bubble the change in P_{O_2} is proportional to the initial P_{O_2} .

Dr Biswas and others also infer that the presence of an air bubble will increase the observed P_{O_2} . This is the case only if the initial P_{O_2} of the sample is less than that of the bubble. If the initial P_{O_2} of the blood is greater than that of the bubble the observed P_{O_2} will be lower than the initial P_{O_2} . Mass transfer will occur to eliminate concentration gradients according to Henry's law.³

Dr Biswas and others did not cite our previous conclusion⁵ concerning P_{O_2} and percentage saturation of oxyhaemoglobin: the presence of a gas phase in blood gas collection devices is a potential source of error for these analyses. This error will be small or clinically unimportant if the sample is analysed immediately after drawing with no mixing before analysis, which is ideal. If, however, there is delay, a change in temperature, or a combination of these two or mixing before analysis—as is dictated by conditions in a hospital—this error will be substantial. Dr Biswas and others did not consider these effects.

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Histopathology services for developing countries

SIR,—I read with great interest the article on histopathology services in developing countries (6 November, p 1327). I hasten to add my own plea for such services to be maintained and even strengthened not only in Britain but in other parts of the world (particularly Europe and the USA) where appropriate skill and experience in histopathology are highly developed.

For the past 12 years a major part of my work has been on the histopathology of leprosy, mainly in association with the Medical Research Council, the World Health Organisation, and other agencies running drug trials in India, Africa, and South America. My colleagues in London, notably at the Hospital for Tropical Diseases and the Leprosy Study Centre, have for many years examined thousands of biopsy specimens from patients in areas where leprosy is endemic and from other areas and have supplied reports on diagnosis, classification, and adverse immunological reactions. Such reports have tremendous value not only to the patient and his doctor in the developing country but also for research and teaching in the receiving centre. During the past 20 years from the United Kingdom alone major contributions have been made to the published work which have been based directly on biopsy material from Malaysia, India, Africa, Nepal, Australia, and South America. Literally hundreds of clinicians, some with limited knowledge of leprosy, have derived great benefit from these reports and publications.

Regrettably, in the near future, this type of work in leprosy is likely to experience the same kind of recession which is currently threatening tropical medicine and histopathology services to developing countries. Unless some determined effort is made soon to correct this situa-

tion the supply of competent and interested people in Britain will dry up. This is all the more regrettable since: (a) the necessary expertise for such work in leprosy can be acquired by a trainee pathologist in a period of about 6-12 months; (b) the field for continuing research on such material is still wide open, especially in immunopathology; and (c) the handling, processing, and reporting of a reasonable number of biopsy specimens each year need not be an impossible burden for many departments of pathology whether in hospitals or universities.

Before any more ground is lost it would be invaluable if a meeting could be arranged between representatives of the schools of tropical medicine, the universities, and the Royal College of Pathology in order to discuss the preservation of histopathology services for developing countries in general including those where leprosy is endemic.

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Death due to overdose of indoramin

SIR,—We would like to comment on certain aspects of Dr R Hunter's case report entitled "Death due to overdose of indoramin" (9 October, p 1011).

The title implies that indoramin was the sole cause of death, and the author comments that: "The serum ethanol concentration though raised is unlikely to have accounted for the severity of the clinical state." While we recognise that such a gross overdose of indoramin is likely to have been a major factor contributing to the patient's death, the role of alcohol cannot be disregarded. Alcohol depresses the central nervous system, and the degree of effect is proportional to the concentration of alcohol in the blood.¹ More than half of subjects are grossly intoxicated when alcohol concentrations reach 150 mg/100 ml²—in Dr Hunter's patient the alcohol concentration in the blood was 220 mg/100 ml. In such high doses alcohol also depresses cardiovascular function.³ In addition, alcohol prolongs the elimination of many drugs from the body^{4,5} and modifies their plasma protein binding.⁶ Indoramin undergoes extensive first pass metabolism and is highly protein bound⁷; it is therefore easy to see how a high concentration of alcohol in this patient may have affected metabolism of the indoramin and led to a more severe clinical response.

As Dr Hunter's patient was the first reported case of overdose with indoramin it is important to compare her clinical course with data from animal studies undertaken in our research laboratory. Rats have survived for up to 24 hours after oral doses of indoramin as high as 1800 mg/kg body weight. The principal effects of overdose in these animals were profound hypothermia and sedation. When hypothermia was corrected convulsions ensued. These were usually fatal and could not be completely controlled even by large doses of lorazepam (5 mg/kg intramuscularly). In a recent controlled study (V Middlefell, personal communication) rats were given an overdose of oral indoramin (500 mg/kg). In one group body temperature was maintained at 37°C while in a second group animals were kept at room temperature (22°C). All animals in the first group convulsed and died within 45

minutes whereas those in the second group survived for 30 hours. Body temperature fell to ambient temperature in the latter group, but convulsions did not occur. Depression of the central nervous system remained profound, and the animals did not attempt to eat or drink. It is noteworthy that normal body temperature was maintained in Dr Hunter's patient and that convulsions were difficult to control despite administration of diazepam. Whether or not the action of diazepam on the central nervous system worsened the depression of the central nervous system must also be given consideration.

In summary, Dr Hunter had a patient who died as a result of drug poisoning. The extent to which additional factors played a part in the clinical course and death of his patient is difficult to determine. Products like oxazepam and temazepam, which were found in therapeutic concentrations, may have contributed to the overall toxic effect in this abnormal circumstance. From what we have seen in animals even the maintenance of body temperature may have played an unwelcome part. In the light of this case report and from data based on animal studies we wonder whether it might be beneficial not to treat too vigorously the hypothermia seen in indoramin overdose. By reducing the incidence of convulsions such an approach may avoid the need to administer drugs which depress the central nervous system, such as diazepam, and might buy time for implementing suitable supportive measures.

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Who is taking their tablets?

SIR,—We read with interest the leading article by Dr R M Pearson (18 September, p 757) on patient compliance. In discussing the use of markers for monitoring drug ingestion he described the characteristics they should possess and listed previous compounds that had been used for labelling formulations in the past. Dr Pearson failed to mention, however, our recent study¹ concerning the potential use of small amounts of isoniazid for this purpose. The markers cited in the article have many important limitations: phenol red and riboflavin are highly coloured, quinine has a bitter taste, and the assay of bromide is far from simple. By contrast, isoniazid is colourless, odourless, and tasteless so that labelled formulations can be made which are effectively indistinguishable from standard preparations, and isoniazid ingestion can be monitored using a simple and specific colorimetric procedure² to detect the metabolites isonicotinic acid and isonicotinylglycine. Furthermore, these two metabolites are stable in urine and their rates of