must be given (and this is partly why the service is expensive) to allow the couple to express any fears and anxieties they may have about the methods, and to help them choose the method best suited to them. Also, poorly motivated couples need constant encouragement and reassurance if they are to persevere with contraception as they are less tolerant of side effects. In Haringey special problems exist (found also in Birmingham and Wandsworth) in that there is a large immigrant population, mostly West Indian, Irish, and Greek Cypriot, with differing cultures which have to be taken into account when birth control advice is given.

Domiciliary family planning should be regarded as preventive medicine—families where it is successful are better able to care for the well-being of their children. While it is to be hoped that the increasing liberalization of attitudes will continue there will still be a need for "individual and sympathetic family planning advice," to use Dr. Wilson's words, to be brought to the homes of a small but disproportionately problem-ridden section of the population.—I am, etc.,

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Crystals in Skeletal Muscle

SIR,—In reply to Dr. G. H. Hitchings (27 November, p. 555), the possibility that the crystals which were observed in frozen sections of muscle tissue from gout patients who had been treated with allopurinol for from six months to three years were attributable to the freezing process was carefully considered by us and investigated experimentally in our laboratory.¹ Your leading article (23 October, p. 185) refers to the paper in which these experiments are reported but Dr. Hitchings does not. This experimental evidence may be summarized as follows:

It was not possible to induce crystal formation by soaking fresh human muscle in aqueous or plasma solutions of hypoxanthine, xanthine, or oxipurinol; by soaking either fresh or ethanol fixed rat muscle in human plasma containing uric acid 9.8 mg/100 ml. Furthermore, no crystal formation was observed in a piece of human muscle which had been stored at -6°C for 25 days. During this time the hypoxanthine content increased from 36 $\mu\text{g/g}$ wet weight to 408 $\mu\text{g/g}$ wet weight, the inosine content reaching a concentration of 336 $\mu\text{g/g}$ wet weight. Inosine monophosphate (IMP) and adenosine monophosphate (AMP) were present in the stored muscle whereas adenosine triphosphate (ATP) had decreased from 1,047 $\mu\text{g/g}$ wet weight to zero.¹

These experiments provided strong evidence that cooling was not a factor in the formation of the crystals. We concluded that the presence of hypoxanthine and xanthine crystals in muscle tissue is related to lack of xanthine oxidase activity and not to gout. This was in agreement with our previous observation on two patients with congenital xanthine oxidase deficiency or xanthinuria.² In these studies 120 sections of muscle tissue from 13 normal untreated subjects (one of whom in fact had asymptomatic hyperuricaemia; serum uric acid was 10 mg/100 ml) had been examined as controls and found to contain no more than two hypoxanthine crystals and no xanthine or other crystals in any of the sections. It was also shown

that gout patients who had not received allopurinol also showed no excess of hypoxanthine or xanthine crystals in their muscle. The presence of oxipurinol crystals in the muscle of the allopurinol-treated gout patients was also reported, and it is of interest that it has been shown that allopurinol can be converted to oxipurinol in vivo in the absence of xanthine oxidase activity.³

In summary, we have demonstrated differences on microscopic examination between two groups of patients—namely, those who were treated with allopurinol and those who were not so treated—and we have presented experimental evidence for the view that these differences are not associated with the cooling procedure needed to produce frozen sections which are suitable for examination by refined optical methods. Thus, Dr. Hitchings's contention that we ignored this possibility is untrue. It is not justifiable to regard striated muscle as a simple aqueous solution, and to relate concentration of solutes per unit volume of muscle to their concentrations and solubility in an equal volume of water. Dr. Hitchings related 12 nanograms of hypoxanthine/mg wet weight of muscle to the saturation of 1,150 nanograms/ml of plasma. But in 1 mg of muscle the volume of free water in which the hypoxanthine can be dissolved is a minute fraction of that weight of muscle, most of which is occupied by protoplasm and by protoplasm-bound water. Striped muscle may be particularly liable to induce the formation of crystals because of its high degree of molecular orientation.¹

Knowing the complex physicochemical environment which prevails within cells, it is, in our opinion, naive to argue that observed phenomena cannot occur because they appear to contravene preconceived patterns of behaviour which have been derived from a consideration of simple aqueous systems.—We are, etc.,

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- 1 Watts, R. W. E., Scott, J. T., Chalmers, R. A., Bitensky, L., and Chayen, J., *Quarterly Journal of Medicine*, 1971, 40, 1.
- 2 Chalmers, R. A., Watts, R. W. E., Bitensky, L., and Chayen, J., *Journal of Pathology*, 1969, 99, 45.
- 3 Chalmers, R. A., Parker, R., Simmonds, H. A., Snedden, W., and Watts, R. W. E., *Biochemical Journal*, 1969, 112, 527.

Cost and Speed of Medical Publication

SIR,—Dr. David Pyke's Personal View (5 February, p. 371) is surely echoing the feelings of the medical profession as a whole when he criticizes the publication of conference proceedings as these usually appear: too late and too expensive. But he is incorrect in implying that the International Diabetes Federation is breaking new ground in publishing abstracts only. The Seventh European Rheumatology Congress held at Brighton in June 1971 omitted the customary postconference proceedings in favour of a bound handbook of abstracts given to each participant on arrival. Copies of this abstract handbook are available for £2 at the address below. They bear study by any student of

"congressology." Each of the 542 abstracts appears in English as well as in one of the other official languages, and the method of photographic reproduction allowed authors to revise their abstracts up to the very last moment, even those in Cyrillic script. Further, appropriate grouping of abstracts enabled our printer to run off separate sections of the handbook for advanced mailing to participants in individual sessions.—We are, etc.,

H. L. F. CURREY
Chairman, Scientific Subcommittee

M. C. G. ANDREWS
General Secretary

Seventh European Rheumatology Congress,
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Generalized Pustular Psoriasis

SIR,—We are disappointed at the final conclusion of your leading article on "Generalized Pustular Psoriasis" (29 January, p. 262) that corticosteroids should continue to be used until a bacteraemia is found and its response to antibiotics confirmed. The papers that you quoted give a strong hint that corticosteroids are concerned aetiologically in many cases, and it would seem undesirable to give them on this score (except as a last resort) even though they may suppress the symptoms and signs temporarily. We would certainly prefer to rely on your alternative suggestion, methotrexate, under these conditions.

The point of our paper¹ was that the six weeks' course of cloxacillin and cephaloridine that we recommended was the safest effective means of controlling generalized pustular psoriasis that we had found. If faced with a case, having taken initial blood cultures, we would not recommend waiting for the result before starting this treatment. As your leader rightly suggests, the significance of the positive blood cultures in our cases is difficult to interpret, but the fact of clinical response to appropriate antibiotics is to us beyond doubt.—We are, etc.,

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- 1 McFadyen, T., and Lyell, A., *British Journal of Dermatology*, 1971, 85, 274.

Unusual Type of Postanaesthetic Jaundice

SIR,—The Dubin-Johnson syndrome, also known as the Dubin-Sprinz disease and as constitutional hyperbilirubinaemia, is a rare condition. Usually seen in young people, it presents as a chronic or intermittent jaundice characterized by an increased concentration of conjugated bilirubin in the serum (but also some increase in unconjugated bilirubin) and by inadequate excretion of bromosulphalein. The aetiology is obscure, but it may be due to an inborn deficiency or deficiencies in the liver cell which result in an inadequate excretion of bilirubin, bromsulphalein, and the dyes used in cholecystography.¹ Investigations in the following case of postanaesthetic jaundice, at first attributed to halothane, suggested that it was probably due to the Dubin-Johnson syndrome.

The patient was a healthy man aged 37

who had had two short episodes of jaundice as a child. Anaesthesia for his operation for varicose veins was induced with thiopentone and continued with nitrous oxide, oxygen, and halothane in a semi-closed circuit. Urine analysis on the day of operation was normal but after the operation the patient was noticed to be jaundiced. Liver function tests showed an increase in the conjugated serum bilirubin to 3.8 mg/100 ml and in the total serum bilirubin to 4.5 mg/100 ml. Concentrations of aspartate transaminase and alanine transaminase were within normal limits. Urine analysis was positive for bilirubin, urobilinogen, urobilin, and bile acids.

The jaundice decreased, but 15 days after the operation both the conjugated and total serum bilirubin were still raised. The only abnormal finding in the urine now was a positive test for urobilin. Five days after the operation the possibility that the jaundice was due to halothane was investigated, but a normal SGPT and SGOT, a normal alkaline phosphatase, absence of eosinophilia, and no undue pyrexia made a diagnosis of halothane hepatitis improbable. It was thought that the patient possibly had the Dubin-Johnson syndrome.

He had meanwhile been discharged after a normal convalescence and had remained in excellent health. Three months later a further bromsulphalein test showed 63% dye retention in 5 minutes, 20% dye retention at 25 minutes, and 18% dye retention at 45 minutes. The second and third percentages, indicating difficulty in excretion of the dye, are consistent with the diagnosis of the Dubin-Johnson syndrome and probably the jaundice was due to that and not to the anaesthetic.—I am, etc.,

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¹ Robbins, S. L., *Pathology*, 3rd edn., p. 185. Philadelphia, Saunders, 1967.

Halothane, Hepatitis, and Dental Anaesthesia

SIR,—While the precise relationship, if any, between halothane and hepatitis remains unsolved, it nevertheless appears likely that it is in the field of multiple administration that the most fruitful observations may be made. There is one branch of anaesthesia which does not appear to have attracted attention in this context, possibly because the multiple sequence is not often encountered in hospital practice. I refer to general anaesthesia for dentistry.

There are two types of dental case which are subjected to more than one anaesthetic within a short space of time: serial extractions for orthodontic purposes, and multiple extractions or "clearance" prior to dentures.

It is the second group which is of interest, for not only is the age group within the susceptible range, but the patients would be remarkably free from extraneous influences such as hospitalization, drug therapy, injections, investigations, transfusions, etc. The usual pattern is that the posterior teeth on one side are extracted at the first session; one or two weeks later the contralateral posterior teeth are extracted; some three months later the anterior teeth are extracted for immediate denture replacement.

It is not possible to say how frequently halothane is administered in this pattern, but certainly the drug has been widely used in

this type of dental anaesthesia for many years. Since there are some 1,250,000 dental anaesthetics administered annually in N.H.S. surgeries, the number of cases which have been "at risk" might be very large indeed. While obscure pyrexia or even transient jaundice following the first administration might well have escaped notice or comment, it seems unlikely that massive hepatic necrosis following closely on the second administration would have for so long remained unrecorded.

I should be interested to hear of examples of jaundice following a dental anaesthetic of any type.—I am, etc.,

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Amphetamine Prescribing in Bristol

SIR,—In 1968 a B.M.A. committee recommended a drastic reduction in stores held and prescriptions of amphetamine-containing drugs.¹ In December 1969 the Ipswich Local Medical Committee obtained the unanimous agreement of members to cease prescribing these drugs and this was effective,² the chemists being able to dispose of stocks and the police noting a dramatic fall in amphetamine abuse.

In 1970 the Bristol Local Medical Committee asked all practitioners to drastically reduce and if possible abandon completely preparations containing amphetamines.

In August 1971 I asked all chemists on the Bristol Executive Council list to record the number of prescriptions and quantity of drug issued for 31 amphetamine-containing preparations during September and October. I asked them not to record the name of the doctor or patient concerned. Out of 108 chemists 63 (58%) sent complete replies and several returned incomplete forms.

	No. Prescriptions	No. Tablets	Mg Amphetamine
Per Week	84	4,531	34,070
Per Year	4,391	235,600	1,719,000

The Table gives figures based on the assumptions that for present purposes the 45 chemists not given adequate data handled the same quantities as those that did and that prescribing rates are similar throughout the year.

A quarter of a million tablets, allowing for their use in narcolepsy and hyperkinesia, is a lot, even for a population of half a million.

Dexedrine, dexamphetamine, Drinamyl, and Durophet were still prescribed in large quantities, though many chemists commented that there had been a fall in amphetamines prescribed in the previous two years. There is no accurate record of the quantities prescribed before, but it does seem that while the quantity has fallen it might be time for a further attempt to discourage most strongly the use of amphetamines both in Bristol and probably throughout the country.

I am very grateful for the help of the secretaries of the Bristol Executive Council, Local Medical Committee, and Local Pharmaceutical Committee.

—I am, etc.,

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¹ *British Medical Journal*, 1968, 4, 572.

² Wells, F. O., *British Medical Journal*, 1970, 2, 361.

Respiratory Depression in Tricyclic Overdose

SIR,—The pattern of tricyclic antidepressant overdose is now well recognized (2 January 1971, p. 3). Complications include convulsions,¹ arrhythmias, and E.C.G. changes.² However, respiratory depression does not generally occur. Doxepin (Sinequan) is a new tricyclic antidepressant and few reports of overdose have been described. Approximately 800 mg caused epileptic fits for 24 hours in a patient who recovered uneventfully; 600 mg taken by another patient resulted in drowsiness for 24 hours. The case report below illustrates that severe respiratory depression may occur in doxepin overdose.

A woman of 54 took 1,500 mg (60 capsules) of doxepin in a suicidal attempt. Within one hour she was having generalized convulsions, and was deeply unconscious. She was cyanosed with extremely poor respiratory effort. No reflexes could be elicited and her pupils were dilated and unreactive. Blood pressure was 65/30, pulse feeble and rapid, and E.C.G. showed a ventricular tachycardia, the rate varying between 60 and 150 per minute.

Assisted respiration produced a dramatic improvement in her cardiovascular state, the E.C.G. returning to normal within an hour. However, respiration remained severely depressed and she needed ventilation for 16 hours altogether. Within 24 hours the endotracheal tube was removed and she subsequently made a good recovery.

The recommended dose of doxepin is 30–300 mg daily in divided doses. The patient reported above took 1,500 mg, only five times the maximum daily dose, but this was sufficient to cause potentially lethal respiratory depression. As another patient has had fits with 800 mg it would seem that where there is a serious risk of suicide no more than 500 mg (twenty 25-mg capsules) should be prescribed at one time.

I am grateful to Dr W. R. N. Friel, Dr. S. Ruttle (Committee on Safety of Drugs), and Pfizer Ltd. for the information which they provided.

—I am, etc.,

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¹ Steel, C. M., O'Duffy, J., and Brown, S. S., *British Medical Journal*, 1967, 3, 663.

² Barnes, R. J., Kong, S. M., and Wu, R. W. Y., *British Medical Journal*, 1968, 3, 222.

Pollution and Population

SIR,—The recent correspondence on pollution and population has aroused considerable interest among several of my colleagues.

The International Federation of Medical Student Associations is planning a symposium on pollution and overpopulation, to take place in Edinburgh on 20, 21, and 22 April before an audience of medical students from medical schools all over the world, and it is hoped, members of the British medical profession. H.R.H. Prince Philip, Duke of Edinburgh is among the patrons of this symposium, and more than 20 speakers of international repute are to participate.

This event is designed to examine in depth the practical means available for dealing with these two great threats to the environment. Perhaps its greatest achieve-