their wives. More can undoubtedly be done to meet the problems, but first is there sufficient interest by doctors in the matter? If so, I would suggest they would write to the B.M.A. with the hope that a co-ordinated plan could be put into action.—I am, etc.,

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Hypotensive Reaction after Propanidid and Atropine

SIR,—I wish to report reactions during anaesthesia using propanidid. The patients were two children aged 12 and 4 years, each undergoing an operation for the evacuation of pus, one from a submandibular abscess, the other from a pelvic abscess. Both children were ill as a result of these conditions, but not severely toxic or with a high fever.

In each case the child received the recommended dose (6–7 mg./kg.) of propanidid intravenously after intravenous atropine, and in each case the child immediately became bright red in colour all over.

This marked peripheral vasodilatation was accompanied by acute hypotension, which demanded immediate resuscitation. A head-down tilt, artificial ventilation with oxygen, and a large and rapid infusion with a plasma-expander were all rapidly instituted. The severe hypotension persisted for a much longer period than expected and constituted a threat to life. The second patient showed some resistance to artificial ventilation, possibly due to bronchospasm, and we wondered whether this was a histamine-release phenomenon. This child had received two similar anaesthetics uneventfully in the preceding six weeks. The first patient had had no previous anaesthetic. The outstanding feature of the reaction was the change in the child's colour from pale to scarlet, rapidly becoming cyanosed as peripheral blood flow ceased.

Reported reactions of this type are rare. Beck, reported by Zindler,¹ observed one very similar case and Radnay² one with some similarities. A further case has recently been reported by Desai.³ I would be interested to receive any reports of similar abnormal reactions attributable to propanidid.—I am, etc.,

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Origin of the Third Heart Sound

SIR,—In your leading article entitled "Origin of the Third Heart Sound" (26 July, p. 193) you state, "there is evidence that myocardial relaxation is an active process, the ventricle sucking blood in early diastole." We presume that you are referring to the elegant experiments of Brecher,^{1–3} who showed that elastic recoil caused ventricular filling in excised hearts and hearts beating against a very low resistance. However, in the conscious dog we were unable to find any evidence of active suction during a variety of physiological circumstances.⁴

We think, when the heart is beating against a normal aortic pressure, the left ventricle does not contract down below the volume of elastic equilibrium during systole. The suction effect can occur when the aortic pressure is very low. There is no reason to suppose that man is any different from the conscious dog in this respect, and we therefore think it very unlikely that "active suction" is occurring at the time of the third heart sound. Rapid filling of the left ventricle can, of course, occur without the presence of a suction effect.⁴—We are, etc.,

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SIR,—We would like to add the following comments on the origin of the third heart sound in mitral incompetence to those in your leading article (26 July, p. 193).

Fleming¹ has produced evidence for a mitral valve origin of the third sound in mitral incompetence based on the finding that replacement of the natural mitral valve by a Starr prosthesis resulted in disappearance of the third sound and the wave in the apex cardiogram associated with this sound. That this constitutes poor evidence of cause and effect is rightly stated in your article, since the loss of the third sound after valve replacement could as easily be ascribed to the correction of the haemodynamic lesion as to prosthetic replacement of the natural valve. We have observed that correction of mitral incompetence by mitral valvuloplasty, an operation in which the haemodynamic lesion is corrected but the natural valve is retained, also results in disappearance of the third heart sound, emphasizing the role of the haemodynamic lesion in the genesis of this physical sign.

We have studied² patients with gross mitral incompetence around a Starr prosthesis and compared the physical signs found in paravalvular incompetence with those present in these same patients with mitral incompetence through their natural valves. We found in each instance, despite severe mitral reflux, that the third heart sound, short decrescendo mitral murmur, and third sound wave on the apex cardiogram were absent in para-prosthetic mitral incompetence, although they had been present with valvar mitral incompetence. These findings support the thesis that the diastolic sounds of mitral incompetence are produced by partial diastolic reclosure of the mitral valve.—We are, etc.,

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Cancer and Mitochondrial D.N.A.

SIR,—Ten years ago Professor C. Lindgren¹ published an illuminating review entitled "Cancer and the Respiratory Grana." In this article he discussed Warburg's theory of the origin of cancer, which is concerned with the irreversible injury to the respiratory grana in the tumour cell. He also suggested that respiratory-deficient mutants of yeast cells may provide a useful model for studying cancer in a wider biological perspective. Because of rapid progress during the last ten years, instead of the vague concept of injury to the respiratory grana, we can now discuss alterations in base composition of mitochondrial D.N.A. of the respiratory-deficient mutants of yeast.

Graffi² showed many years ago that carcinogenic hydrocarbons preferentially accumulate in mitochondria. More recently the same author³ has demonstrated significant differences in mitochondrial protein synthesis between tumour and normal cells maintained in vitro. A high content of D.N.A., accompanied by a slow rate of synthesis of proteins and lipids in tumour mitochondria, indicates that the mitochondrial D.N.A. in tumours is inefficient.

The respiratory-deficient mutants of yeast may serve as useful models of tumour metabolism,⁴ because the organization of mitochondria in the respiratory-deficient mutants of yeast has much in common with the organization of tumour mitochondria.⁴ The recent discovery of a drastic alteration in base composition of mitochondrial D.N.A. from these mutants⁵ is of great interest. In some respiratory-deficient yeast mutants mitochondrial D.N.A. is extraordinarily rich in adenine and thymine. Adenine and thymine are present in equimolar amounts to the extent of 96% of the D.N.A., whereas guanine and cytosine form only about 4%. In other yeast mutants with impaired respiration alterations may go in the opposite direction. Since ethidium bromide induces mutation of yeast mitochondria, such that complete transformation of cells into respiratory-deficient mutants occurs,⁶ the way is open for the study of how drastic alterations in mitochondrial D.N.A. base composition are associated with respiratory deficiency.

Alterations of D.N.A. base composition have also been described in a number of respiratory-deficient bacterial mutants,⁷ and the similarity between such mutants and tumour cells has been stressed.⁸

It has been noted that respiratory-deficient mutants with altered D.N.A. base composition can be induced by ultraviolet radiation only in some strains of colon bacteria, and in these strains the repair of ultraviolet light-induced lesions in D.N.A. is insensitive to the effect of tryptophan.⁹ The possible meaning of this insensitivity for the induction of mutants remains to be investigated.

The selective heat sensitivity of cancer cells¹⁰ enables them to be regarded as temperature-sensitive mutants. The greater heat susceptibility of cancer cells might point to a decrease in the temperature at which a number of their enzymes are inactivated. This abnormal thermosensitivity is best accounted for by a defect in the structure of as yet unidentified proteins involved in the respiration and biosynthesis of the malignant cell. It is of considerable interest, therefore, that both the respiratory-deficient mutants