurs, 4 also had non-ejection clicks.

The murmurs, usually loudest at the apex, were best heard in the left lateral position. The effect of respiration was variable and intensity was sometimes increased by inspiration. With the exception of 1 musical murmur, the late systolic murmurs were never louder than grade 3. An intermittent musical quality (Fig. 2) occurred in 7 cases. In 1 this was audible only in the left lateral position, in 3
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only on standing, and in another musical vibrations were maximal during inspiration. A musical intonation was not present at every examination in the remaining 2 patients.

Forty-seven late systolic murmurs were clearly crescendo-decrescendo on phonocardiograms, whereas in 6 this configuration was less definite. In order to represent diagrammatically the configuration of the 53 late systolic murmurs, the time intervals from Q of the simultaneous electrocardiogram to the points of onset, maximal accentuation, and the end of the murmur were measured (Fig. 3). The Q wave was chosen because of the difficulty in determining the exact onset of the mitral component of the first heart sound especially during vasoactive manoeuvres. In most instances maximal accentuation occurred near the middle of the murmur. In only 4 was maximal intensity recorded very early, while in 3 it was very late so that the terminal decrescendo was short. The murmurs always extended to the aortic component of the second sound and in 14 definite vibrations passed through this sound (Fig. 3).

The responses of the murmurs to the vasoactive procedures (Valsalva manoeuvre in 33 patients, amyl nitrite inhalation in 34, and phenylephrine injection in 27) were easily assessed. Irrespective of whether late systolic murmurs were isolated or associated with clicks or with "pathological" murmurs, they behaved in a manner characteristic of a regurgitant murmur of mitral incompetence. They

![Graph showing the distribution of late systolic murmurs and non-ejection clicks among males and females.](http://heart.bmj.com/)

**Fig. 1.**—Ninety subjects, 33 male, 57 female, with late systolic murmurs (sm) and non-ejection clicks (sc). For details of classification, see text.

![Phonocardiogram, recorded in mid-expiration, of a musical late systolic murmur in a 15-year-old girl. A non-ejection click is also present. Left ventricular cine-angiocardiology demonstrated mild mitral regurgitation and abnormal billowing of the posterior leaflet. Abbreviations for this and subsequent figures: MA = mitral area; MF = medium frequency; SM = systolic murmur; SC = systolic click; M = mitral component of first heart sound. In all tracings the distance between the heavy vertical lines equals 0·20 sec.](http://heart.bmj.com/)

**Fig. 2.**—Phonocardiogram, recorded in mid-expiration, of a musical late systolic murmur in a 15-year-old girl. A non-ejection click is also present. Left ventricular cine-angiocardiology demonstrated mild mitral regurgitation and abnormal billowing of the posterior leaflet. Abbreviations for this and subsequent figures: MA = mitral area; MF = medium frequency; SM = systolic murmur; SC = systolic click; M = mitral component of first heart sound. In all tracings the distance between the heavy vertical lines equals 0·20 sec.
Fig. 3.—Diagrammatic representation of the 53 late systolic murmurs showing the time of onset, maximal intensity, and end of each murmur expressed as a percentage of the Q–A interval—see text. The mitral component of the first heart sound (M) is indicated, at an arbitrary distance of 0·06 sec. after Q, in order to demonstrate the cadence of the murmurs on clinical auscultation. The positions of the systolic clicks are represented by vertical lines. In 2 instances the clicks had marked spontaneous movement and are omitted from the diagram. It can be seen that clicks commonly occur at, or shortly after, the onset of the murmurs and that maximal intensity of the latter is usually near their mid-point. In 14 cases vibrations extended beyond A (aortic valve closure) and these are shown on the diagram.

therefore became softer with amyl nitrite (Barlow and Shillingford, 1958; Vogelpoel et al., 1959; Endrys and Bártová, 1962; Perloff and Harvey, 1962), louder with phenylephrine (Beck et al., 1961; Endrys and Bártová, 1962), and showed a delayed return following release of the straining phase of the Valsalva manoeuvre (Zinsser and Kay, 1950; Polis et al., 1960) (Fig. 4). Their timing and configuration were essentially unchanged with phenylephrine, but there was a movement towards early systole with amyl nitrite and during the straining phase of the Valsalva manoeuvre.

In all of the 18 patients auscultated in the standing position the late systolic murmurs became louder and longer and they accentuated earlier. In fact, the murmurs were shown to have become pansystolic in 6 of the 13 patients who had phonocardiograms performed in the erect position (Fig. 5).

Intracardiac phonocardiography recorded the late systolic murmur in a position just beneath the mitral valve in 4 of the 5 subjects in whom this procedure was attempted.

Non-ejection Systolic Clicks. A total of 75 subjects had non-ejection systolic clicks. The 6 which followed mitral commissurotomy (Group 5) differed in several respects from the others, and are discussed separately and in some detail later. There were 21 isolated non-ejection clicks (Group 2), 34 accompanied by a late systolic murmur (Group 3), and 14 by a “pathological” murmur (Group 4). The clicks were loudest at the apex or left sternal border and were often best heard in the left lateral position, though in 2 subjects they disappeared in this position. The timing of the clicks commonly varied slightly with respiration and they were often about 0·02 sec. earlier during inspiration. In 2 cases clicks disappeared with inspiration. In 3 patients there was a marked spontaneous movement of the clicks, independent of respiration or change of posture. Two or more clicks were recorded in 12 patients though the additional clicks were frequently transient. Most non-ejection clicks were situated well after mid-systole and there was no difference in their timing or character within the 3 groups. In
the presence of a late systolic murmur, the click commonly occurred at or near its onset (Fig. 3).

Changes in the timing and intensity of non-ejection clicks in response to the same vasoactive manoeuvres were assessed in patients from Groups 2, 3, and 4. Thirty-eight phonocardiograms were satisfactory for analysis during a Valsalva manoeuvre, 38 with amyl nitrite and 28 with phenylephrine. In 2 patients with amyl nitrite inhalation and 1 with phenylephrine injection, the clicks disap-

Fig. 4.—Phonocardiograms of an 8-year-old girl in group 3, showing the effect of haemodynamic alterations on the late systolic murmur. During amyl nitrite inhalation and the straining phase of the Valsalva manoeuvre, the murmur softens and moves earlier in systole. The delayed return of the murmur to control intensity after release of the Valsalva is demonstrated. After phenylephrine injection, the murmur becomes louder but its position in systole is essentially unchanged.

FIG. 5.—Late systolic murmur and non-ejection click in a 13-year-old boy recorded in the supine and erect positions. On standing, the murmur becomes louder and pansystolic, with accentuation near mid-systole. The click increases slightly in intensity and moves to a position (0.04 sec. after M) compatible with an ejection click.
peared and movement could not be assessed. The responses of the clicks to the vasoactive procedures were again similar within the 3 groups. The majority moved earlier and softened with amyl nitrite or the Valsalva manoeuvre whereas after phenylephrine the alterations were inconstant.

Non-ejection clicks moved earlier in systole (Fig. 5) in all but 2 of 21 subjects auscultated in the erect position. In these 2 patients the clicks disappeared so movement could not be assessed. Alteration in intensity was variable but the majority of clicks became louder. Phonocardiograms, recorded in 15 cases, confirmed the clinical observations.

Intracardiac phonocardiograms from the left ventricle recorded the non-ejection clicks in all 6 patients tested.

The post-valvotomy clicks differed from the other non-ejection clicks. They were of lower frequency, louder, and less clicking in quality. They commonly occurred in early systole in a position compatible with that of an ejection click or a component of the first heart sound. However, they were identified as non-ejection clicks by their variable timing (Fig. 6 and 7) and by their frequent spontaneous movement into mid-systole (Fig. 6A and 7B). Neither the phase of respiration, the position of the patient, vasoactive manoeuvres, nor the length of the preceding diastolic period in the 3 patients with atrial fibrillation, had a constant effect on the timing or intensity of these clicks. Phonocardiograms revealed that post-valvotomy clicks sometimes comprised several vibrations which would divide spontaneously into 2 or more single vibrations (Fig. 6A and 7A). All 6 patients had systolic murmurs of mitral insufficiency. The timing and intensity of these murmurs were also variable. They usually followed the clicks, and early systole could thus be silent when a click spontaneously moved to mid-systole (Barlow, 1965). In one instance, the systolic murmur ended with a click in mid-systole (Fig. 7B).

**Radiological Features**

Fifty-three of the 66 patients in Groups 1, 2, and 3 had normal cardiac silhouettes. The 13 exceptions comprised 5 with congenital heart disease, 3 with left ventricular enlargement due to systemic hypertension, 1 with cor pulmonale, and 4 with left atrial dilatation, 1 of whom also had slight left ventricular enlargement. One of the 4 patients with left atrial enlargement had previously had severe mitral regurgitation, with rupture of chordae tendineae, which had been corrected surgically. Of the 18 patients in Group 4, 13 had enlargement of either the left atrium or left ventricle, or of both these chambers; 9 of these had haemodynamically sig-

ificant valvular disease, and 2 had previously had ruptured chordae tendineae with severe mitral regurgitation; the remaining 2, one of whom had mild hypertension, had ischaemic heart disease. All 6 patients in Group 5 had retained their abnormal cardiac outlines following mitral commissurotomy.

**Cardiac Catheterization and Cine-Angiocardiography**

Twenty-one patients from Groups 1, 2, and 3 had left ventricular pressures recorded, 7 of whom had left atrial pressures measured and 10 were subjected to right heart catheterization. All pressures were normal except for mild pulmonary hypertension in one patient (Group 2) with an atrial septal defect, and a gradient of 20 mm. Hg within the left ventricle in another patient (Group 3) with hypertrophic obstructive cardiomyopathy. Normal intracardiac pressures were also recorded in the 7 patients in Group 4 who were subjected to left and right heart catheterization.

Mild mitral incompetence was confirmed in the 20 patients with late systolic murmurs in Groups 1, 3, and 4, who were subjected to left ventricular cine-angiocardiography. In many instances, the regurgitation appeared to be confined to late systole. The posterior leaflet of the mitral valve was mobile in all 20 patients and billowed abnormally into the left atrium during systole in 17. The degree of billowing was regarded as mild in 8, moderate in 2, and marked in 7. Large mobile anterior leaflets were demonstrated in 7. The cine-angiocardiographic appearances of 2 patients with musical murmurs were indistinguishable from the non-musical ones. There were no detectable differences in the cases with late systolic murmurs whether they belonged to Group 1, 3, or 4. Left atrograms in 6 patients confirmed the mobility of the leaflets but were otherwise non-contributory.

The only patient with an isolated non-ejection click who was subjected to cine-angiocardiography had normal leaflets and no regurgitation.

Left ventricular cine-angiocardiograms in the 5 patients in Group 4 with pansystolic murmurs and non-ejection clicks showed moderate mitral regurgitation. In 2 of these there was considerable billowing of the posterior leaflets and in a third, a 37-year-old man with Marfan's syndrome, voluminous and extremely mobile leaflets were outlined.

Two of the 6 subjects in Group 5 had cine-angiocardiograms, but no specific appearances to account for the post-commissurotomy clicks were detected. The pathology of these 2 mitral valves (Cases 86 and 89, Table II) is discussed later in this paper.
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Fig. 6—(A) Phonocardiogram of a 31-year-old woman in sinus rhythm showing spontaneous variation in timing and intensity of the post-valvotomy clicks. A soft pansystolic murmur (SM) and opening snap (OS) are present. (B) Phonocardiogram of a 56-year-old man with atrial fibrillation. The post-valvotomy click again varies in position and intensity. P = pulmonary component of second sound; MDM = mid-diastolic murmur.

Fig. 7—(A) Phonocardiogram of the 48-year-old woman who had avulsion of the anterior head of her medial papillary muscle following closed mitral commissurotomy. In sinus rhythm at the time of recording. In the first cycle, 2 clicks, and in the next, 1 click comprising several vibrations, are shown in early systole. The mitral regurgitant systolic murmur follows the post-valvotomy clicks. (B) Phonocardiogram of the same patient as in Fig. 6A. In the second cycle the murmur ends with a loud post-valvotomy click.
Coronary arteries were usually outlined during left ventriculograms and no abnormalities were observed. The direct coronary arteriograms in 2 subjects in Group 3 appeared normal.

**Electrocardiographic Features**

Electrocardiograms were normal in 54 cases. Twenty-two patients, including all those in Group 5, had electrocardiographic abnormalities attributable to associated congenital, hypertensive, or ischaemic heart disease or to haemodynamically significant mitral or aortic valvular pathology.

The remaining 14 patients (1 in Group 1, 11 in Group 3 and 2 in Group 4) showed a characteristic electrocardiographic pattern suggestive of postero-inferior myocardial ischaemia or infarction (Fig. 8). The typical pattern consisted of small Q waves, elevated S-T segments, and inverted T waves in leads II, III, and AVF (Fig. 8B). Similar changes in lead V6, and sometimes also in V5, suggested anterolateral extension. Tall T waves were sometimes present in the mid-praeordial leads. One patient, a 17-year-old boy with a late systolic murmur and click, had very deep Q waves compatible with severe infarction (Fig. 8C). The mildest degree of the abnormality consisted of flattened or inverted T waves in leads II, III, and AVF, producing a frontal plane QRS-T angle of more than 60° (Fig. 8A). Post-exercise electrocardiograms recorded in 2 of the 14 patients showed no change. Repeat electrocardiograms at 6-monthly to yearly intervals in 11 patients were unaltered in 8 but slightly improved in 3. Ectopic beats were detected at some stage in 5 of the 14 patients, and 2 had a P-R interval longer than 0·20 sec.

In 3 patients, all younger than 40 years, electrocardiograms were normal but transient episodes of atrial fibrillation were recorded. Two had isolated clicks and the third had a late systolic murmur and click. One of the patients with an isolated click was the father of the 8-year-old girl who had a late systolic murmur and click together with a typical electrocardiographic pattern (Fig. 8B).

**Discussion**

At the end of the last century Griffith (1892), and later Hall (1903), suggested that an apical late systolic murmur denoted mitral regurgitation. However, following the teachings of Lewis (1918) and Mackenzie (1925), systolic murmurs unaccompanied by other evidence of heart disease were regarded as of no consequence, and Evans (1943) emphasized the innocence of late systolic murmurs. This view gained wide acceptance and murmurs confined to late systole were, until recently, regarded as innocent (Wells, 1957; Shabetai and Marshall, 1963; Segal and Kalman, 1964) and probably of extracardiac origin (McKusick, 1958; Leatham, 1958a; Vogelpoel et al., 1959; Butterworth et al., 1960; Humphries and McKusick, 1962; Fowler, 1962; Deuchar, 1964). The common association of so-called "mid-late" systolic clicks with these murmurs has long been recognized. In 1913, Gallavardin attributed such clicks to pleuroperi-
cardial adhesions, and the theory of an extracardiac origin eventually became so firmly established (Johnston, 1938; Wolfert and Margolies, 1940; Lian, 1948; Luisada and Alimurung, 1949; Reid and Humphries, 1955; McKusick, 1957; Leatham, 1958b; Humphries, 1962) that it was regarded (McKusick, 1957) as evidence for a similar origin of the frequently associated late systolic murmurs. An exception to the general trend of opinion was Paul White (1931) who suggested that mid-systolic sounds might sometimes arise from abnormal chordae tendineae. Reid (1961) revived the postulate that mid-late systolic clicks and late systolic murmurs were of mitral valvular origin. Recent evidence (Barlow et al., 1963; Segal and Likoff, 1964; Barlow, 1965; Pocock et al., 1965; Ronan, Perloff, and Harvey, 1965; Kesteloot and Van Houte, 1965; Tavel, Campbell, and Zimmer, 1965; Criley et al., 1966; Linhart and Taylor, 1966; Hancock and Cohn, 1966; Leighton et al., 1966; Leon et al., 1966; Stannard et al., 1967) supports our belief that these late systolic murmurs always denote mitral incompetence and that the clicks are intracardiac, and probably chordal, in origin.

The late systolic murmur of mitral incompetence has a characteristic cadence and may periodically develop a musical intonation. Where a non-ejection click accompanies it, the murmur is even more easily recognized. Other murmurs may bear some resemblance to late systolic murmurs but can be distinguished (Barlow and Pocock, 1965) by differences in their character and site of maximal

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**Fig. 8.—Electrocardiograms of 3 patients in group 3.**

(A) A 6-year-old boy who had moderate billowing of the posterior leaflet in cine-angiocardiography. The T wave is inverted in lead III and flattened in AVF producing a mean frontal plane QRS–T angle of at least 80°.

(B) An 8-year-old girl (the same case as shown in Fig. 4) with a billowing posterior leaflet on cine-angiocardiography. Small Q waves and inverted T waves are present in leads III and AVF; in lead II the T wave is biphasic. (C) The most severe electrocardiographic pattern represented by a 17-year-old boy who refused cine-angiocardiography. Deep Q waves in leads II, III, AVF, and V4 to V6, and tall T waves in the mid-precordial leads are compatible with postero-inferior myocardial infarction with antero-lateral extension.
intensity as well as by associated diagnostic physical signs. Non-ejection clicks should not be confused with the extracardiac clicking sounds heard in mediastinal emphysema (Hamman, 1945), which are crunchy and have a superficial crackling quality. Systolic clicking sounds may also occur with left pneumothorax (Scadding and Wood, 1939) but are very variable with both respiration and posture and are, of course, transient. In addition, other features of pneumothorax are apparent.

There are insufficient anatomical data from patients with late systolic murmurs and non-ejection clicks to explain unequivocally the pathogenesis of the mitral valvular lesion or the mode of production of the auscultatory features. No patient of ours with a late systolic murmur has come to necropsy, but one of Dr. B. van Lingen's, a 39-year-old man with phonocardiographic confirmation of a late systolic murmur and non-ejection click, died suddenly while mowing a lawn: no cause of death was established at necropsy nor was any coronary artery abnormality detected. We later examined the mitral valve which had an extremely voluminous posterior leaflet and thin elongated chordae tendineae (fig. 9). The remarkable size of this leaflet accords with the cine-angiographic appearances in many other cases with these auscultatory signs. One of our patients with an isolated non-ejection click, a 63-year-old woman (Case 22, Table II), died from polyarteritis nodosa, and necropsy showed ischaemic fibrosis of both papillary muscles. Three patients (Cases 52, 74, and 78, Table II) who had severe mitral incompetence due to ruptured chordae tendineae were treated by insertion of nylon chordae (Marchand et al., 1966) and developed non-ejection clicks postoperatively. Two of these patients also have late systolic murmurs and the third has a grade 1 apical pansystolic murmur. Six other patients, 5 of whom (Cases 9, 24–27, Table II) have been previously documented (Barlow, 1965), provide further anatomical evidence for the mitral origin of late systolic murmurs and clicks. The sixth patient, a 4-year-old Bantu child (Case 46, Table II) with a ventricular septal defect, developed heart block and a late systolic murmur and click after radio-opaque dye had inadvertently been injected directly beneath her posterior leaflet. This morphological evidence confirms that late systolic murmurs are sometimes associated with voluminous posterior leaflets of the mitral valve, and that the non-ejection clicks may be associated with pathological changes in the chordae tendineae or papillary muscles.

A mitral regurgitant murmur confined to late systole or, when pansystolic, accentuating in late systole, implies that the valve is incompetent only or maximally at that time. Such late systolic regurgitation cannot be explained on a pressure basis because the gradient between the left ventricle and left atrium is then rapidly decreasing; a fact that caused Leatham (1960) to doubt the intracardiac origin of late systolic murmurs. However, Criley and associates (1966), using left ventricular cine-angiography and a simultaneous electrocardiographic timing device, have now conclusively demonstrated the late systolic regurgitation, and the explanation must rest upon the functional anatomy of the mitral valve mechanism. These workers have shown that maximal billowing of the posterior leaflet coincides with the click in mid-late systole. This would be the time when an elongated chorda is put on stretch and the observation is therefore compatible with the postulate that clicks are chordal in origin. Prominent billowing of the posterior leaflet, without mitral regurgitation, has been noted (Criley et al., 1966; Stannard et al., 1967) in patients with isolated non-ejection clicks. Billowing of the posterior leaflet was not seen in 3 of our 20 patients with late systolic murmurs who were subjected to cine-angiography, nor in our only patient with an isolated click who had this investigation, but it is possible that in these instances the billowing is localized and therefore not demonstrable angiographically.

We have shown that non-ejection clicks and late systolic murmurs move earlier under certain conditions. The changes in timing and length of late systolic murmurs and in the position of non-ejection clicks, produced by the adoption of the erect position and by some vasoactive manoeuvres, must depend on alteration in the functional anatomy of the valve mechanism. This in turn will be affected by differences in left ventricular end-diastolic volume and in the time-sequence and force of papillary muscle and ventricular wall contraction. Amyl nitrite inhalation, the straining phase of the Valsalva manoeuvre, and the adoption of the erect posture, all of which result in a decreased end-diastolic volume, cause late systolic murmurs to move earlier in systole. In the former two instances the murmur is softer, and this is perhaps due to the accompanying hypotension. With the adoption of the erect posture, however, the murmur is both louder and longer. This change may depend on both the rise in blood pressure and the augmented force of ventricular contraction produced by the increased sympathetic activity in this position (Tuckman and Shillingford, 1966), and we have observed (J. B. Barlow and W. A. Pocock, unpublished data) a similar effect during anxiety or after the intravenous infusion of the sympathomimetic drug, isoprenaline. It is noteworthy that the administration of phenylephrine,
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which produces systemic hypertension but has little inotropic action or effect on left ventricular end-diastolic volume (Beck et al., 1961), causes the murmurs to become louder without significantly changing their configuration. The earlier movement of non-ejection clicks in response to amyl nitrite, to the Valsalva manoeuvre, to the adoption of the erect posture, and to inspiration probably also depends on a decrease in end-diastolic left ventricular volume and consequent altered functional anatomy of the mitral valve. A similar mechanism would account for the earlier position of a click during atrial fibrillation as opposed to sinus rhythm (Barlow, 1965). The failure of phenylephrine to have a constant effect upon the timing of clicks could be predicted because its action does not significantly alter the position or configuration of late systolic murmurs but simply increases their intensity. In summary, it appears that a decreased end-diastolic ventricular volume is present in circumstances where the murmurs and clicks move earlier in systole. Changes in pressure and the force of myocardial contraction are the main factors influencing the intensity of murmurs, whereas changes in intensity of clicks do not correlate with pressure factors and are apparently influenced by differences in the end-diastolic volume and in the force of myocardial contraction.

The differences between post-valvotomy and other non-ejection clicks are difficult to explain. The mitral valves were examined in 3 patients (Cases 86, 89, and 90, Table II) who had had postcommissurotomy clicks. A common feature in all was immobile leaflets with shortening and thickening of some chordae, while other, more normal ones, remained mobile and longer. Because the valve leaflets are rigid, maximal tension might be reached in the relatively normal chordae earlier than in the case of mobile valves associated with other non-ejection clicks, and the resulting click would occur earlier. In view of the early position of most post-valvotomy clicks and the fact that other clicks may at times move into the first half of systole, the commonly used term “mid-late” is inaccurate and misleading. The term “non-ejection” was therefore introduced (Barlow, 1965) to describe these sounds.

It is our contention that a non-ejection click denotes uneven distribution of tension in the chordal mechanism and that one or more chordae are lengthened or are relatively longer than other fibrosed chordae. Similarly, with late systolic murmurs, we believe that chordae are invariably lengthened, functionally lengthened, or ruptured. In either instance the leaflet to which such chordae attach probably always billows abnormally to a greater or lesser degree. This billowing is accompanied by an increase in surface area of the leaflet and, though this may affect the anterior leaflet, the available evidence suggests that it is the posterior leaflet which is chiefly involved. Unlike the anterior leaflet, the posterior leaflet has chordae of the third order (Chiechi, Lees, and Thompson, 1956) which insert into the central portion of its ventricular surface (Du Plessis and Marchand, 1964). Such central insertion is presumably required for support of the posterior leaflet, and elongation or rupture of these chordae could allow the central portion of the

Fig. 9.—Posterior leaflet of the 39-year-old man with a late systolic murmur and click who died suddenly during mild exercise. The valve is viewed from the atrial aspect. At necropsy the voluminous leaflet was inadvertently cut and this has been sutured. The chordae are thin and elongated. PL = posterior leaflet; LA = left atrial wall.
leaflet to billow, in the same way as the anterior leaflet billows naturally. Indeed, Stannard and co-workers (1967) have now demonstrated experimentally that billowing of the posterior leaflet is produced when these chordae are cut. Once the prolapse has started, the process, following La Place's law, should be progressive and the leaflet would stretch and become more voluminous. Furthermore, it is reasonable to presume that greater strain would then be thrown onto chordae of the first and second order, and it is possible that it is only when these chordae, which control the leaflet edges, are stretched that mitral regurgitation ensues.

This concept would explain how diverse aetiological factors (Fig. 10) could result in a billowing posterior leaflet with mitral regurgitation. Elongated and ruptured chordae are suspected in the 2 patients who developed a late systolic murmur after trauma. In one (Case 46, Table II) this followed the injection of contrast medium beneath the posterior leaflet, and the other, a 56-year-old man, had sustained a crush injury of the chest. In 2 patients with Marfan's syndrome, involvement of the mitral valve by the disorder of connective tissue has presumably resulted in elongated chordae and voluminous leaflets, features well recognized in this condition (McKusick, 1955; Raghib et al., 1965). A similar defect of the valve may apply in the 5 patients who have no skeletal manifestations of Marfan's syndrome but are either related to each other or have close relatives with non-ejection clicks. Such familial incidence of late systolic murmurs and non-ejection clicks has previously been recognized (Barlow, 1965; Barlow and Bosman, 1966; Linhart and Taylor, 1966; Hancock and Cohn, 1966; Leighton et al., 1966; Stannard et al., 1967). A similar congenital weakness of the valve mechanism might be a factor in some of the 17 patients in whom no cause is apparent. True or functional lengthening of chordae may occur with rheumatic endocarditis, and this aetiology is suspected in 13 patients in Groups 1 and 3 on the basis of a positive history, and in 7 patients (Cases 67–73, Table I) in Group 4 because of associated “pathological” murmurs. Myocardial ischaemia producing papillary muscle dysfunction (Phillips, Burch, and De Pasquale, 1963) or possibly dysfunction of the ventricular myocardium adjacent to the posterior leaflet, the site of origin of some chordae of the third order, is favoured as causing functionally lengthened chordae in 3 patients. Unequal length of chordae in the 3 patients (Cases 52, 74, and 9, Table II) who developed late systolic murmurs after operation for severe mitral regurgitation is readily understandable. The unusual finding of a typical late systolic murmur of mitral regurgitation in a patient with proven hypertrophic obstructive cardiomyopathy is unique in our experience of 90 cases of that condition (Tucker et al., 1966). This observation can perhaps be explained by inequality of chordal length resulting from the asymmetrical muscular hypertrophy. Of the 21 patients with isolated systolic clicks in Group 2, 3 were thought to be rheumatic, 3 secondary to papillary muscle dysfunction, one of whom had polyarteritis nodosa (Case 22, Table II), and in 4 a familial factor was present. No cause could be found in 11 patients and included among these are the 2 patients with secundum atrial septal
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defects, an association also noted by Hancock and Cohn (1966).

The combination of a late systolic murmur of mild mitral incompetence, a non-ejection click, and billoving of the posterior leaflet, together with a characteristic electrocardiographic pattern (Fig. 8), constitutes a specific syndrome. This “auscultatory-electrocardiographic” syndrome (Barlow, 1965; Barlow and Bosman, 1966) has now been studied by others (Hancock and Cohn, 1966; Stannard et al., 1967), but the electrocardiogram, which is compatible with postero-inferior myocardial ischaemia, has yet to be explained. We have considered (Barlow and Bosman, 1966) the possibility that the circumflex branch of the left coronary artery might be distorted or occluded in the atroventricular groove as a result of the billowing posterior leaflet, but no coronary abnormality has been demonstrated by arteriography (Stannard et al., 1967). Hancock and Cohn (1966), who recently emphasized the high incidence of this electrocardiographic pattern in their patients with late systolic murmurs and clicks, suggested that it might be related to potassium depletion and hyperventilation. However, there is no evidence to support this, and the cause of the abnormal electrocardiogram remains unknown. Although it is our impression that leaflet billowing is usually more pronounced in patients with the most widespread electrocardiographic change, pronounced billowing can occur with a normal electrocardiogram (Criley et al., 1966). Conversely, mild billowing with an abnormal electrocardiogram was present in 2 patients in this series. It is tempting to suggest that primary coronary artery disease results in myocardial ischaemia, functional lengthening of chordae, and consequent mitral insufficiency, but the occurrence of this electrocardiographic pattern in children, and of auscultatory signs without electrocardiographic changes in relatives of patients with the syndrome (Barlow and Bosman, 1966), are against this postulate. Furthermore, the electrocardiographic pattern has been observed in Marfan’s syndrome (Bowers, 1961; Segal, Kasparian, and Likoff, 1962), a condition in which mitral valve pathology is well recognized but primary papillary muscle or myocardial pathology is rare (Bawa, Gupta, and Goel, 1964). A history of chest pain was obtained in a number of our patients and has also been noted by others (Tavel et al., 1965; Hancock and Cohn, 1966; Stannard et al., 1967). The pain was usually ill defined and fleeting but was indistinguishable from angina in 2 of our patients. One of these, a 22-year-old woman in Group I with the typical electrocardiographic pattern, developed more widespread T wave inversion during an attack of “angina” a few hours after cardiac catheterization.

Differentiation between this “auscultatory-electrocardiographic” syndrome and occlusive coronary artery disease with postero-inferior myocardial ischaemia and secondary papillary muscle dysfunction may be difficult or impossible. We believe that only one patient in our series falls into the latter group. He was a 46-year-old man with an isolated click who gave a history of angina dating from an acute episode 2 years previously. At that time serial electrocardiograms had shown typical evolution and regression of the infarct pattern and had been accompanied by increased serum transaminase levels. The non-ejection click and the electrocardiogram have not changed during the 2 years of observation. There are 2 other patients over 45 years of age with postero-inferior electrocardiographic abnormalities, late systolic murmurs, and non-ejection clicks, both of whom have been discussed in an earlier communication (Barlow and Bosman, 1966). One, a 48-year-old woman, has several relatives with late systolic murmurs or clicks, whereas the other, a 56-year-old woman, has known of a cardiac abnormality since the age of 23. These are reasons for believing that both have the “auscultatory-electrocardiographic” syndrome rather than primary occlusive coronary artery disease. Nevertheless, it is apparent that differentiation is difficult in patients in the older age-group and must depend upon ancillary evidence.

There is a significant incidence of arrhythmias in patients with late systolic murmurs and clicks. Atrial fibrillation and ectopic beats, either atrial or ventricular, have been observed in this and other series (Hancock and Cohn, 1966; Leighton et al., 1966; Stannard et al., 1967). Atrial flutter and short runs of ventricular tachycardia have also been reported (Hancock and Cohn, 1966). Sudden death, possibly related to arrhythmias, occurred in 2 close relatives of the 17-year-old boy with an abnormal electrocardiogram (Fig. 8C). The death during exercise of the 39-year-old man, whose extremely voluminous posterior leaflet is shown in Fig. 9, has been mentioned. Unfortunately his electrocardiogram is unobtainable, but standard lead II of the simultaneous electrocardiogram on the phonocardiogram shows T wave inversion. The recent report by Hancock and Cohn (1966) of the sudden death of a 29-year-old woman with this syndrome confirms the uncertain prognosis. We have used propranolol to treat some patients. Chest pain has been lessened, and it is hoped that the incidence of fatal arrhythmias will be reduced. Irrespective of any electrocardiographic abnormality, the prognosis of patients with late systolic murmurs must remain guarded at the present time. Complicating bacterial endocarditis has been encountered...
by us and by others (Facquet, Alhomme, and Raharison, 1964; Linhart and Taylor, 1966), and a change in the murmur from late to pansystolic has been observed (Facquet et al., 1964). Prophylaxis against bacterial endocarditis is therefore advisable, and where a rheumatic aetiology is suspected, long-term penicillin should be administered. The haemodynamic disturbance in subjects with late systolic murmurs is minimal and may well remain so for many years. On the basis that “mitral insufficiency begets mitral insufficiency” (Edwards and Burchell, 1958; Levy and Edwards, 1962), however, it is possible that the regurgitation will progress to severe mitral incompetence with or without ruptured chordae tendineae (Marchand et al., 1966; Barlow et al., 1967). We have noted marked billowing of the posterior leaflet in patients with late accentuating pansystolic murmurs and, furthermore, voluminous leaflets have been found at operation and necropsy in patients with pure severe mitral incompetence (Marchand et al., 1966; Barlow et al., 1967), some of whom are known to have had systolic murmurs for many years. We have witnessed this progression in only one patient, a 37-year-old man (Case 84, Table I) with Marfan’s syndrome.

**Summary**

Studies were made of 90 patients with either a late systolic murmur (15), a non-ejection systolic click (37), or both (38). Cine-angiocardiology, the responses of the auscultatory signs to vasoactive manoeuvres, intracardiac phonocardiology, and anatomical evidence confirm that late systolic murmurs denote mild mitral incompetence and suggest that non-ejection clicks result from functionally unequal length of chordae tendineae. From the fairly constant pattern of response of late systolic murmurs and non-ejection clicks to haemodynamic alterations (erect posture, amyl nitrite, phenylephrine, the Valsalva manoeuvre, anxiety, and isoprenaline), the factors that affect the functional anatomy of the mitral valve mechanism, and hence the intensity and timing of the murmurs and clicks, can be determined.

An abnormally billowing mitral posterior leaflet is often demonstrated cine-angiocardiographically in patients with late systolic murmurs. A voluminous posterior leaflet was observed at necropsy in one case. A not infrequent association of this posterior leaflet anomaly with an abnormal electrocardiographic pattern, the appearances of which suggest postero-inferior myocardial ischaemia, constitutes a specific “auscultatory-electrocardiographic” syndrome. The prognosis of this syndrome is uncertain and sudden death may occur. The cause and explanation of the electrocardiographic changes still require elucidation.

Diverse aetiological factors affecting the mitral valve mechanism can result in a late systolic murmur or non-ejection click. These include direct or indirect trauma, rheumatic endocarditis, Marfan’s syndrome, hypertrophic obstructive cardiomyopathy, myocardial or papillary muscle ischaemia, and mitral valve surgery. Although in many instances no aetiological factor has been incriminated, in some of these an hereditary factor exists. Irrespective of the aetiology, it is believed that functional inequality of chordae and an abnormal degree of leaflet billowing occur in all patients with late systolic murmurs or non-ejection clicks. The possibility that these changes may progress to cause more severe mitral regurgitation is briefly discussed.

An unusual form of non-ejection systolic click, occurring early in systole but varying spontaneously in timing, developed after mitral valvotomy in 6 patients. Such “post-valvotomy clicks” have hitherto seldom been recognized and have to be distinguished from components of the first sound and from ejection clicks.

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