repeatedly fulfilled Whipple's diagnostic criteria—(*a*) neurological disturbances occurring while fasting, (*b*) blood sugar below 50 mg. per 100 ml., and (*c*) rapid relief on the administration of glucose.

In all the previously reported cases of adenomatosis of the islets the condition has been discovered either at necropsy or after subtotal resection of the pancreas occasioned by relapse of symptoms following previous removal of single adenomata. Many authors, including Black *et al.* (1954) recently, stress the dark red or plum-coloured appearance of these neoplasms, and their firm consistency as compared with normal pancreatic tissue.

Our case illustrates, however, that a state of adenomatosis may exist without any visible or palpable abnormality in the pancreas at operation. Indeed, though immediate examination of the excised body and tail revealed two small palpable nodules, neither of these in fact corresponded to any of the adenomata later demonstrated. (Such areas can often be felt in the normal pancreas, and may be due to localized increase in the interlobular fibrous tissue.) Though histological examination showed some of the tumours to be on the surface of the pancreas, a great number were deeply embedded in the glandular tissue, and are very unlikely ever to have been palpated. Again, the adenomata in this case showed no distinct colour which might separate them from normal pancreatic tissue. It is therefore evident that if the surgeon is convinced by the adequacy of the investigations that a patient's symptoms are due to hyperinsulinism, he should be prepared to perform a subtotal pancreatic resection even in the presence of an apparently normal pancreas.

As, normally, islet tissue is found in the greatest quantity in the tail and body of the pancreas, it would not be surprising if multicentric tumour development resulted in the adenomata being concentrated in these areas. Serial sections of the excised portion in the present case supported this view, and showed a diminishing number of tumours as the head was approached. This is, of course, of practical importance, as excision of the whole of the tail and the body will give the best chance of eradicating completely the tumour tissue. The process is simplified and its completeness ensured by removing the spleen at the same time. Despite these facts, the presence of some adenomata in the sections nearest the head makes it probable that there are further tumours in the head itself. The prognosis is therefore uncertain and further resection may be required.

Another lesson to be learnt from this case is that focal neurological disturbances may result from hypoglycaemia. This was shown by focal pareses in the early history, focal twitchings in the later fits, and predominantly unilateral E.E.G. abnormality, corresponding to these manifestations. Black *et al.* (1954) reported a case developing a hemiplegia, and it seems that vascular insufficiency may be superimposed on the more diffuse pathological changes of hypoglycaemia described by Lawrence *et al.* (1952), and resembling the findings in cerebral anoxia.

In obscure cases of epilepsy of late onset when investigations have failed to reveal a cerebral neoplasm, the diagnosis of cortical atrophy or cerebral arteriosclerosis is sometimes too easily accepted. Even if the fits are of focal type the possibility of hyperinsulinism should always be explored. A single normal early morning blood sugar should not, however, be considered to exclude the diagnosis, and complete starvation for at least twelve hours may be essential to produce the characteristic clinical picture and abnormally low blood sugars.

Summary

A case is described in which many of the well-known clinical features of hyperinsulinism were associated with unusual focal neurological manifestations.

The characteristic clinical, biochemical, and electroencephalographic abnormalities could be induced at will, but required very long preliminary starvation.

Subtotal resection of an apparently entirely normal pancreas revealed the very rare condition of adenomatosis of the islets of Langerhans.

This patient was originally referred to one of us (E. R. B.) by Mr. J. M. Small. We wish to thank Mr. S. G. Smith, of the Biochemistry Department at Dudley Road Hospital, for carrying out the blood-sugar estimations, and Dr. W. Whitelaw, Director of Pathology, Dudley Road Hospital, for his advice and encouragement.

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SYSTEMIC EMBOLISM AND LEFT AURICULAR THROMBOSIS IN RELATION TO MITRAL VALVOTOMY

BY

J. R. BELCHER, M.S., F.R.C.S.
Surgeon, London Chest Hospital; Assistant Thoracic Surgeon, the Middlesex Hospital

AND

WALTER SOMERVILLE, M.D., M.R.C.P.
Assistant Physician, Department of Cardiology, the Middlesex Hospital; Cardiologist, Harefield Hospital

The vast literature on systemic embolism in rheumatic heart disease was largely compiled before the introduction of surgery in the treatment of mitral valve disease. Some of the recent papers, such as those of Jordan, Scheifley, and Edwards (1951), and of Wallach, Lukash, and Angrist (1953), were based on necropsy findings and must have included a number of cases which would have been too advanced or too complicated for surgery.

The incidence of embolism and auricular thrombosis may well be different in the fatal and in the operable cases. Apart from Wood (1954), few authors have referred in any detail to embolism in the latter group. We have therefore reviewed our cases in order to ascertain: (1) the clinical features of patients with systemic embolism before operation; (2) whether it is possible to diagnose left auricular thrombosis before operation; (3) the significance of previous embolism and of left auricular clot in relation to operative and post-operative embolism; (4) the influence of valvotomy on the incidence of late embolism.

From a series of 430 patients on whom mitral valvotomy was performed, we have studied 118 who fall into one or more of the following three groups (Table I): (*a*) those with systemic embolism before operation; (*b*) those with left auricular thrombi found at operation; (*c*) those developing systemic embolism during or after valvotomy.

The surgeons concerned were Mr. T. Holmes Sellors, at the Middlesex, London Chest, and Harefield Hospitals; Mr. K. S. Mullard, at Harefield Hospital;

and Mr. E. F. Chin, at Southampton Chest Hospital. Seventy-one of the patients were operated on by one of us (J. R. B.) at the London Chest and Middlesex Hospitals.

TABLE I.—*Systemic Embolism and Left Auricular Thrombosis: Composition of Series*

	Middlesex	London Chest	Harefield	Southampton Chest	Total
Total cases ..	181	67	92	90	430
Embolism: Pre-operative	16	12	21	5	54 (13%)
Operative and post-operative ..	14	3	4	3	24 (6%)
Left auricular thrombi ..	25	16	18	9	68 (16%)

The selection of cases and technique of mitral valvotomy followed the usually accepted principles (Baker, Brock, Campbell, and Wood, 1952; Sellors, Bedford, and Somerville, 1953). The diagnosis of pre-operative embolism was based on the clinical history. With a few exceptions, the operative or post-operative emboli were observed in hospital.

Clinical Features of Cases Developing Systemic Embolism Before Mitral Valvotomy

Study was made of 54 patients, in whom 75 separate embolisms occurred. Of these patients 19 (35%) suffered two or more embolic accidents. The sites were: brain, 59%, with equal numbers on each side; right leg, 13%, and left leg, 11%; aorta, 7%; right arm, 4%; and other sites (kidney, spleen, mesentery), 7%. Pulmonary embolism occurred in 10 of these cases, but have not been included in this study.

The clinical findings were compared in the 54 cases with embolism and 200 successive cases of mitral valvotomy without embolism, to find out whether they had any distinguishing features.

TABLE II.—*Systemic Embolism Before Mitral Valvotomy: Sex and Age Incidence*

Group (%)	Sex		Age			
	Male	Female	20–29	30–39	40–49	50–59
Embolic	31	69	5	28	54	13
Control	16	84	18	44	30	8

TABLE III.—*Systemic Embolism Before Mitral Valvotomy: Incidence of Certain Symptoms and Signs*

Group (%)	Rhythm		Dyspnoea*		Orthopnoea	Paroxys. Dyspnoea	Mitral Incomp.	R.V. Enlarg. in E.C.G.		Heart Size (C.T.R.)			
	Reg.	A.F.	Grades 1–2	Grades 3–4				No	Yes	<50–54	55–59	60–64	65–69
Embolic	22	78	65	35	28	19	41	68	32	55	25	5	15
Control	61	39	58	42	45	41	25	70	30	58	20	13	9

* Dyspnoea, grades 1–4, correspond respectively to "mild," "moderate," "severe," and "extreme."

Tables II and III show that the patients with embolism differed from the control group in five main respects: (i) the ratio of men to women was 1:2.2, compared with 1.5; (ii) the average age was slightly higher; (iii) auricular fibrillation was present in 78%, as against 39%; (iv) dyspnoea was less severe, and orthopnoea and paroxysmal cardiac dyspnoea were less commonly encountered; (v) higher incidence of mitral incompetence (significant mitral systolic murmur and/or regurgitant jet at operation). There was no difference in the incidence of right ventricular enlargement as shown on the electrocardiogram, or in the heart size. The duration of auricular fibrillation was known with reasonable certainty in 24 patients whose rhythm was irregular when the embolism occurred. It ranged from a few weeks to over 12 years (two weeks to six months, 7 cases; one to three years, 9 cases; four to six years, 5 cases; over ten years, 3 cases). These figures show no remarkable difference from the data for cases without embolism. Multiple attacks of rheumatic fever or of rheumatic fever and chorea, with the associated liability to endocardial damage, had no influence on the incidence of embolism. In fact, embolism occurred in only one of 11 patients who had had two or more attacks of rheumatic fever, and in one of 10 patients with a history of both rheumatic fever and chorea.

Factors which might influence the rate of blood flow in the heart, such as congestive failure, the degree of mitral stenosis, and the size of the left auricular appendage, were reviewed (Table IV). Figures for the size of the left auricle proper are not included, because there was no difference between the two groups. Three patients with "giant" left auricles were operated upon; there was no history of embolism in any of them. Values for cardiac output were not available for the majority of the cases with embolism, because cardiac catheterization was considered inadvisable. However, a low output can be inferred from a mitral facies (Wood, 1954), and from a small pulse. The presence or absence of these signs was recorded in all cases.

TABLE IV.—*Systemic Embolism: Incidence of Certain Signs*

Group %	Congestive Failure	Size of L. Auric. Appendage			Mitral Facies	Pulsus Parvus	Degree of Mitral Stenosis	
		Large	Mod. or Normal	Small			Severe or Mod.	Slight
Embolic..	22	51	41	9	16	29	76	24
Whole ..	17	28	40	32	27	31	86	14

Table IV shows that a history of congestive failure and a somewhat larger left auricular appendage were commoner in the patients with embolism. There was little difference in the severity of the stenosis as judged by the size of the mitral opening or by the presence of a pulsus parvus. The mitral facies was less often found in the embolic group.

These findings may be summarized as follows. In the group of patients with embolism prior to operation compared with 200 successive cases of mitral valvotomy without embolism, the sex incidence was less dominantly female; the age at operation was somewhat higher; auricular fibrillation was more common than sinus rhythm; dyspnoea was less severe; orthopnoea and paroxysmal dyspnoea were less frequently encountered; the incidence of mitral incompetence was slightly greater; and the left auricular appendage was larger. More than one-third of the patients developed a second or a third embolism.

Operative and Post-operative Embolism

Systemic embolism was closely related to mitral valvotomy in 24 patients (6% of 430 valvotomies), occurring during operation in 17, within a few hours in 2 and within fifteen days in 5. There were 4 late emboli—after seven weeks, one year (2 cases), and sixteen months. The sites involved were: brain, 17; aortic bifurcation, 4; left arm, 4; left leg, 2; and right leg, 1. Four patients sustained two emboli, making a total of 28 separate embolic incidents. There were 7 fatalities—5 from cerebral embolism during or within a few days of operation. The sixth death followed a cerebral embolism one year after an apparently successful valvotomy. Saddle embolus of the aorta developing during operation accounted for the seventh; immediate embolectomy was performed, but gangrene of the legs necessitated bilateral amputation, and the patient died nine weeks after valvotomy. Of the 24 patients in this category, 5 (21%) had a history of pre-operative embolism.

A few features distinguished these patients from 200 others without embolism who underwent valvotomy. The ratio of males to females was 1:1.4, compared with 1:5; a large heart (cardio-thoracic ratio, 60% or greater) was found in 58%, as against 22% of the controls; clot was present in the left auricular appendage in 64% of the patients with emboli, but in only 16% of the whole series;

and the mitral valve was calcified in 50%, compared with 35% in the control series. A large left auricular appendage was present as often in the group with emboli (29%) as in the controls (28%), and the incidence of mitral incompetence was of the same order in both groups (31% and 25% respectively). Other features such as the degree of dyspnoea, the electrocardiogram, congestive failure and the size of the left auricle were similar in both groups.

Relation of Operative and Post-operative Embolism to Pre-operative Embolism and Left Auricular Thrombosis

Five of the 54 patients (9%) with pre-operative emboli suffered a further embolic incident at or after valvotomy. This compares with an incidence of 6% in 376 patients without an embolic history who underwent valvotomy.

At operation 68 patients had a thrombus in the left auricular appendage; 11 (16%) of them developed an embolism during or after operation. The relationship between thrombus in the left auricular appendage and operative embolism is better shown by the higher incidence of thrombus (64%) in the embolic group than in the controls (16%). From the limited figures available, it is impossible to state the magnitude of the extra risk involved in operating on a patient with a history of embolism. However, it would not appear to be sufficient to justify withholding valvotomy, especially in view of the beneficial effect on the incidence of repeated embolism, referred to below.

Influence of Valvotomy on Late Embolism

The successful results following valvotomy soon raised the possibility that recurrent embolism complicating mitral stenosis might itself be an indication for surgery. Removal or lessening of the obstruction at the mitral valve seemed likely to reduce the chances of auricular thrombosis by increasing blood flow and by preventing stagnation in the auricular appendage. Four patients have developed late emboli—after seven weeks, one year, (2 cases), and sixteen months. One of these had two embolisms before operation. Thus in a follow-up period ranging from a few months to four years, the incidence of embolism after valvotomy has been less than 1%.

Pre-operative Diagnosis of Left Auricular Thrombosis

Clot was found in the left auricle or its appendage in 68 (16%) of the 430 cases of mitral valvotomy. It was more than twice as common (30%) in those with a history of previous embolism as in those without such a history (13%). The ratio of males to females was 1:2.3, compared with 1:5 in the control series; auricular fibrillation was present in all cases; and mitral calcification was found in over half the cases (53%), compared with 35% in the controls. Calcification was equally common in those above and those below 40 years of age. The average size of the heart and of the auricular appendage was similar in both groups, but in a quarter of those with thrombi the appendage was shrivelled and its lumen obliterated. Other features reviewed were equally unrewarding in pointing to any distinguishing clinical pattern of cases with left auricular thrombosis.

Pathology of Auricular Thrombosis

When a thrombus forms in the auricle or in its appendage, organization starts as soon as it becomes adherent to the living endothelium. The clot is invaded by capillaries, and fibrosis and, later, myxomatous degeneration may occur. The lumen of the appendage becomes obliterated and finally disappears, the appendage itself shrivelling up.

The organizing thrombus is rapidly covered with endothelium. One this process is complete, the risk of further thrombosis on the surface of the original thrombus is considerably reduced. Similarly, once the organization is well established, there is very little chance that the "grey" thrombus so formed will become detached, for emboli almost always consist of "red" thrombus which has become dislodged before organization has had time to start.

The majority of organized thrombi found in the left auricle have been wholly or partially in the appendage. Bailey *et al.* (1952) state that all thrombi arise in the appendage. Jordan *et al.* (1951), however, noted that less than half of the auricular thrombi found post-mortem were confined to the appendage, and in 16% of their cases the clots were localized in the auricle proper. Once a thrombus has formed, its tendency to remain in the appendage and to become organized there is explained by the presence of the columnae carneae which tend to entangle the clot as they traverse the lumen of the organ.

Jordan and his associates have stressed that thrombi eventually form in both the left and the right appendages in the majority of patients with long-standing mitral stenosis. Bull (1922) and Graef and others (1937) have stated that in their series the emboli arose from the thrombi in the auricle. However, it is more likely, in the light of the above description, that the presence of clots in the auricle merely indicates a tendency towards thrombosis at that site; those clots which adhere to the endothelium becoming organized *in situ*, whereas those which do not become fixed are carried into the systemic circulation as emboli. This suggestion is borne out by the clinical similarity between those patients who have had systemic emboli before operation and those who were found to have auricular thrombi.

The presence of organized clot in the appendage predisposed to the formation of further fresh clot there, and so increased the risk of post-operative emboli. "Red" clot was found alone in 6% of the cases in whom the type of clot was reported in detail, whereas it was present in 23% of those in whom there was already organized thrombus in the auricular appendage.

From the above description, once organization of a fresh "red" thrombus has occurred and a "grey" thrombus has been formed, there should be little risk of its dislodgment in the form of embolus. It should therefore follow that the risk of embolism at operation should be no greater when organized clot is present on its own than when it is absent. In this series, when "grey" clot was found in the auricle the incidence of systemic embolism complicating valvotomy was 10%; this figure is comparable with the 6% risk of this complication when no clot was found.

Where "red" clot was present, whether on its own or in combination with "grey" clot, the rate of embolism might be expected to be higher. In fact, systemic emboli were dislodged in 25% in this group. On the occasions when it was possible to determine the type of clot responsible for the embolus it was always the "red" variety.

A history of embolism prior to operation in no way makes it inevitable that clot will be encountered when the appendage is explored, for, although it may have formed there, the clot may have become dislodged in the form of an embolus before it had time to become organized and innocuous. In this series the appendage was found to be quite free from clot in 70% of cases with a history of embolism.

The finding of Jordan *et al.* (1951) of cases where the thrombus was confined to the auricle may account for some of the 10 post-operative emboli in our series where no auricular clot was found. In only one of our cases was thrombus described as being confined to the auricle proper, but this may be explained by the fact that the smooth surface of the thrombus is indistinguishable on palpation from the auricular wall.

A second cause of embolism from an apparently empty auricle is the dislodgment of pieces of calcium from the surface of the valve (Bolton, Maniglia, and Massey, 1952). This accident was thought to be responsible for four of the operative emboli in this series.

Technical Problems

The normal approach to the mitral valve through the auricular appendage may be impossible when the appendage either is filled by organized clot or has become so fibrosed and shrunken that even the little finger cannot be insinuated through its lumen.

Various methods have been described by which the mitral valve may be reached when the usual route is impassable. Harken did his earliest valvotomies through the superior pulmonary vein (Harken *et al.*, 1948). Although this approach is feasible, it has three disadvantages: the lumen of the vein may be too small to admit the finger; there is a risk that the vein may become occluded after it has been sutured; and it may be impossible to reach the valve with the finger if the auricle is unduly large.

In 1953, Temple described a method whereby an opening is made directly into the auricle at the bases of the pulmonary veins, where it may be "tented" and clamped. An incision is made into the muscular wall and the veins are separately controlled by tapes. This method avoids some of the disadvantages of the previous technique.

The approach via the auricular wall itself is undoubtedly the best. A purse-string suture is inserted into the auricular wall and haemorrhage is controlled by means of a Rumel tourniquet. The cavity can then be entered and re-entered with ease and with very little blood loss.

The method used at the Middlesex and London Chest Hospitals is as follows. The thrombosed appendage is palpated to determine whether the isthmus between it and the auricle is large enough to admit the index finger. If an approach via the appendage is thought possible, it is opened without the previous application of a clamp in the hope that any loose "red" clot may be washed out. (Clot has been removed in this way on 10 occasions.) The "grey" clot is dissected off the appendicular wall and the valve is approached in the usual way.

When the approach through the appendage is not possible, the lumen of the auricle is usually reached through the auricular wall direct, although the superior pulmonary vein has been used on three occasions and the base of the veins twice. Despite the fact that the finger had to be forced through the thrombus on several occasions, emboli were dislodged in only one of 10 patients in whom these methods were used.

The second technical problem is the prevention of systemic embolism at the time of operation, and the mitigation of its effects should it occur.

The risk of embolism during valvotomy is considerable; it was closely related to operation in 21 patients in this series (5%) and in 10% of the cases analysed by Wood. The embolus may lodge in either the cerebral or the peripheral vessels.

The mortality from cerebral embolism during valvotomy is high (45% in the present series and 66% according to Bailey), and in consequence various methods have been described to divert the clot from the cerebral vessels into those where its effects would be less disastrous. Carotid compression was advocated by Brock (Baker *et al.*, 1950) and others; this does not give protection to the vertebral arteries, but does lead to a temporary standstill in the column of blood between the point of compression and the aorta, and so emboli tend to be swept into the peripheral circulation.

Bailey *et al.* (1952) have described a method in which a clamp is applied to the innominate artery and a tape around the left common carotid is pulled tight during intracardiac manipulations. This technique has diminished the incidence of cerebral embolism, although it is not clear whether peripheral embolism has increased. It may be that emboli which would cause grave cerebral symptoms would be small enough to pass unnoticed when they lodged in peripheral vessels.

It has been suggested that the clamp used to control the haemorrhage from the appendage may crush a "red" thrombus which is projecting into the auricle, and that therefore the appendage should be opened before the clamp is applied. In this way, any loose thrombi will be swept out of the auricle.

In this series the method of carotid compression has been used particularly where there has been auricular fibrillation, where calcification has been present, and where clot has been felt in the appendage before it has opened. Although cerebral emboli have occurred despite this, the complication has been uncommon enough to justify the continuance of its use.

The third technical problem is concerned with the prevention of late emboli. Prior to the general acceptance of mitral valvotomy, it was proposed by Madden (1949) that the auricular appendage should be ligated or amputated in patients who were having repeated emboli. It was postulated that all emboli arose in the appendage and that therefore its removal would prevent the discharge of any more. More recently Bailey has recommended that the appendage should be removed in all cases after valvotomy, as he is of the opinion that if this is not done the cul-de-sac left behind is a potential source of danger. Although we have found that the size of the appendage bears little relation to the risk of post-operative embolism, whether early or late, it has latterly been our practice to amputate the organ when it has been at all large.

Summary

From a series of 430 mitral valvotomies, 118 cases have been studied to investigate the significance of systemic embolism and left auricular thrombosis in relation to mitral valvotomy.

There was a history of embolism in 54 patients (13%). Compared with 200 successive cases of valvotomy without embolism, these patients showed certain trends: the average age at operation was higher, the sex incidence was less dominantly female, auricular fibrillation was more common than sinus rhythm, dyspnoea was less severe, the left auricular appendage was larger, and the incidence of mitral incompetence was slightly greater.

Embolism was closely related to valvotomy in 6% of the 430 cases. When a previous embolism had occurred the incidence was 9%, and when left auricular thrombosis was present, 16%.

Left auricular thrombosis could not be diagnosed before operation. In general, it was found more often in males with auricular fibrillation and mitral calcification. It was more than twice as common (30%) in patients with a history of previous embolism as in those without such a history (13%), and was present in almost two-thirds of those who developed an embolus at operation. Embolism was encountered more than twice as often when "red" thrombus was found as when "grey" thrombus alone was present.

A successful valvotomy will not prevent further systemic embolism, but there is reason to believe it will reduce its incidence.

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