heparin neutralization. We have previously pointed out that this clotting-test is a poor indicator of heparin activity (Rothnie and Kinmonth, 1960). With the use of the more sensitive thrombin clotting-time some of our experimental cases showed incomplete neutralization of heparin with this 1:1 ratio of the antidote. Evidence was found in other cases that such a dose was only just enough to complete neutralization. This slight variation in polybrene requirements is most likely due to the variable amount of heparin present after perfusion. Since it is important to neutralize the anticoagulant completely, we have used a polybrene-to-heparin ratio of 1.5:1, and this has consistently been satisfactory.

With this dose of polybrene we have noted no inhibitory effects of the drug on coagulation. The problem of the anticoagulant effect of polybrene, and of protamine (Andersen *et al.*, 1960), has been investigated and will be the subject of another report. There appears to be a wide margin of safety with both agents and no danger of inhibiting coagulation with the doses used clinically.

Neutralization by polybrene, as with protamine, is prompt, and once the heparin has been completely neutralized we have found no evidence of the reappearance of the anticoagulant in the circulation. This theoretical reappearance must not be confused with the term "heparin rebound" which has been given to a period of hypercoagulability of the blood after prolonged heparin administration (Cate *et al.*, 1954).

If a transfusion of heparinized blood is given to the patient after perfusion, we have found it advisable to cover this extra heparin with polybrene. A dose of 1 mg. of polybrene for each milligram of heparin in the transfused donor blood is a convenient and adequate amount.

The slow administration of polybrene produced no hypotensive effects, but careful observation of the arterial pressure should be made during the injection, which should be temporarily stopped if the pressure falls.

Although our comparison of the amount of post-operative drainage after each antidote involved only a small number of patients, our findings that polybrene was superior to protamine are in agreement with those of a larger comparative series studied by Lillehei *et al.* (1960).

This investigation has shown that polybrene, when compared with protamine, is more consistent as a heparin neutralizer after perfusion and more effective in eliminating residual heparin as a cause of abnormal bleeding.

Summary

An investigation of the neutralization of heparin by protamine and "polybrene" (hexadimethrine bromide) after perfusion of experimental and clinical cases has been made, using the thrombin clotting-time as the indicator of heparin activity.

Protamine was found to be variable and uncertain in its neutralizing activity and the reasons are briefly discussed. Polybrene was the more consistent and effective antiheparin agent, and a dose of 1.5 mg. for each milligram of the heparinizing dose given to the patient was found to be satisfactory.

The hypotensive and anticoagulant side-effects of these agents were not noted with the doses and method of administration recommended.

We are indebted to Miss Sheila Maughan and Miss Diana Hulkes for skilled technical assistance, to Dr. G. I. C. Ingram for much helpful advice, and to other members of our surgical perfusion team for their help in the work. The polybrene was kindly supplied by Abbott Laboratories Ltd.

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TRANSVENTRICULAR MITRAL VALVOTOMY DURING PREGNANCY

BY

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The surgical relief of rheumatic mitral stenosis now meets with universal acceptance. In pregnancy the mechanical impediment of the narrowed valve is further aggravated by the physiological alterations in the circulation, particularly during the second trimester. The place of mitral valvotomy during pregnancy is still under discussion, and references to the operation in such circumstances in the world literature are still sparse. The earliest reports were by Brock (1952), Cooley and Chapman (1952), and Logan and Turner (1952). These three papers described a total of seven cases of valvotomy during pregnancy. Since then the total has risen to 133. All these operations were performed by the finger method or by a suitable knife via the atrium.

Present Series

The purpose of this communication is to add a description and an analysis of a further 10 patients operated on during pregnancy by the transventricular route assisted by a mechanical splitter, first used and described by Logan and Turner (1959).

The Table summarizes the salient features of the 10 patients in this series.

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Seven patients were at the stage of pregnancy when the physiological burdens were either developing or at their maximum. It is relevant to note here that in all these patients deterioration in their grading occurred progressively. This is in accord with the general experience. Five had weathered pregnancy on previous occasions. In four instances they had shown evidence of congestive failure at that time and all had been coped with by orthodox medical measures with rest in bed, diuretics, etc.

Pulmonary congestion was uniformly present in all our cases, and some had pleural effusions. Atrial fibrillation was the rhythm pre-operatively in Case 3, and it persisted afterwards. At operation tight mitral stenosis was confirmed on each occasion. One patient (Case 10) died 18 hours after operation. Fuller consideration is given to this fatal outcome below. Four patients developed transient atrial fibrillation. In one instance pulmonary congestion increased post-operatively, but responded to diuretic therapy. Another patient developed thrombophlebitis, which subsided uneventfully. Otherwise the operation was tolerated as satisfactorily in these patients as in the non-gravid state.

The immediate result in the first nine patients was excellent. Of the nine, four who were totally incapacitated and two who were moderately so were enabled, after operation, to become ambulant and to pursue limited activities in their own homes during the remainder of their pregnancy. The other three, all of whom were in the early weeks of pregnancy and were not seriously incapacitated, had a normal mitral valvotomy and continued their pregnancy actively and successfully. Premature labour occurred in Cases 6 and 10, and in the former the foetus was macerated.

The follow-up of our patients has varied from one to three years. Their functional gradings in May, 1960, compare favourably with their pre-operative status, and are shown in the Table. One patient (Case 2) has undergone a further pregnancy without any cardiac disability. One other patient (Case 4) was at the time of writing five months pregnant, and, although slightly breathless, was coping adequately with her normal household duties.

Discussion

During pregnancy the blood volume begins to increase in the second trimester to reach a peak early in the third, after which it gradually falls, only to rise again during labour and immediately afterwards. The augmentation of blood volume to its highest level (50% above normal) at the 32nd week is accompanied by a corresponding rise in cardiac output, heart rate, and oxygen consumption. These alterations in circulatory dynamics are well tolerated by the normal heart, but in patients with mitral stenosis such a haemodynamic burden seriously embarrasses the heart, and may well precipitate severe cardiac failure with acute pulmonary oedema. The effect of this progressive load on the circulation is well illustrated by the steady increase of symptoms shown by seven of our patients. In functional grading they all increased at least two grades in severity, and five developed intractable cardiac failure only partially held by orthodox medical treatment.

Prior to the introduction of operation during pregnancy, the corner-stone of treatment was protracted bed rest. Under the influence of medical measures pregnancy could be continued in the lower grades of functional disability with comparative safety to the mother. Friedberg (1956) quoted a maternal mortality of 2% in grades 0-II. However, in the more severe grades, III and IV, there is a drastic increase in maternal mortality to 40% (16 deaths in 40 patients). That author found it difficult to foretell when serious failure might occur in individual cases. Mendelson (1955) arraigned cardiac disease as to-day's single greatest cause of maternal mortality. Hamilton (1947) reviewed 1,335 cases of heart disease in pregnancy, of which 93% were rheumatic. The foetal mortality in this series was 8.6% in the favourable group and 31% in the unfavourable group. In essence medical treatment can offer in favourable cases a high survival rate for both mother and child, but with severe restrictions on the mother's activity for the duration of pregnancy. In unfavourable cases the alarmingly high maternal and foetal death rate warrants a more active policy in the way of surgical intervention.

Although up to the present comparatively few reports of valvotomy during pregnancy have been published,

Summary of Cases

Case No.	Age	Pregnancy	C.C.F. in Previous Pregnancies	Grading at Start of Pregnancy and Pre-operatively	Duration of Pregnancy (Weeks)	X-ray Appearances	Date of Operation	Fate of Foetus	Method of Delivery	Grade in May, 1960	Subsequent Pregnancies
1	23	3rd	During 2nd	I-III	18	No pulmonary congestion	26/6/57	Alive and well	Normal P.V.	I	Nil
2	22	1st	Nil	I-I	6	" " "	1/7/57	" " "	" " "	0	One—alive and well
3	27	1st	"	I-IV	20	Severe pulmonary congestion with bilateral effusions	9/8/57	" " "	P.V. (forceps)	I	Nil
4	28	1st	"	0-II	8	No pulmonary congestion	2/12/57	" " "	Normal P.V.	I	5 months pregnant now
5	26	2nd	During 1st	I-I	8	No pulmonary congestion. Kerley's lines present	24/2/58	" " "	" " "	0	Nil
6	34	2nd	" "	I-III	29	Pulmonary congestion present	26/2/58	Macerated. Stillborn (13/3/58)	" " "	I	"
7	21	1st	Nil	0-IV	20	Marked pulmonary congestion	30/4/58	Alive and well	" " "	0	"
8	26	2nd	During 1st	I-IV	28	" "	17/4/59	" " "	Caesarean section + sterilization	I	"
9	24	3rd	" 2nd	I-IV	22	" "	17/8/59	Twins, alive and well	Normal P.V.	0	"
10	22	1st	Nil	II-IV	20	Severe pulmonary congestion with bilateral effusions	4/12/59 (died 18 hours later)	Died	"		

and experience must therefore be necessarily limited, certain inescapable facts have come to light. Among the total of 133 cases so far accumulated there have been five maternal and nine foetal deaths. The majority of these patients fell into the unfavourable group (grades III and IV), and in most of them surgery was tolerated as well as in the non-pregnant state. They were able to continue the remainder of their pregnancy without undue limitation on their activities. In addition, Watt, Bigelow, and Greenwood (1959) followed up their series of 24 patients operated on during pregnancy, with neither maternal nor foetal mortality, for one to six years. They found that all had reverted to either grade I or II from a pre-operative grading of III or IV.

Our 10 patients were operated on by the trans-ventricular route, using a mechanical dilator, the method we have employed exclusively since late 1956. In our unit 250 valvotomies have been performed with this instrument, and the uniformly satisfactory commissurotomy compares, we feel, very favourably with the uncertainty of the digital methods. The previous operations described in pregnancy appear to have been carried out through the atrium by the combination of finger and knife. In the series of 37 cases reported by Dogliotti *et al.* (1960) no mention is made of the actual technique, but as his cases date from 1953 the implication is that a conventional digital method has been used. Our experience is that instrumental valvotomy is tolerated equally well in the pregnant and non-pregnant state. In addition, we believe that the more certain relief of mitral obstruction obtained by the instrument is of double importance in the overburdened circulation of a pregnant woman suffering from mitral stenosis.

One of our patients (Case 10) died 18 hours post-operatively. At the beginning of pregnancy she was in grade II, but she progressed steadily to grade IV by the twentieth week. By this stage she was orthopnoeic, showed marked pulmonary congestion, and had bilateral pleural effusions. Operation was urgent if the mother's life was to be saved. During anaesthetic induction, cyanosis and peripheral circulatory collapse became rapidly obvious. Thoracotomy, promptly performed, revealed the heart in asystole. Expeditious valvotomy was carried out, and after cardiac massage for several minutes cardiac contractions returned, though the output was manifestly ineffective. She failed to regain consciousness and died next morning. Surgery at an earlier stage of this woman's pregnancy or prior to pregnancy might well have saved her life.

From the accumulated accounts of the surgical treatment of mitral stenosis in pregnancy and in the light of our own experience, we believe that operation is a safe and valuable procedure in those patients. In the absence of a reliable guide to the stability of functional grading in pregnant women with mitral stenosis, it seems reasonable to advocate operation if serial assessments indicate progressive cardiac disability. In grades III and IV the case for operation is even stronger. From the point of view of maternal safety, operation in the early months of pregnancy would avoid entirely the necessity for urgent intervention in the face of grave circulatory embarrassment.

Summary and Conclusions

The relevant literature on mitral valvotomy during pregnancy is briefly reviewed and a further 10 cases are described.

All patients were subjected to a transventricular operation, with very satisfactory short- and long-term results in all but one instance. A plea is made for the serious consideration of operative intervention in those patients, in view of their established tendencies to deteriorate clinically during the course of pregnancy.

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TREATMENT OF SEVERE HYPERTENSION WITH BRETYLIUM TOSYLATE

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Bretylium tosylate ("darenthin") is N-*o*-bromobenzyl-N-ethyl-N:N-dimethylammonium *p*-toluenesulphonate.

Pharmacology of Bretylium Tosylate

The pharmacology of this drug and the first clinical applications in the treatment of hypertension in man were described by Boura *et al.* (1959), in a joint paper from the Wellcome Foundation and University College, ten years after Arnold and Rosenheim (1949) first reported the use of the salts of hexamethonium in the treatment of hypertensive disease. A benzyl quaternary ammonium compound, it has no evident anticholinergic action, but selectively blocks the peripheral sympathetic (adrenergic) nerves, where its preferential accumulation has been demonstrated by radioactive techniques. Its action therefore differs in an important way from that of the earlier ganglioplegic agents, in which the concomitant parasympathetic block is a clinical disadvantage, and also from that of the secondary and tertiary amines, mecamylamine and pempidine, which enter the body cells and may, in addition, cause side-effects by their central action (Bennett *et al.*, 1957).

Adrenergic nerve blockade is not, it should be recalled, the same as adrenergic effect. On the contrary, just as denervated vessels become hypersensitive to the action of circulating adrenaline and noradrenaline, so

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