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 Radnay[2] 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).

Fleming[1] 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 studied[2] 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. Lindegren[1] 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.

Graffi[2] showed many years ago that carcinogenic hydrocarbons preferentially accumulate in mitochondria. More recently the same author[3] 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 mutants[5] 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 trypaflavine.[9] The possible meaning of this insensitivity for the induction of mutants remains to be investigated.

The selective heat sensitivity of cancer cells[10] 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

of yeast with altered mitochondrial D.N.A. and the respiratory-deficient mutants of bacteria with altered D.N.A. base composition are extremely heat sensitive.[11]

It is widely felt at present that cancer research requires inspiration and stimulation from biology. Considering the magnitude of the human effort and resources now being used in the important study of the nature of cancer, it is very important to make careful selection of appropriate biological model systems. Respiratory-deficient mutants of micro-organisms deserve consideration in this respect.—I am, etc.,

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Immunological Reaction and Hodgkin's Disease

SIR,—We read with great interest the paper by Dr. D. Crowther and others (24 May, p. 473) on changes in the circulating lymphoid cells in Hodgkin's disease, since they are in keeping with some findings recently observed in our laboratory.

We have detected anti-lymph-node antibodies in the serum of patients with Hodgkin's disease.[1] Sera of 32 patients with this disease have been tested so far against autologous and/or homologous lymph-node homogenates, using a passive haemagglutination technique. All the sera gave a positive reaction against one or more lymph-node preparations from Hodgkin's disease at titres up to 320. Serum antibodies from six patients whose own lymph nodes were available for testing proved to be autoactive. The fluorescein-conjugated serum of three such patients was tested for immunofluorescence on auto-lymph-node sections: 6 to 10% cells (lymphoid type) showed fluorescence.

One of these three patients, with advanced (stage IVb) and untreated disease was available for more detailed studies. Her serum gave passive cutaneous anaphylaxis against the auto-lymph-node homogenate. The maximum haemagglutinating titre was found in the IgG fraction. The lysate from peripheral blood lymphocytes, containing IgG only, gave also positive passive haemagglutination test against auto-lymph-node homogenate (titre 1/10,240). The fluorescein-conjugated IgG from both serum and peripheral lymphocyte lysate gave a positive immunofluorescence test on about 10% of the cells in auto-lymph-node sections, whereas the test was positive on only a few peripheral lymphocytes (2%).

The above findings suggest that anti-lymphocyte autoantibodies are present in the serum of patients with Hodgkin's disease, and that they are possibly released by blood lymphocytes while their target lymphoid cells seem to be preferentially trapped in the lymphnodes.

Dr. Crowther and others say that their findings "suggest that an immunological reaction is in progress, but it is not clear against what antigen it is directed." Dr. G. Hamilton Fairley, in his scholarly review on immunity to malignant disease (24 May, p. 467), takes a step forward when he hypothesizes that "lymphocytes may be committed to react against Hodgkin's tissue." Our observations seem to show that this is the case. Their analogy with Klein and colleagues' findings[2] in Burkitt's lymphoma is quite obvious. However, the fact that, in the context of Hodgkin's tissue, only lymphoid cells are antibody-coated might be rather confusing to the conventional pathologist. In fact, Reed–Sternberg cells are not attacked by the antibody. At this point perhaps one should consider that these giant cells might be far less important as "neoplastic cells" than their morphology would suggest.[3] We postulated[1] that antilymphocyte antibodies might be only a marginal by-product of the immunological system—that is, of the system in which this peculiar neoplastic disease is mainly localized.

But the reverse mechanism should be considered too, as a particular case of immuno-oncogenesis. The immunological situation able to induce Hodgkin's disease could be lymphocyte chimaerism as, by analogy with experimental models, Professor Sir David Smithers has suggested.[4] The presence of antibody-releasing and antibody-coated lymphoid cells in the same individual, which we have shown, might indicate that two lymphocyte populations are at work and in conflict, one of the two playing "the tumour" role.—We are, etc.,

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Cost of Medical Publications

SIR,—I am one of those students who hold a "special grant" for books, and, surprising as it may seem to Dr. R. Greene (26 July, p. 229), all this grant is needed and indeed used for its intended purpose. The extra grant is inadequate to buy even a selection of the best texts available. Often, inferior volumes are purchased simply because they are cheaper. Dr. Greene goes on to suggest these problems would be eliminated by the use of a medical school library. How many libraries could afford to buy enough volumes to guarantee continuous access to the required books at all times? Very few, I think.

Students, like publishers, have also experienced rising costs—the former more extensively. Dr. Greene suggests publishers' problems are not fully appreciated by their customers; obviously publishers have little idea of the problems facing students.—I am, etc.,

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SIR,—Three articles (26 July, p. 227) dealt with the price of books, but not very much with the efficiency of books in their present form. Of course there are other means of providing information, but the book is going to be with us for some years, and isn't it time that some bold publisher considered changing the form of the medical textbook, with his eye on greater efficiency?

Let us be more specific. Consider how a general medical textbook quickly gathers moss, how a new edition is ushered in before the old edition has left the bookshop shelves. How much of the material in the old edition has to be replaced? Is a completely new volume necessary?

Then consider how most of us use a large textbook. We do not read it from cover to cover; instead we use it to read about specific subjects in a sporadic fashion. We know what we want to read and we start at the index. We insist that the book is not rusty, because we must be up to date, but can we afford to replace the book, presumably one of several on our shelves, every four years?

Now, may I suggest that one approach to providing a new form would be to produce a book in either card-index or loose-leaf form. We would buy the book and pay a regular subscription for new sections to replace outworn ones. This type of book might have disadvantages, the initial cost might be higher than the usual textbook, the regular subscription might be unpopular, and the book would be inconvenient to carry and certainly could not be taken to bed. On the other hand, publishers would be able to keep us up to date at a less total cost, and they would have the advantage of knowing the number of their subscribers.

May I make it quite clear that I know there are medical encyclopaedias available which have supplements added to them from time to time. I don't care for this uneasy mixture of the old and the new.—I am, etc.,

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SIR,—To many doctors reference to the cost of publication of journals in your leading article (26 July, p. 189) must surely bring to mind the half-dozen or more free medical periodicals which have been regularly circulated to the medical profession for the last two or three years. Presumably we have to thank the drug industry for sponsoring and maintaining this expensive luxury, and after you remind us of the rising cost of even modest publications their generosity is truly staggering. Two of the papers I find useful for their medical content; the rest I find invaluable for wrapping my apple and pear crop in the autumn. Their glossy paper is much superior to newspaper, superior for that matter to the *B.M.J.*—I am, etc.,

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