Surely the essential feature is the presence of a significant degree of mitral stenosis —that is to say, enough to raise left atrial pressure under various conditions such as exercise, emotion, pregnancy, or tachycardia from any cause. Operation for removal of clot is not an accepted procedure apart from valvotomy.

The statement that valvotomy is indicated "provided the valve is suitable for it" is in our experience meaningless because what the surgeon will be able to achieve cannot by any method be predicted preoperatively. The unreliability of the signs of a so-called pliant valve have been previously stressed.[5] An excellent valvotomy may be achieved in a patient without the signs of a pliant valve, and it may be difficult to make a good valvotomy in a patient in whom the signs are clear.

It will be apparent that we do not believe the case has been made for a greater role of long-term anticoagulant treatment in mitral disease, but we do consider that multicentre controlled trials are long overdue. In Britain the difficulty increases each year with the decreasing number of patients who require a first valvotomy. The opportunity lies in such countries as India and Pakistan. If young patients in sinus rhythm are to be put on long-term anticoagulants not only will the task be formidable but there will be many complications. Apart from the difficulties inherent in laboratory techniques, drug interference with anticoagulant control is an increasing hazard. We do not at present believe that there is any evidence for permanent, long-term treatment of patients with anticoagulants after valvotomy.

In conclusion, we consider that possibly anticoagulants could, at a price, make a modest contribution to decreasing the incidence of systemic embolism, but as yet there is inadequate evidence because appropriate trials have not been carried out.

It must be remembered that oral anticoagulants have no effect on platelet aggregation, and in other situations at least little effect on the systemic side of the circulation in comparison with that on the venous side. Once again, multicentre controlled trials are long overdue.—We are, etc.,

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Imipramine and Pregnancy

SIR,—The recent publicity (*The Times*, 4 March) given to the alleged relationship between the prescribing of imipramine to pregnant women and fetal abnormalities prompts me to put before your readers some facts which should help them to decide whether the drug should be prescribed to pregnant women.

I have been using imipramine as an antidepressant since 1959 after conducting a clinical trial.[1] I soon realized it was an effective antidepressant and, being rather conservative in these matters, I have used it continuously and almost exclusively ever since. At the time Dr. McBride's report on the possible dangers of imipramine to the fetus was given such wide publicity I was preparing a report to the Lane Committee on the Abortion Act. While indexing my extensive material relating to mental instability and pregnancy the following facts emerged.

Since 1959, 211 of my patients have exhibited instability during their pregnancies, and of these 81 were given imipramine for depressive symptoms, the dose invariably being 50 mg three times a day and the duration not less than two months. All these pregnancies were followed up with particular reference to the mother's mental health and the child's mental and physical development. In no instance did these children suffer from fetal abnormalities sufficiently material to be reported by the Maternity and Child Welfare Service, by the family doctor, or by the mother.

Among those patients who were treated since 1959 for instability following pregnancy there were nine patients who had an abnormal child. These included two with Down's syndrome, one with multiple deformities which died, one with spina bifida which also died, one with a congenital heart defect which died following a corrective operation, and four who were still-born. Not one of the mothers of these children had been given imipramine during pregnancy. The mother of the spina bifida baby had imipramine a year prior to her pregnancy and so had a mother with a still-born child.

These fairly substantial figures do not support the view that imipramine is liable to cause fetal abnormalities if given to pregnant women either early or late in their pregnancies; in fact, a number became pregnant while on the drug. I shall therefore continue to prescribe the drug to pregnant women and shall not withdraw it from a patient should she become pregnant. I do not see the issue even as a calculated risk for I have no evidence of such risk.—I am, etc.,

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1 White, H. C., and Sim, M., *Birmingham Medical Review*, 1959, **20**, 480.

Malformed Infant

SIR,—I have recently examined at necropsy a grossly malformed infant born to a mother who had been taking Tofranil (imipramine) during the first four weeks of pregnancy. The patient was 28 and had had one previous miscarriage and one normal infant. This latter pregnancy had been complicated by puerperal mania, which was treated with Tofranil. She was maintained on this drug for 15 months prior to her most recent conception and for four weeks subsequently. Her dose while pregnant was 10 mg b.d. There was marked hydramnios at 32 weeks by dates, and shortly thereafter she delivered a female stillborn infant.

This infant had an exencephaly, cleft palate, adrenal hypoplasia, and a large right-sided diaphragmatic hernia. Postmortem radiography of the fetus demonstrated iniencephaly, cervical and upper thoracic dysraphia, and multiple rib defects. No abnormality of the limbs was observed. It is likely that the primary fault was a disturbance of neurulation in the cephalic half of the embryo and that the other anomalies were secondary to this. Neurulation is normally completed by the end of the fourth gestational week.

The significance of single observations of this type can only be assessed in the light of the accumulated evidence. In relation to the widespread use of the drug there are few such reports in the literature, and they are probably no more in number than that which might be anticipated to occur by chance. Statistical proof for mild degrees of teratogenicity of any drug is very dependent on the frequency with which possible instances are referred to central bodies such as the Committee on Safety of Drugs. It will be interesting to see how current interest in the possible teratogenic properties of imipramine will stimulate the collection of this information.—I am, etc.,

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Rapid Irregular Movements of Eyes and Limbs

SIR,—The description by Drs. G. Pampiglione and Maria Maia of a syndrome of rapid irregular movements of eyes and limbs in childhood (R.I.M.E.L.) (19 February, p. 469) brings to light once more a group of motor disorders of unknown cause which frequently prove difficult to classify clinically. It is suggested that R.I.M.E.L. may be a distinct entity, distinguishable from acute cerebellar ataxia of childhood on clinical grounds but more accurately by electrophysiological criteria.

I should like briefly to draw attention to an intriguing syndrome of involuntary movements which includes components of both cerebellar ataxia and R.I.M.E.L. This disease, originally known as encephalitis tremens,[1] is virtually restricted to a single region of Western Nigeria around the town of Ilesha. It consists of a "flu-like" illness often associated with giddiness, which after a short prodromal phase is accompanied by gross, generalized ataxia. Despite the severity, ataxic symptoms are of short duration and often remit within a week. All age groups may be affected and a review of 109 cases[2] showed an age range from three months to 68 years. This is in distinction to the previously described and clinically similar syndrome of acute cerebellar ataxia of childhood.

I think two aspects of this disease justify further report. Firstly, the clinical features, which are of acute cerebellar ataxia—manifested by intention tremor, truncal ataxia, and broad-based gait, but also accompanied by irregular shivering or shuddering movements of the limbs, trunk, and head. These occur during voluntary movement and equally during static extension of the arms and legs, and are abolished by resting or sleep. Irregular conjugate jerking of the eyes in the horizontal plane is seen in a number of cases and occurs independently of tremors.

Secondly, review of cases admitted between 1964 and 1967[2] revealed a marked seasonal incidence with outbreaks occurring every September, October, and November.