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THE DIASTOLIC MURMUR OF MITRAL STENOSIS*

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BECAUSE of the great interest currently demonstrated in the surgical correction of mitral stenosis, it has become essential for the clinician to be able to diagnose this condition with the greatest possible accuracy and also to estimate the degree of disability caused by it. A thorough knowledge of the murmurs of mitral stenosis and of the variations in these murmurs under different physiologic and pathologic conditions should be of assistance in diagnosis. It is our purpose to present in this paper a brief history of the murmurs of mitral stenosis and various factors affecting these murmurs, as well as brief discussions of the opening snap and the third heart sound. We conclude with a summary of factors affecting the detection of the diastolic murmur of mitral stenosis and of factors in clinical examination that will aid in its detection.

DESCRIPTIVE HISTORY

A review of the descriptive history of the diastolic murmur of mitral stenosis indicates that during the past fifty years little has been added to knowledge of its cause and only minor points have been contributed to its clinical description.

Laënnec[1,2] gave impetus to auscultatory investigation by his invention of the stethoscope in 1819. For the next fifty years, French, German and English physicians recorded their impressions, which were frequently erroneous, to be sure, but contained surprisingly often the germ of what appears presently to have been the truth.

Foremost in the French assemblage were Gendrin,[3] Fauvel,[4] Beau,[5,6] Hérard,[7] Bouillaud,[8,9] Lemaire[10] and Racle.[11] The Germans were represented by Constatt,[12] Wintrich,[13] Friedrich,[14] Felix von Niemeyer[15] and Paul Niemeyer,[16] who patterned their investigations along similar lines. Concurrently, contributions from the British Isles were made by Hope,[17] Williams,[18] Markham,[19] Walshe[20] and Gairdner[21-23] and from America by Austin Flint.[24-33]

The English physician, James Hope,[17] in 1832, described the murmurs as follows:

> . . . murmurs are not, as is often supposed, louder, *caeteris paribus,* in proportion as the valvular contraction is greater. On the contrary, the loudest murmurs are produced by a moderate contraction, and they become weak when it is extreme . . . a contraction of the mitral or tricuspid valve to only two, three, or four lines [one line = *1/12* inch] in diameter, I have frequently known to occasion little or no murmur.

In 1841, Gendrin,[3] of the French group, first used the term presystolic. Two years later, Fauvel[4] was the first to demonstrate that the murmur of mitral stenosis was presystolic. Hérard,[7] who closely followed Fauvel in his writings, seems to have been well aware of the effects of atrial fibrillation and congestive heart failure on the murmurs of mitral stenosis.

The early German literature on the mitral diastolic murmur closely followed the patterns of the French. These writings were well reviewed in 1872 by Fagge.[34]

Much of the early British concern with cardiac murmurs was voiced by the writers mentioned above. Hope[17] early recognized that the intensity of an apical diastolic murmur did not necessarily indicate the degree of mitral stenosis. Williams[18] distinguished the diastolic murmur of mitral stenosis from that of aortic regurgitation, and Markham[19] described the loud apical first heart sound in some cases of mitral stenosis. Later, Gairdner,[21-23] of Scotland, introduced the concept that the presystolic part of the murmur of mitral stenosis was due to atrial systole.

Concurrently with the investigation of Gairdner[21-23] in Scotland, Austin Flint,[24-33] in the United States, was following a similar line of thought and was writing extensively on the presystolic murmur, but he paid little attention to the murmur occurring during mid-diastole.

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Various Factors Affecting the Murmurs

Effect of Change of Rhythm on the Presystolic Murmur

Fagge[34] was one of the first to note that the presystolic murmur could be altered by a change in rhythm. In his treatise he reported a case in which the heart was liable to sudden changes in rhythm, from regularity to a bigeminy, with probable dropping of every third beat and corresponding changes in the mid-diastolic and presystolic murmurs.

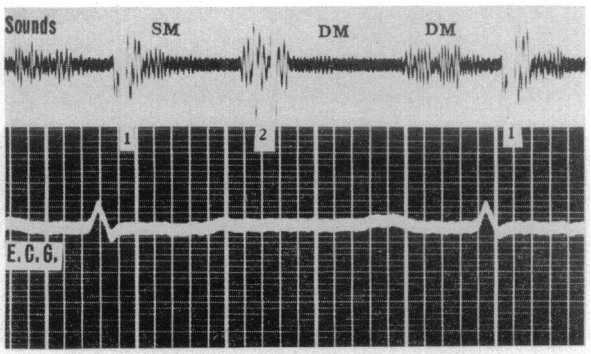

FIGURE 1. *Apical Tracings in M.B., a Forty-four-Year-Old Woman with a History of Rheumatic Heart Disease since Childhood and Considerable Limitation of Activity during the Last Few Years.*

The phonocardiogram shows the effect of a long PR interval on the atrial systolic murmur (DM), which becomes late diastolic rather than presystolic.

The first diastolic murmur (DM) is a rumbling, low-pitched, low-intensity murmur occurring around the time of the normal third heart sound.

The second diastolic murmur (DM) is equivalent to an atrial systolic murmur that follows the P wave of the electrocardiogram (E.C.G.) and is separated by a considerable interval from the first heart sound.

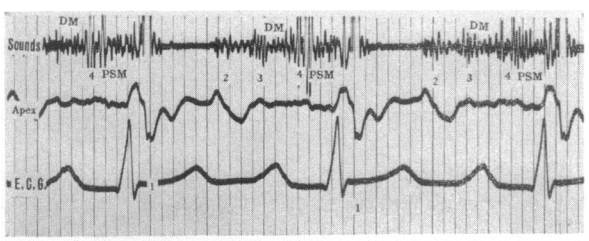

FIGURE 2. *Apical Tracings in M.A., a Twenty-two-Year-Old Man with Rheumatic Heart Disease and Mitral Stenosis.*

The phonocardiogram illustrates the fact that with intense atrial activity and a slightly prolonged PR interval (0.26 second), a presystolic gallop (4) may be present together with a presystolic murmur (PSM), which is thus not crescendo in type. If the PR interval had been normal, the murmur would doubtless have been a presystolic crescendo.

The earlier part of the diastolic murmur (DM) becomes evident at the time of the third heart sound (rapid ventricular filling) although it starts before it at the opening of the mitral valve.

Effect of First-Degree Heart Block on the Presystolic Murmur

Galabin,[35] using a modification of Marey's cardiograph, found, in 1875, that in certain cases the diastolic murmur began shortly after the second sound and was separated by a short pause from the first sound (Fig. 1-3).

Effect of Second-Degree and Third-Degree Heart Block on the Diastolic Murmur

Many years after Galabin,[35] Sir Thomas Lewis[36,37] pointed out the effect of atrial systole on the mitral diastolic murmur in cases of heart block, noting that a murmur occurred with each atrial contraction (Fig. 4).

Effect of Atrial Fibrillation on the Presystolic Murmur

There is no doubt that a murmur can be heard in presystole in cases of mitral stenosis with atrial fibrillation when diastole is short. This murmur is not the atrial systolic murmur described by Gairdner[21-28] but is due simply to the falling of the first heart sound earlier than usual in diastole because of the rapid heart rate. If the rate slows, or if there is a long diastolic pause, the diastolic murmur will be found to fade off in a decrescendo fashion (Fig. 5 and 6).

The best description of this phenomenon occurs in Sir James MacKenzie's[37] detailed discussion of the subject in 1913.

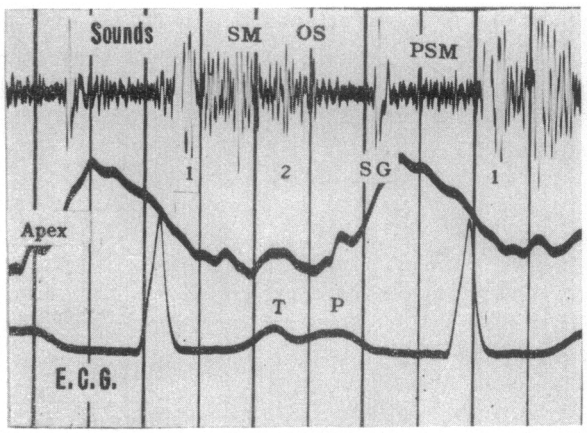

FIGURE 3. *Apical Tracings in D.M., a Nineteen-Year-Old Girl with Active Rheumatic Fever (Third Attack), Mitral Regurgitation, Mitral Stenosis, Aortic Regurgitation and First-Degree Heart Block.*

The phonocardiogram illustrates another effect of a long PR interval on the cardiac sounds. The first heart sound is moderately intense despite the long PR interval of 0.29 second. The second sound is of rather low intensity at the apex, and an opening snap (OS) of the mitral valve, consisting of several moderately high-frequency vibrations, is seen. The third heart sound is unusually prominent and is considerably louder at the apex than the second heart sound, which is to some extent obscured by the systolic murmur (SM). The atrial sound may be summated with the third heart sound and is also concerned with the murmur (PSM) that fills the interval between the third and first sounds but without presystolic crescendo. The systolic murmur is crescendo-decrescendo and fills systole. The summation gallop (SG) results from an accentuation of the normal third heart sound as a result of relatively early atrial contraction secondary to the prolonged PR interval.

Effect of Ventricular Premature Beats on the Presystolic Murmur

It is obvious that no atrial systolic murmur will be heard before the first heart sound of a ventricular premature beat, since there is no preceding atrial contraction. It is interesting that the presystolic murmur

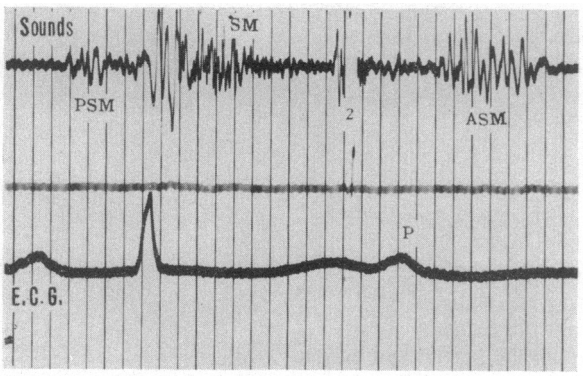

FIGURE 4. *Apical Tracings in N.M., a Sixty-five-Year-Old Woman with a Long History of Hypertension and Complete Heart Block.*

There was no definite history of rheumatic fever. The phonocardiogram demonstrates the fact that atrial systole is capable of causing a loud atrial systolic murmur (PSM) and (ASM) and that its position in diastole varies with the position of the P wave of the electrocardiogram.

resulting from atrial contraction may also be absent in the beat that follows the ventricular premature beat. A possible explanation for this is the fact that, owing to the long compensatory pause, the left ventricle may become filled with blood so that the atrium cannot push enough extra blood through the mitral orifice in late diastole to create a murmur (Fig. 7).

Effect of the Valsalva Maneuver on the Diastolic Murmur of Mitral Stenosis

It has been shown that the mitral diastolic murmur can be affected in many different ways, depending on variations in cardiac rhythm. It is also possible to alter the murmur considerably by such a simple maneuver as forced expiration against a closed glottis (Valsalva's maneuver). The positive pressure that develops within the thorax decreases venous return and in turn decreases flow through the mitral-valve orifice. The enlarged left atrium continues to beat forcibly, and a presystolic murmur may be converted into an atrial sound, giving a presystolic gallop (Fig. 8*A* and *B*).

Effect of Exercise and Change of Position on the Diastolic Murmur of Mitral Stenosis

Friedrich[14] stated in 1867 that a dull or reduplicated diastolic tone could frequently be converted into a distinct diastolic murmur when a patient was made to walk up and down to accelerate the heart's action.

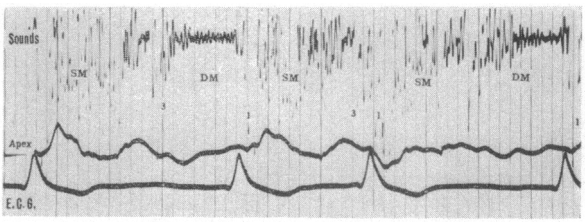

FIGURE 6. *Apical Tracings in L.S., a Thirty-two-Year-Old Woman with Rheumatic Heart Disease, Mitral Stenosis, Mitral Regurgitation, Aortic Regurgitation (Slight) and Atrial Fibrillation.*

The phonocardiogram demonstrates the great variability in the diastolic murmur in relation to cycle length. In the first and third cycles the murmur runs throughout diastole and is of moderate intensity. In the second cycle the third sound is followed so rapidly by the first sound of the next cycle that a crescendo effect results on auscultation.

Bramwell,[38] in 1881, further observed that "in some cases of mitral stenosis the murmur disappears when the position of the patient is altered, when he gets up, but the rhythm of the murmur does not change; it always remains presystolic." The subject of the effect of change in position (Fig. 9) was more fully studied by Gowers.[39]

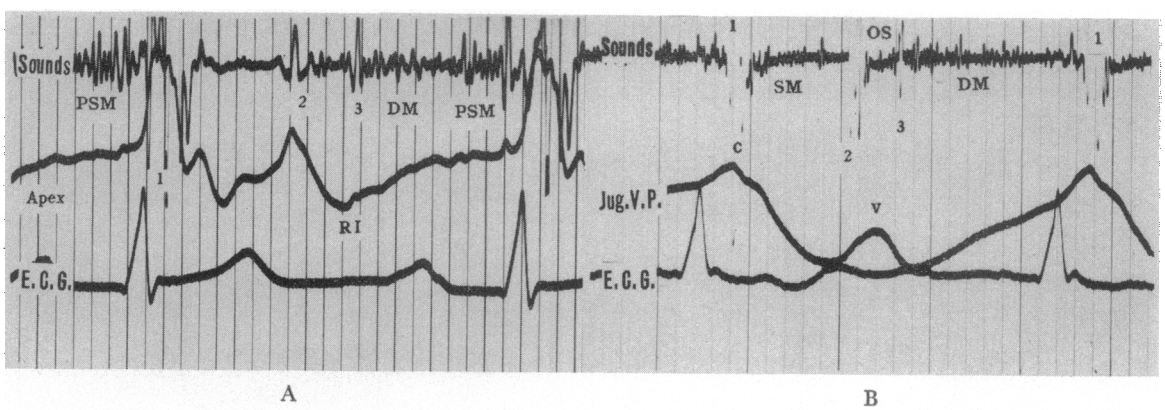

FIGURE 5. *Apical Tracings in M.A., a Thirty-two-Year-Old Man.*

The phonocardiogram (A) *demonstrates a presystolic crescendo murmur (PSM) when normal rhythm is present. (RI = rapid inflow).* B *shows phonocardiogram in the same patient after the onset of atrial fibrillation. Note that the diastolic murmur still extends into presystole but that there is no crescendo effect.*

Effect of Mitral-Valve Surgery on the Diastolic Murmur of Mitral Stenosis

Mitral-valve surgery may have no effect whatso-

ever or may affect the diastolic murmur of mitral stenosis in many ways. If there is a very slight murmur before operation, because of tight mitral stenosis, this murmur may greatly increase after operation because of the increased blood flow over the roughened and torn valve margins. Moreover, a murmur of moderate to loud intensity may be decreased after operation if the split is relatively smooth and no increased vibration results. In some cases the murmur is relatively quiet for a few weeks to a few months after operation and then seems to increase in intensity, perhaps owing to the development of further stenosis. In some patients who have been fibrillating before operation a return to normal sinus rhythm after operation may be accompanied by the return of a presystolic crescendo murmur. Conversely, in patients who have normal sinus rhythm and who fibrillate in the first few days or weeks after operation the atrial systolic murmur will disappear. The development of other bizarre rhythms will, of course, alter the murmur in various ways. It is thus seen that the effects of mitral-valve surgery on the diastolic murmur may vary greatly, as one would expect (Fig. 10*A* and *B*).

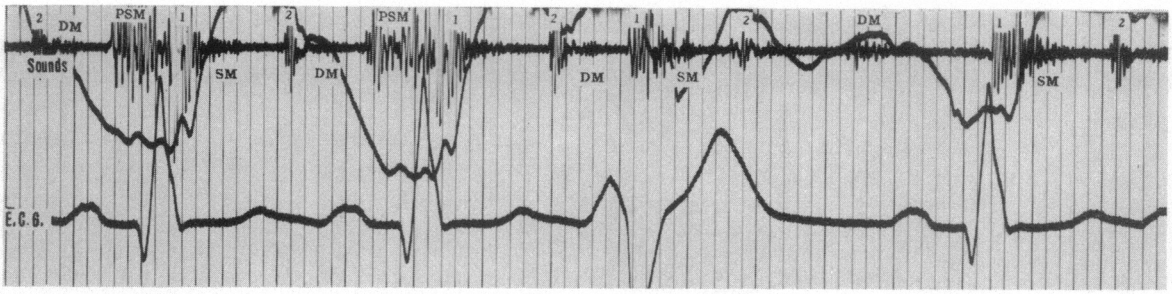

FIGURE 7. *Apical Tracing Illustrating the Absence of the Presystolic Murmur in the Ventricular Ectopic Beat and Also after the Compensatory Pause.*

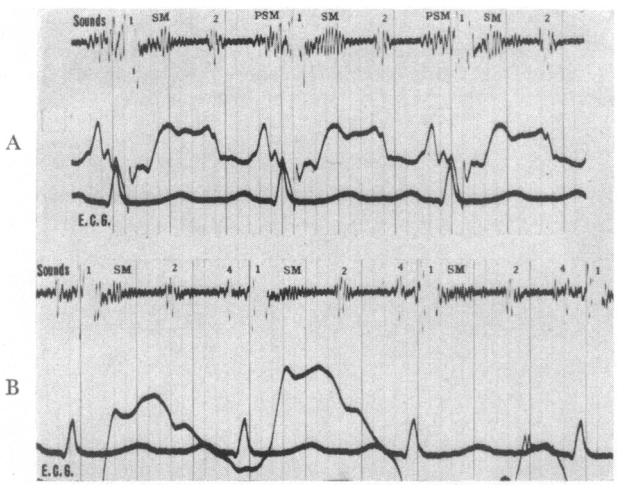

FIGURE 8. *Apical Tracing, Showing Presystolic Murmur (PSM) before the Valsalva Maneuver* (A) *and* (B) *Alteration of the Presystolic Murmur to an Atrial Sound (4), Giving a Presystolic Gallop Secondary to the Valsalva Maneuver.*

Disappearance of the Presystolic Murmur during Congestive Heart Failure

Although in 1854 Hérard[7] had described the fact that the diastolic murmur of mitral stenosis sometimes disappears during congestive heart failure, it was not until 1901 that Broadbent[40] called attention to the disappearance of the presystolic murmur in failure and presented possible causes for this, the most probable one being the establishment of tricuspid incompetence. The giving way of the tricuspid valve and the occurrence of considerable reflux into the right atrium make it impossible for the right ventricle to sustain the high pressure in the pulmonary circulation and the left atrium that was present previously.

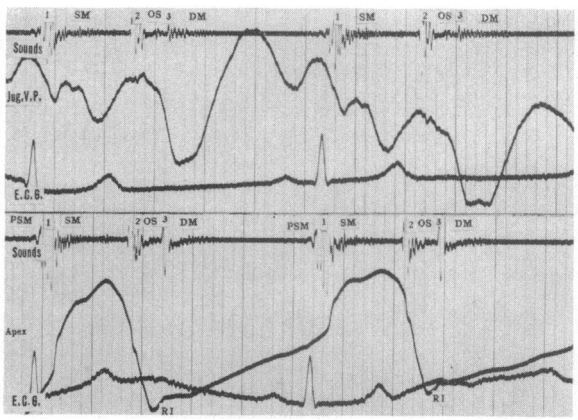

FIGURE 9. *Apical Tracings, Showing the Effect of Exercise on the Diastolic Events in a Case of Mild Mitral Stenosis. In the upper tracing the second sound can be seen followed by an opening snap and then by a third heart sound and a short diastolic murmur, which, owing to the slow heart rate, is early diastolic rather than mid-diastolic. A slight presystolic murmur is also present. After exercise (lower tracing) the only significant alteration is in the greatly increased intensity of the third heart sound. For some reason the opening snap has lessened in intensity and would doubtless be inaudible. The presystolic murmur has altered very little.*

There is not, therefore, sufficient pressure to force the blood through the mitral orifice rapidly enough to generate a murmur.

Despite the many brilliant clinical observations concerning the presystolic murmur, the theory of its causation and indeed of its actual existence was by no means universally accepted.

Ormerod,[41] in 1864, disputed the atrial systolic origin of the murmur described by Gairdner[21] on the grounds that the atrial contraction was too weak and brief to cause so loud a sound, which he held to be due rather to the contraction of the ventricle and to be regurgitant.

Barclay,[42] eight years later, maintained that the so-called presystolic murmur was really systolic and that although indicative of a contracted mitral orifice, it was regurgitant. He called attention to the absence of valves in connection with the pulmonary veins, pointed out that with no means of closing the outlet backwards, the atrium could expand but had little power to drive the blood forwards, and claimed that it "was scarcely possible that one of the loudest and roughest murmurs ever heard in cardiac disease should be produced by contraction of the auricle."

The suggestion has been made that the presystolic murmur heard in cases of mitral stenosis with atrial fibrillation is really a systolic murmur and is due to the combined effect of mitral regurgitation occurring very early in systole and followed by a delayed first sound.

Opening Snap of the Mitral Valve

The opening snap of the mitral valve may be heard in many cases of mitral stenosis. It is due simply to a delay and an accentuation of the normal fourth component of the second heart sound—that is, the opening of the atrioventricular valves. It was first described by Duroziez[43,44] in 1862, when he introduced his onomatopoeia, "ffouttatarou." The "ffout" corresponds to the crescendo presystolic murmur and ends abruptly in a snapping first heart sound; the "tata" refers to the second heart sound closely followed by the opening snap of the mitral valve, and the "rou" to the low-pitched diastolic rumble. The actual term "opening snap," or its French equivalent, was introduced by Rouches[45] in 1888 as "claquement d'ouverture de la mitrale."

A third sound coming close after the second sound may be difficult to differentiate clinically from the opening snap, but usually the opening snap, being of higher frequency than the third sound, has a high-pitched, dry quality, whereas the third sound is dull and low pitched.

Another difficulty occasionally encountered is the differentiation of an opening snap from a split second sound. There is a very short interval between the two components of a split second sound, and the components are usually of similar intensity to the ear. No reliance can be put on the fact that a split second sound is said to be heard best at the base and an opening snap at the apex. Margolies and Wolferth,[46] in 1932, pointed out that the opening snap is often best heard at the base, and we have also recorded this fact on a number of occasions.

The phonocardiogram often helps differentiate a split second sound, a second sound combined with opening snap, and a second sound together with a third heart sound or any combination of these three sounds. If a good tracing of an apex cardiogram can be obtained simultaneously with the sound tracing, differentiation is easy. However, a good apex cardiogram is not always obtainable, and time intervals may then be of some assistance.

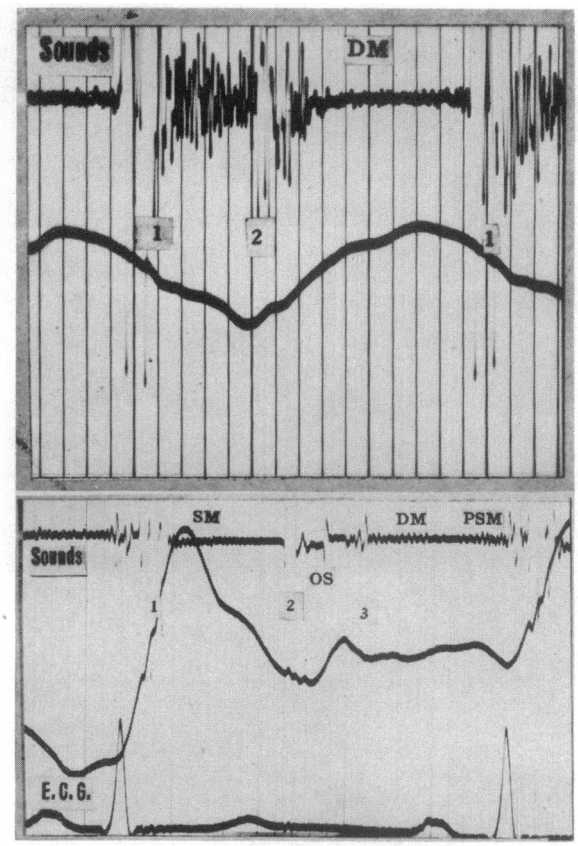

Figure 10. *Apical Tracings in D.H., a Thirty-seven-Year-Old Woman with Rheumatic Heart Disease, Mitral Stenosis and Atrial Fibrillation.*

Before operation in 1951 (A) *the patient had a very loud systolic murmur just medial to the apex, and the apical diastolic murmur could not be identified with any degree of certainty. It was thought that the systolic murmur might have been due to tricuspid incompetence* (B). *Two years after operation the systolic murmur of tricuspid regurgitation has disappeared. The rhythm has reverted to normal; an opening snap, third heart sound, diastolic murmur and presystolic with slight crescendo are now easily identified. (This patient was converted from a cardiac cripple before operation to a relatively normal, active, healthy woman.)*

In relation to the apex cardiogram, the split second sound has its second component before the 0 point (opening of the atrioventricular valves). An opening snap is synchronous with the 0 point, and a third sound occurs at the summit of the rapid inflow wave (Fig. 11*A* and *B*).

So far as time intervals are concerned, the duration between the two components of a split second heart sound is usually less than 0.07 second. The interval between the beginning of the second sound and the opening snap is at least 0.08 second, and that be-

tween the beginning of the second-sound complex and the third sound is about 0.12 second.

It is important to realize that the opening snap is one of the few signs in mitral stenosis that may persist even when the murmurs become equivocal or absent, as during atrial fibrillation or failure, or both.

In 1951 Messer et al.[47] studied the interval between the onset of the valvular component of the second heart sound and the opening snap in cases of atrial fibrillation. They found that this interval depended largely on the duration of the preceding RR interval. They also noted that the opening snap sometimes appeared closer than 0.07 second to the valvular elements of the second heart sound, emphasizing the importance of relating the duplicated second sound to the apex cardiogram for accurate interpretation of the nature of this reduplication.

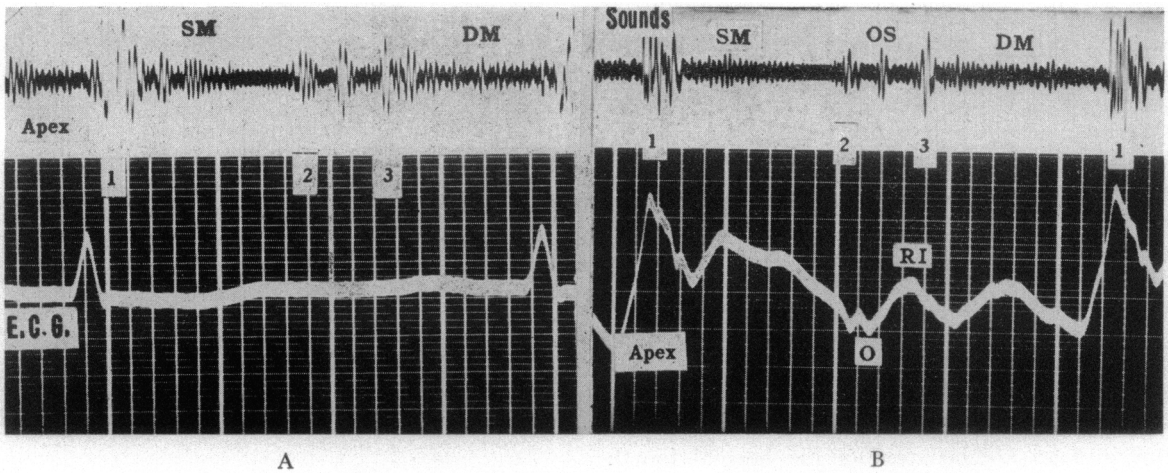

FIGURE 11. *Apical Tracings in F.O., a Sixty-nine-Year-Old Woman with Atrial Fibrillation, Minimal Aortic Regurgitation, Mitral Regurgitation and Mitral Stenosis.*

The phonocardiogram demonstrates the need for taking an apex cardiogram to be sure whether three sounds following close together in diastole are due to a split second sound combined with an opening snap or a second sound combined with an opening snap and a third sound.

In tracing A, with a simultaneous electrocardiogram, it is not possible to be certain of the origin of the sound between the second and the third heart sounds. However, in the lower tracing the apex cardiogram makes identification easy, showing the middle one of the three sounds to coincide with the valley or "0" point of the apex cardiogram. This is the opening of the atrioventricular valves and the beginning of the rapid inflow wave; hence, the intermediate sound is an opening snap. The third sound falls at the apex of the rapid inflow wave and so is a true third heart sound.

First Heart Sound in Mitral Stenosis

Accentuation of the first heart sound, giving it a loud, snapping quality at the apex, is another important and fairly common sign in mitral-valve disease. It is sometimes the first suggestion of fibrosis and early stenosis but may, of course, result from other conditions, such as exercise, thyrotoxicosis, neurocirculatory asthenia and nodal rhythm. There are many cases of long-standing mitral stenosis, however, in which the first heart sound is of low intensity or is masked by a systolic murmur that follows immediately. Accentuation of the first sound is more significant of mitral stenosis when found in association with other signs, such as an enlarged left atrium or an accentuated pulmonic second sound.

Even when the first sound is not increased in intensity it may be abnormal by phonocardiogram. This is shown by a delay of the maximum vibrations of the first heart sound in relation to the QRS complex of the electrocardiogram. This was described by Cossio and Berconsky[48] in 1943 and again by Wells[49] in 1952. Wells considered the delay to be more significant than abnormality of frequency or intensity of the first heart sound. However, in many cases of mitral stenosis, no delay can be detected. Wells[49] states that the main components of the first heart sound should occur within 0.06 second of the onset of the QRS complex and that, if they occur at 0.07 second or later, it should be classified as "late."

Third Heart Sound in Mitral Stenosis

It has been stressed that all possible aid is required to estimate the degree of disability caused by mitral stenosis. In this regard the presence or absence of a third heart sound may be of some assistance. Since it is generally accepted that the third heart sound results from the rapid inflow of blood from the left atrium to the left ventricle early in diastole, it is not unreasonable to suppose that as blood flow becomes diminished secondary to tight mitral stenosis the third heart sound progressively lessens in intensity and finally disappears. In our limited number of cases, we have found this to be true. We have also observed the converse — namely, that some patients with typical murmurs of mitral stenosis and good tonus of the left ventricle but with a prominent third heart sound have not been unduly incapacitated by

their mitral stenosis, supporting the concept that a loud, apical, third heart sound means good filling of the left ventricle. As pointed out by Hope[17] over a hundred years ago, the moderate cases of mitral stenosis often had the loudest murmur, and this may be misleading clinically since a loud mitral diastolic murmur frequently suggests to the physician or surgeon that the degree of stenosis is marked. It is suggested that the presence of a loud third heart sound at the left ventricle in the presence of the diastolic murmur of mitral stenosis indicates that the degree of stenosis is not unduly severe (Fig. 11*A* and *B*).

Factors Affecting the Detection of the Diastolic Murmur

If a loud systolic murmur is present at the apex or if a loud opening snap or loud second heart sound is heard in the same region, the diastolic murmur may be missed because of fatigue and masking effects on the human hearing mechanism. This is especially so in cases in which the diastolic rumble is low pitched or of short duration.

The murmur may be missed in the presence of tachycardia, either with regular rhythm or in the presence of atrial fibrillation or flutter.

Even though mitral stenosis may be considered to be present clinically this does not mean that the hemodynamics are identical in all cases. The valve mechanism, the size of the mitral orifice, the direction of blood flow from atrium to ventricle, the point whether the valve orifice is centrally or eccentrically placed, and the question whether the valves are moderately or greatly thickened or calcified may all be involved in varying the nature and intensity of the diastolic murmur of mitral stenosis.

Especially in patients in the older age group, the presence or absence of heart failure may cause one to miss or detect the murmur. This is particularly true in patients with a very tight stenosis.

A word of warning is necessary in the assessment of mitral stenosis based on the intensity of the apical diastolic murmur with or without presystolic crescendo. Hope[17] pointed out that moderate stenosis gives the loudest murmur and that tight mitral stenosis may exist with little or no murmur. Hérard[7] observed that in patients in failure or with rapid irregular rhythm the murmur may be absent. Other authors have emphasized the fact that many conditions other than mitral stenosis may be accompanied by an apical diastolic murmur.

We have repeatedly observed patients in the older age group with a long history of rheumatic heart disease and the clear-cut murmurs of mitral stenosis who suffer very little disability and who can do a full day's work. These patients, who often survive to a ripe old age and live full and useful lives (Fig. 11*A* and *B*), should not be subjected to surgery, which carries a definite risk at any age and a greater risk in the later decades. On the other hand, patients in failure, even without a murmur, who have an enlarged left atrium, right-axis deviation by electrocardiogram and a history of hemoptysis and perhaps even of rheumatic fever, should be very fully investigated to rule out the possibility of mitral stenosis. A loud apical first sound or the finding of an opening snap, possibly in the presence of an accentuated pulmonic sound, may be all the auscultatory evidence available to make the diagnosis in these cases.

Factors in Clinical Examination Helping Detect the Diastolic Murmur

It is essential that the physician carry out his auscultation under ideally quiet conditions.

The patient should hold his breath comfortably in moderate expiration.

As Levine and Harvey[50] have emphasized, the physician must acquire the habit of listening specifically to the individual events of the cardiac cycle. He must concentrate on the first sound to the exclusion of all else, then on the second sound, then on systole and finally on diastole. There is no other way of accurately timing murmurs and heart sounds or even of being certain of the existence of the lower-pitched murmurs and sounds.

In listening for the low-frequency mid-diastolic rumble of mitral stenosis, the bell of the stethoscope is generally more useful than the diaphragm, which tends to screen out the lower-frequency sounds so that it may enable those of higher frequency to be heard more easily.

When the bell is used, one should apply it first of all firmly to the chest wall and, while listening intently, gradually relax the pressure of the bell against the skin. A murmur at first inaudible with firm pressure may become clearly audible with light pressure. The reason for this is that firm pressure of the bell against the chest causes the skin to be stretched tightly across the mouth of the bell so that a high-frequency diaphragm is created. Relaxing this pressure converts the bell to a low-frequency recorder, and so the murmur may be heard.

Exercising the patient and turning him on his left side, a maneuver known to all physicians but not always employed, should be done in every case.

Careful searching in the area of the apex is essential, since, although some murmurs may be heard over a reasonably large area, others are often restricted to small areas of 2.5 to 5 cm. in diameter. Hence, careful and diligent listening is required in any suspected case if errors are to be avoided.

The murmur in some cases may vary, depending on such factors as heart rate, the presence or absence of atrial fibrillation and congestive heart failure and the natural progression of the disease. The murmur may thus be heard by an observer one day and not

by the same observer on the next day or even six months or a year or more later. Conversely, a patient entering the hospital in failure may have no detectable murmur, and yet, when the rate and rhythm are controlled by digitalis and by bed rest and the failure benefited by drugs, a salt-free diet and mercurial diuretics, a mid-diastolic murmur, possibly with presystolic crescendo, may become clearly audible. These changes, which may occur with varying degrees of valve damage, depend on the relation between the shape of the valve orifice and the rate of blood flow through the orifice and on whether or not turbulence results in the blood stream.

If a patient is admitted to the hospital with failure or a condition resembling cor pulmonale and no mitral diastolic murmur is heard, and if the record shows that some previous observer heard a murmur of mitral stenosis, one should not be too hasty in deciding that the earlier observer was in error. It is not impossible that as the stenosis has increased the murmur has lessened until finally it has become inaudible. We have frequently encountered this situation. In such cases, if the first sound seems too "good,"—that is, louder than appears consistent with the degree of myocardial failure,—mitral stenosis should be suspected. This is especially true if atrial fibrillation and hypertrophy of the right ventricle are present.

The presystolic crescendo of the mitral diastolic rumble is not present in all cases of mitral stenosis. This fact was pointed out by Sansom,[51-56] Johnston[57] and Battro and Braun-Menéndez.[58] Sometimes, the mid-diastolic murmur is recorded as diminuendo and may in fact almost disappear just before the first heart sound. This occurs especially during the long diastole in patients with a slow heart rate or when the atrial contraction is feeble or absent.

On the other hand, cases are often reported in which a presystolic crescendo murmur has been heard on auscultation but no abnormality of the mitral valve is detected at autopsy. Alimurung, Rappaport and Sprague[59] reviewed the causes for this phenomenon in 1949.

In any case in which an opening snap is heard, it is well to suspect mitral stenosis, even if no diastolic murmur is heard and especially if the condition clinically resembles mitral stenosis.

When a loud snapping first sound is heard at the apex with no obvious cause, such as thyrotoxicosis or neurocirculatory asthenia or nodal rhythm, one should search carefully for a mid-diastolic or presystolic murmur. However, a quiet or normal first sound at the apex does not exclude the possibility of mitral stenosis.

Conclusions

The diagnosis of mitral stenosis may be very easy or extremely difficult, and all possible information is desirable in the evaluation of each case. A good clinical history, physical examination, electrocardiogram and x-ray fluoroscopy are all essential. Often auxiliary aids, such as a jugular-pulse tracing, help differentiate mitral regurgitation from tricuspid insufficiency in cases in which a systolic murmur is heard just medial to the apex.

Even with the greatest of care in diagnosis in the best of clinics, errors are not infrequent. Some patients with clinical diagnoses of mitral stenosis have been found at operation to have free mitral regurgitation and no stenosis. Some cases diagnosed as cor pulmonale have been found at autopsy to be tight mitral stenosis, and others diagnosed as severe mitral regurgitation with slight mitral stenosis have turned out to be cases of tricuspid regurgitation with tight mitral stenosis.

These errors are occurring in clinics where excellent clinicians are working under ideal conditions. It is therefore essential that every physician examine his patients with the utmost care.

References

1. Laënnec, R. T. H. *De l'auscultation médiate, ou traité du diagnostique des maladies des poumons et du coeur.* 2 vol. Paris: Brosson et Chaudé, 1819.
2. *Idem. Traité de l'auscultation médiate et des maladies des poumons et du coeur.* Fourth edition. 3 vol. Paris: Chaudé, 1837.
3. Gendrin, A. N. *Leçons sur les maladies du coeur et des grosses artères faites à l'Hôpital de la Pitié pendant les années 1840-41.* 648 pp. Paris: Germer Ballière, 1841 and 1842. Pp. 110 and 648.
4. Fauvel, A. Mémoire sur les signes stéthoscopiques du rétrécissement de l'orifice auriculo-ventriculaire gauche du coeur. *Arch. gén. de méd.* **1**(Series 4):1-66, 1843.
5. Beau, J. H. S. Nouvelles recherches sur les mouvementes et bruits du coeur, et examen critique des principaux travaux qui ont été publiés sur ce sujet. *Arch. gén. de méd.* **11**(Series 3):265-301 and 407-439, 1841.
6. *Idem.* Du bruit de souffle cardiaque: du rétrécissement absolu et du rétrécissement relatif des orifices du coeur. *Rev. de thérap. méd.-chir.* 396-398, 1862.
7. Hérard. Des signes stéthoscopiques du rétrécissement, de l'orifice auriculo-ventriculaire gauche du coeur, et spécialement du bruit de souffle au second temps. *Arch. gén. de méd.* **1**(Series 5, Tome III):165-194, 1854.
8. Bouillaud, J. Quelques recherches et expériences nouvelles sur divers bruits des artères et du coeur, étudiés à l'état normal et anormal. *J. hebd. de méd. et chir.* (Prat. 1) **11**:561-590, 1833.
9. *Idem. Traité clinique des maladies du coeur, précédé de recherches nouvelles sur l'anatomie et la physiologie de cet organe.* 2 vol. Paris: Baillière, 1835.
10. Lemaire, M. Quatre cas de souffle au second temps à la pointe du coeur, coincident avec un triple bruit. *Union méd.* April, 1854.
11. Racle, V. A. *Traité de diagnostic médical: ou guide clinique pour l'étude de signes caractéristiques de maladies.* Third edition. 697 pp. Paris: Ballière, 1864.
12. Constatt. Cited by Fagge.[34]
13. Wintrich, M. A. Ueber den semiotischen Werth der Gerausche am linken Herzventrikel. *Arch. f. physiol. Heilk. Jahrb.* **8**:399-419, 1849.
14. Friedrich, N. Cited by Fagge.[34]
15. von Niemeyer, F. Cited by Fagge.[34]
16. Niemeyer, P. Cited by Fagge.[34]
17. Hope, J. *A Treatise on the Diseases of the Heart and Great Vessels: Comprising a new view of the physiology of the heart action, according to which the physical signs are explained.* Second edition. 612 pp. London: Kidd, 1832. P. 57.
18. Williams, C. J. B. *Disease of the Chest: The pathology and diagnosis of diseases of the chest: illustrated especially by a rational exposition of their physical signs: with new researches on the sounds of the heart.* Third edition. 209 pp. London: Churchill, 1835. P. 198.
19. Markham, W. O. Remarks concerning diastolic mitral murmur. *Month J. M. Sc.* **18**:26-31, 1854.
20. Walshe, W. H. *A Practical Treatise on the Diseases of the Lungs and Heart, Including the Principles of Physical Diagnosis.* 512 pp. Philadelphia: Blanchard and Lea, 1851. Pp. 103, 214 and 215.
21. Gairdner, W. T. Further remarks on auricular systolic murmur. *M. Times. & Gaz.* **2**:460-462, 1864.
22. *Idem. Clinical Medicine: Observations Recorded at the Bedside, with Commentaries.* 741 pp. Edinburgh: Edmonston and Douglas, 1862. P. 597.
23. *Idem.* Auricular-systolic murmur or murmur of mitral obstruction. *M. Times & Gaz.* **2**:193, 1864.
24. Flint, A. Reduplication of both sounds of heart: case and remarks. *West. J. M.* **3**:245-265, 1855.
25. *Idem.* On cardiac murmurs. *Am. J. M. Sc.* **44**:29-54, 1862.

26. *Idem.* Mitral direct and regurgitant murmurs, and probably tricuspid direct murmur. *M. J. & Rec.* **2**:259, 1867.
27. *Idem.* On diagnostic characters, mechanism, and pathological significance of mitral direct or obstructive cardiac murmur, and on occurrence of tricuspid direct murmur. *Bellevue & Char. Hosp. Rep.* Pp. 135-141, 1870.
28. *Idem.* On varieties, mechanism, diagnostic significance, etc., of mitral presystolic cardiac murmur. *Am. J. M. Sc.* **83**:442-449, 1882.
29. *Idem.* Heart murmurs. *Med. Gaz.* **9**:313-315, 1882.
30. *Idem.* On mitral presystolic and mitral diastolic heart-murmur. *Lancet* **1**:418, 1884.
31. *Idem. A Practical Treatise on the Diagnosis, Pathology, and Treatment of Diseases of the Heart.* 473 pp. Philadelphia: Blanchard & Lea, 1859.
32. White, P. D., and Reid, W. D. Diagnosis of mitral stenosis. *M. Clin. North America* **4**:383, 1920.
33. Flint, A. Lecture on occurrence of mitral direct or presystolic murmur without mitral stenosis. *Lancet* **1**:131, 1883.
34. Fagge, C. H. On murmurs attendant upon mitral contraction. *Guy's Hosp. Rep.* **16**:247-342, 1871.
35. Galabin, A. L. On interpretation of cardiographic tracings, and evidence which they afford as to causation of murmurs attendant upon mitral stenosis. *Guy's Hosp. Rep.* **20**:261-314, 1875.
36. Lewis, T. Time relations of heart sounds and murmurs with special reference to acoustic signs in mitral stenosis. *Heart* **4**:241-254, 1913. *Lectures on the Heart, Comprising the Herter Lectures (Baltimore): a Harvey Lecture (New York), and an address to the faculty of medicine at McGill University (Montreal).* 124 pp. New York: Hoeber, 1915.
37. MacKenzie, J. *Diseases of the Heart.* Third edition. 502 pp. London: Frowde, 1914. Pp. 222 and 223.
38. Bramwell, B. Lecture on differential diagnosis of cardiac murmurs. *Lancet* **1**:41-44 and 87-90, 1881.
39. Gowers, W. R. On influence of posture on presystolic cardiac murmurs. *Practitioner* **91**:401-407, 1873.
40. Broadbent, W. H., and Broadbent, J. F. H. *Heart Disease: With special reference to prognosis and treatment. Third edition.* 420 pp. New York: Wood, 1900. P. 207.
41. Ormerod, E. L. Observations of direct mitral or tricuspid murmur. *M. Times & Gaz.* **2**:276, 1864.
42. Barclay, A. W. Remarks on presystolic cardiac murmur. *Lancet* **1**:283, 353 and 394, 1872.
43. Duroziez, P. Essai sur les maladies du coeur: du rhythme pathognomonique du rétrécissement mitral. *Arch. gén. de méd.* **2** (Series 5):385-401, 1862.
44. *Idem. Traité clinique des maladies du coeur.* 509 pp. Paris: Steinheil, 1891. P. 258.
45. Rouches, F. J. M. Claquement d'ouverture de la mitrale. Étude clinique séméiologique. Thèse de Paris, July, 1888.
46. Margolies, A., and Wolferth, C. C. Opening snap ("claquement d'ouverture de la mitrale") in mitral stenosis, its characteristics, mechanism of production and diagnostic importance. *Am. Heart J.* **7**:443-470, 1932.
47. Messer, A. L., Counihan, T. B., Rappaport, M. B., and Sprague, H. B. Effect of cycle length on time of occurrence of first heart sound and opening snap in mitral stenosis. *Circulation* **4**:576-580, 1951.
48. Cossio, P., and Berconsky, I. El primer ruido cardíaco y el soplo presistólico en la estrechez mitral con fibrilación auricular. *Rev. argent. de cardiol.* **10**:162-185, 1943.
49. Wells, B. G. Graphic configuration of apical diastolic murmurs. *Brit. Heart J.* **14**:261-270, 1952.
50. Levine, S. A., and Harvey, W. P. *Clinical Auscultation of the Heart.* 327 pp. Philadelphia: Saunders, 1949.
51. Sansom, A. E. Presystolic cardiac murmur. *Proc. M. Soc.* **2**:56, 1874-1875.
52. *Idem.* Case illustrating mode of causation of mitral stenosis. I. On causes and significance of reduplication of sounds of heart. *Proc. M. Soc.* **5**:191-210, 1881.
53. *Idem.* On causes and significance of reduplication of sounds of heart. *M. Times & Gaz.* **2**:32 and 57, 1881.
54. *Idem.* Post-graduate clinical lecture on mitral stenosis. *Brit. M. J.* **1**:1641-1644, 1898.
55. *Idem.* Murmurs of mitral stenosis. *Lancet* **1**:195, 1900.
56. *Idem.* Cases illustrating anomalous conduction of mitral murmurs. *Med. Exam.* **2**:65, 1877.
57. Johnston, F. D. Value of sound records in diagnosis of mitral stenosis. *Am. Heart J.* **10**:654-661, 1935.
58. Battro, A., and Braun-Menéndez, E. Estudio fonocardiográfico de la estrechez mitral. *Rev. argent. de cardiol.* **4**:1-19, 1937.
59. Alimurung, M. M., Rappaport, M. B., and Sprague, H. B. Variations in first apical sound simulating so-called "presystolic murmur of mitral stenosis": phonocardiographic study. *New Eng. J. Med.* **241**:631-636, 1949.

PELGER–HUËT ANOMALY OF THE LEUKOCYTES*

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IN 1928, Pelger,[1] a Dutch physician and specialist in tuberculosis, examined the blood smear of a tuberculous patient and noted the absence of the usual nuclear segmentation in the granulocytic leukocytes. A large percentage of the cells were stab forms. The rest showed only two segments, and a few showed three segments but none more than three. In spite of this apparent immaturity, the nuclear chromatin was coarse, grouped into irregular clumps and obviously quite mature. In 1931, he had another case, again in a patient with tuberculosis, and thus the condition was first associated with this disease.[2] Later in the same year, a Dutch pediatrician named Huët[3] examined a ten-year-old girl suspected of having tuberculosis. He found the Pelger anomaly but no tuberculosis; on carefully taking the family history, he discovered that the girl was a niece of one of Pelger's patients. He then demonstrated the familial and hereditary nature of the condition and suggested that it was inherited as a nonsex-linked mendelian-dominant characteristic. He traced this family tree back three generations and found elders possessing the anomaly who were in good health. Huët concluded that no pathologic implications could be attributed to the condition. Schilling subsequently proposed that the condition be called the Pelger–Huët anomaly. It has also been called by the descriptive term, "familial false shift to the left of the leukocytes."

Since 1932, when Huët[4,5] described 2 more families from Holland with this anomaly, many additional cases have been discovered and reported. By 1940, 210 patients in 32 families had been described.[6] Most of these reports appeared in the European literature, and a few in other parts of the world, such as Japan, Java, the West Indies, Israel and Australia.[7-55]

Interestingly enough, as far as we know, no report has emanated from Great Britain, and only 2 cases have been described in the United States. Peterson[34] reported the anomaly in a Chinese family in 1935, and Tileston[45] presented a case in 1937.

The actual number of cases certainly exceeds that reported in the medical literature. Probably, they are not as rare in the United States as the scarcity of reports suggests.

Since recognition of this hematologic anomaly has practical significance and very little on the subject has been written in English, it was considered timely to review the problem in connection with a recently encountered case. It is of additional interest that the

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