also right in supposing that bronchodilator aerosols can become less effective if excessively used. They do not, however, explain exactly how the resultant worsening asthma caused the special kind of sudden and unexpected deaths which mainly contributed to the reported rise in death rate.

In our view, a more likely cause of the unexpected deaths is massive overdosage with isoprenaline by hypoxic individuals, because the victims were often found with empty inhalers. This explanation is incompatible with the Conolly group's hypothesis if only because it is hard to see why any patient should die after an overdose of a substance to which he is tolerant. It also conflicts with their claim that inhaled isoprenaline is not well enough absorbed to cause serious systemic effects. This is certainly untrue for dogs. We found^{2,3} that overdosage with an aerosol containing isoprenaline and Arctons 11 and 12 as propellents caused deaths in conscious dogs if they were deprived of air during the dosing procedure; no deaths occurred after similar treatment with aerosols containing only propellents, or propellents and salbutamol. Large doses of isoprenaline by aerosol are, therefore, potentially lethal to hypoxic dogs. The same may well be true for hypoxic human beings because human beings and dogs are usually alike in their cardiovascular responses.

This explanation is consistent with all the facts known to us concerning unexpected deaths associated with aerosol bronchodilators. If it is essentially correct it would be a pity if, as a result of the warning in your leading article, patients resumed the use of isoprenaline-containing aerosols instead of those containing drugs such as salbutamol which are likely to be safer even if they are abused.—We are, etc.,

DAVID JACK
Research Director

DAVID HARRIS
Head of Medical Services, Research Division,
Allen and Hanburys Ltd
Ware, Herts

- 1 Conolly, M. E., Davies, D. S., Dollery, C. T., and George, C. F., *British Journal of Pharmacology*, 1971, 43, 389.
- 2 Poynter, D., and Sourling, N. W., *Postgraduate Medical Journal*, 1971, 47, Suppl. (M-rch) 21.
- 3 Jack, D., *British Medical Journal*, 1971, 2, 708.

SIR,—I was most interested to read your leading article "Resistance to β -Adrenoceptor Stimulants" (15 January, p. 127). I have pointed out (30 March, 1968, p. 837) that overusage of isoprenaline not only results in failure to induce the desired bronchodilator effect but also may bring about bronchoconstriction.

Conolly *et al.*¹ have suggested that the rise in deaths from asthma could have resulted from lowering of the sympathetic drive on which asthmatics greatly rely to maintain bronchodilation. This seems a most reasonable explanation, but I suggest that it is only part of the mechanism. In my work on the uterus² I have induced resistance to isoprenaline and I have found that in this situation resistance to all catecholamines occurs and the response of the tissue reverses, becoming motor instead of inhibitory. Induction of resistance coincides with the liberation of prostaglandin³ and furthermore I have found that resistance to catecholamines can be induced by first subjecting the tissue to prostaglandin.

The response of the tissue to prostaglandin is motor.

Thus in the instance where the asthmatic has so overused isoprenaline as to induce a state of resistance he has not only lowered the effectiveness of his sympathetic drive but also he may be releasing prostaglandin and possibly inducing bronchoconstriction. This in itself would be quite sufficient to account for the reported rise in deaths from asthma.

Since the use of isoprenaline sprays is largely in the hands of unsupervised patients would it not be worth forestalling the synthesis of prostaglandin with concomitant use of analgesic agents⁴ or their release by the use of certain psychotropic drugs?⁵—I am, etc.,

ANNE TOTHILL

London N.W.8

- 1 Conolly, M. E., Davies, D. S., Dollery, C. T., and George, C. F., *British Journal of Pharmacology*, 1971, 43, 389.
- 2 Tothill, Anne, *British Journal of Pharmacology*, 1967, 29, 291.
- 3 Tothill, Anne, Rathbone, L., and Willman, Eve, *Nature*, 1971, 233, 56.
- 4 Vane, J. R., *Nature, New Biology*, 1971, 231, 232.
- 5 Tothill, Anne, Bamford, D., and Draper, J., *Lancet*, 1971, 2, 381.

Carcinoma of the Vulva

SIR,—I have read Mr. A. H. Charles's article "Carcinoma of the Vulva" (12 February, p. 397) with great interest. As one who formerly practised the Way radical vulvectomy but who now tends to a more conservative approach, I should like to add a few comments, particularly on the aspect of wound closure. While the delayed rotation flap principle is most commendable in itself, I would point out that, in the particular circumstances of the radical vulvectomy operation, conventional skin grafting still has much to offer. An open vulvectomy wound becomes covered with reasonably healthy granulations two to three weeks after the primary operation; if split skin grafts of intermediate thickness taken from the thigh are managed by the open method, an 80-90% take results. The patient can be discharged after a relatively short period of hospitalization, without contractures or similar disability in the grafted area.

The choice of skin cover is further influenced by the extent of the primary operation. Few would deny that in the vulva proper wide ablation is mandatory; apart from removal of at least 4 cm of tissue from the area around the primary growth, which may be multicentric, the whole leukoplakic or potentially leukoplakic skin area must be sacrificed. The dissection must be carried laterally to the inguino-crural folds. It is probable, indeed, that the poor results from the older literature of the conventional simple vulvectomy operation are largely attributable to neglect of this principle. As regards the skin over the groin and Scarpa's triangle, however, it is questionable whether the somewhat liberal skin sacrifice of the Way operation is justified; too pessimistic a view has been taken of the results of primary wound closure there, and primary closure means a smaller vulvectomy wound without the attendant problems of saline and plasma replacement.

A related problem is the role of excision of the inguinal glands, where these are clinically uninvolved. This is but one example of an issue currently much debated in the whole field of cancer surgery. For the older patient an "extended simple

vulvectomy," as above, without gland dissection but supplemented with cancer chemotherapy is, in my experience, adequate. I give chemotherapy routinely. Secondary open grafting will then generally also be required. Where, in other cases, block dissection of the inguinal glands is added, a choice has to be made between secondary grafting and the delayed flap rotation method. As already mentioned, I find no practical advantage as regards texture in full thickness skin cover for the vulva. Again, the risk to grafted skin of recurrent leukoplakia, with its due cancer potential, is offset by the hazard of cancer cell mobilization during the manipulations inherent in flap fashioning in a malignant field prior to definitive surgery. Indeed, from the practical standpoint recurrent leukoplakia is seldom a problem in the woman who has had vulvectomy for cancer.

Hence it is submitted that there is a place, particularly in old patients, for the relatively simple method of open grafting, combined where necessary with primary groin wound suture.

A. W. BANKS

Congleton, Cheshire

Vaccination against Rubella

SIR.—Drs. P. T. Penny and J. V. S. Pether (5 February, p. 375) refer to vaccination against rubella in high-risk non-pregnant workers such as nurses. For the past four years there has been a staff occupational health department at Bedford Hospital. Routine blood examination is done to assess the haemagglutination-inhibition antibodies (H.A.I.) of female staff and where there is an H.A.I. titre less than 64 rubella immunization is offered. Our results bear out those of Drs. Penny and Pether.

	1970	1971
Total tested	170	135
Susceptible	37	28
Immune	133	107

I also confirm the unreliability of a history of rubella. Our figures are that in 1971 out of a total of 135 tested, there was a definite history of rubella of 43, two of whom were susceptible and 41 immune. Those with no history of rubella were 92, out of whom 25 were susceptible and 67 immune.—I am, etc.,

JOHN D. HARTE

Staff Occupational Health Department,
Bedford General Hospital,
Bedford

Payment by Colour

SIR.—In 1969, you highlighted the pay discrimination of doctors' salaries in South Africa, and in a leading article entitled "Payment by Colour" (7 June 1969, p. 586) reminded us that "this inequity is of concern to doctors beyond the boundaries of South Africa."

I have recently returned from King Edward VIII Hospital, Durban, where I was the last and at that time only white house physician in that vast black hospital. Mine was one of the rare remaining opportunities left in South Africa for a white to

work under and with black doctors and I believe it gave me a unique opportunity to see something of their dilemma. I would like to draw your attention to some aspects of professional life which may be of interest to your readers.

That I was earning £800 a year more than my fellow African houseman indicates only a fraction of the total injustice. The fame of white South African medicine too often obscures the basic facts about the black South African scene. South Africa is one of the richest countries on the continent and yet I believe the level of poverty, malnutrition, ignorance, and social instability enforced on the majority of that country is incompatible with health.

The 1970 white infant mortality (rate per 1,000 live births) was 21.1.¹ The Government will not publish African figures but a recent estimate² has suggested an infant mortality rate as high as 400-450 in some African areas. Diseases such as tuberculosis have a high incidence in South Africa. In 1966 the number of reported cases/100,000 African population was 446.5 and in 1968 was 469.9.³ The degree of poverty may be gauged by comparison of wages with a recently estimated minimum effective (subsistence) level of R.100.69 a month for an African family of five.⁴ My patients at King Edward's frequently had incomes as low as R.28 a month and rarely above R.64 a month. Official statistics show that in 1970 the average monthly cash earnings per head of African gold miners was R.17.⁵

The medical manpower and facilities available to black South Africa are stretched to their limits, and a political ideology which will not allow the different coloured groups to mix only aggravates the situation. Despite the imbalance of the doctor/patient ratios between the different coloured groups (approximately 1 per 455 white and 1 per 100,000 African population⁶) in 1970 several Indian doctors who were practising in grossly underdoctored African areas were prosecuted for occupying consulting rooms illegally in an African region (Group Areas Act).

The standard of medical education in the one black medical school (to which King Edward's is attached) was impressive, as were their graduates, but they are depressingly few. In 1970, there were 3,918 white and 157 African medical students enrolled in South African universities.⁶ A main factor underlying the low output of black doctors is undoubtedly the low standard and high cost of pre-university African education. Though this group have the lowest incomes, the Africans are the only group who have to pay almost entirely for their own education.

Once qualified, the black postgraduate horizon is bleak. The academically barren "homelands" into which so many African doctors are being forced have virtually no facilities for specialist training. At King Edward's I found disillusionment among some of the senior black staff members as to whether they would ever be allowed to run their own medical school. Despite its 20-year history, there are still no black professors and almost all the consultants are white, though at least two of the original group of students are now professors outside South Africa.

In our relative safety in Britain we should seriously consider what pressures we can bring to bear on South Africa to alleviate the suffering and injustices imposed on our

colleagues, who for reasons of survival in that police state may not speak out.

I find the policy of the B.M.A. and B.M.J. towards South Africa inconsistent. The *Journal* has carried a leader condemning "payment by colour" and yet it continues to carry frequent large advertisements for hospitals and universities which will take white applicants only at the stated white discriminatory salaries. By continuing to carry these advertisements, the *British Medical Journal* appears to be condoning medical prejudices based on colour and race.—I am, etc.,

SUE DOWLING

Brook General Hospital,
London S.E.18

- ¹ Republic of South Africa, House of Assembly Debates (Hansard) Minister of Statistics. 1971. No. 18. Cols. 977-8. Cape Town. Government Printer.
- ² United Nations Unit on Apartheid. *Inequality in Health Care in South Africa*. New York, U.N. 1970.
- ³ Republic of South Africa, Department of Statistics. *South African Statistics 1970*. Pretoria, Government Printing Office.
- ⁴ South African Institute of Race Relations. *Survey of Race Relations in South Africa, 1971*, 25, 178. Johannesburg, 1972.
- ⁵ Republic of South Africa, Department of Mines. *Mining Statistics 1970*. Cape Town.
- ⁶ Republic of South Africa, House of Assembly Debates (Hansard) Minister of National Education. 1970. No. 2, cols. 539-40. Cape Town. Government Printer.

Immune Suppression, Gliomas, and Tuberculosis

SIR,—Dr. R. Finn and others (8 January, p. 111) refer to some clinical observations which seem to support the theory that neoplasia may partly be due to a deficiency in immunological surveillance. They suggest that in this respect the cellular immune system seems to be more important than the humoral antibodies. Pertaining to this view is the unifying concept of natural ageing and carcinogenesis in man.^{1 2} It assumes that, at least in part, somatic mutations may account for both processes. This concept emphasizes that an increase in the number of normal cells mutated into cancer cells will not necessarily lead to a corresponding increase in the incidence of cancer because the terrain must be propitious before a tumour can develop.

This theory could account for the increasing number of reports in which latent carcinoma has been found in the prostate, lung, kidney, and elsewhere. Little is known of the factors which influence the cellular immune system, but there is experimental evidence on the effect of calcium on the radiosensitivity at cellular level. From extensive studies a general hypothesis has evolved that chromosomes are inherently more sensitive to breakage at reduced levels of calcium.³ These observations could explain why patients with ankylosing spondylitis who had received x-ray treatment show an increased incidence of leukaemia. Owing to the calcium-depleted vertebral bodies, x-radiation may lead to increased frequency of chromosome aberrations in the bone marrow, thus predisposing to the development of leukaemia.⁴

On the other hand, the observation of a negative calcified atherosclerosis-cancer relationship led to the concept that an ageing process in which the proteins and the lipoids have an increased affinity to calcium show a relative immunity to cancer, in particular to carcinoma of the stomach and colon,⁵ and may also be a factor in the latency and in

the slow progression of some malignant tumours.⁶—I am, etc.,

A. ELKELES

Prince of Wales General Hospital,
London N.15

- ¹ Failla, G., *Radiology*, 1957, **69**, 23.
- ² Henshaw, P. S., *Radiology*, 1957, **69**, 30.
- ³ Steffensen, D., *Genetics*, 1957, **42**, 239.
- ⁴ Elkeles, A., *Nature*, 1962, **193**, 1089.
- ⁵ Elkeles, A., *British Journal of Cancer*, 1959, **13**, 403.
- ⁶ Elkeles, A., *British Journal of Cancer*, 1963, **17**, 572.

Menstrual Blood Loss and Fibrin Degradation Products

SIR,—May I comment on the paper by Drs. Susan K. Cole and A. R. Clarkson on the relationship between menstrual blood loss and serum concentrations of fibrin degradation products (8 January, p. 78)? The authors were unable to confirm my findings (10 January, 1970, p. 74) of increased serum fibrin degradation products (F.D.P.) levels in women complaining of menorrhagia.

I wonder if the apparent lack of correlation between menorrhagia and high serum F.D.P. levels may be ascribed to differences in patients studied rather than to differences in laboratory methods as suggested by Drs. Cole and Clarkson. In the study reported by me, in all 70 women menorrhagia was the presenting symptom and the bleeding was severe enough to warrant gynaecological investigation as inpatients. Over half of these had haemoglobin values of less than 10.5 g/100 ml. In my experience, collection of menstrual discharges by women attending hospital outpatients tends to be incomplete and creates a number of practical difficulties. It is well known that there is a wide variation of the normal range of menstrual blood loss.¹ Thus an arbitrary upper limit of normal menstrual loss may not be valid for all women. It would seem reasonable and practicable to consider menstrual bleeding as excessive when the disability is severe enough for the woman to seek hospital treatment, and particularly when this is associated with diminished haemoglobin levels.

The criteria used for the definition of menorrhagia in the report by Drs. Cole and Clarkson are not clear. It is known that at least 40% of women with menstrual blood loss of 80 ml or more per cycle do not complain of menorrhagia.¹ Is it possible that the series reported by Drs. Cole and Clarkson has a preponderance of women with apparently normal menstrual loss? Of 331 women, 25 had losses in excess of 80 ml and only 15 had losses in excess of 100 ml per cycle. It may be of interest to ascertain how many of these women had complained of menorrhagia, were anaemic, or underwent gynaecological investigations. It is probable that a number of women considered to have menorrhagia by Drs. Cole and Clarkson would have been considered as having normal menstruation by standards employed in my study.

I am conscious of the dangers of drawing firm conclusions from the results of a single study. It is thus possible that the differences in serum F.D.P. levels observed between various groups of women reported in my study were not due to variations in the degree of menstrual blood loss but to some other factors. Nevertheless, the results presented by Drs. Cole and Clarkson do not necessarily contradict my findings of