after the pregnancy has occurred. The ante hoc promise would have contractual significance, but the practitioner could not know that he would be able to fulfil the contract.—I am, etc.,

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Sensitivity to Rifampicin

SIR,—In the summary of their paper on this subject (25 May, p. 415), Dr. J. C. Pujet and his colleagues draw two main conclusions: firstly, that rifampicin dosage and serum concentration are "predominating factors" in the occurrence of adverse reactions to the drug and, secondly, that if it is considered necessary to continue giving rifampicin to a patient known to be intolerant to the drug, antibody titres during the 24 hours after the administration of a dose "must be measured to find when they are lowest, which determines the 'un-reactive period,' and when a further dose may be safely given." Neither of these conclusions is warranted by the information presented or by other published work.

Their conclusion on serum rifampicin concentration is based on measurements from only three patients with adverse reactions, two of whom had acute episodes (one of haemolysis, the other of anuria) which could have produced a temporary failure to metabolize or excrete the drug. Furthermore, though the authors refer to "hepatic disorder" in 39 patients, they do not state whether these 39 included one or more of the three on whom the serum rifampicin concentrations were measured. This is an unfortunate omission since rifampicin clearance may be considerably impaired during transient abnormalities of liver function.¹ It cannot in any case be assumed that patients who develop adverse reactions to rifampicin do so because of impaired clearance of the drug from the serum until a properly controlled study has provided evidence for such a hypothesis. The impaired clearance could just as well be an effect of intolerance as a cause of it.

We have compared our own data on maximum serum rifampicin concentrations in two groups of patients on once-weekly rifampicin, the first during adverse reactions,¹ the second with no adverse reactions.^{2,3} The geometric mean of the peak serum concentrations for 10 patients during reactions was 38.0 µg/ml, whereas the mean for 12 patients with no reactions was 25.7 µg/ml. Even though this difference is significant ($P = 0.01$) there was no evidence of variation from patient to patient in their serum concentrations among those with no reactions.³ Thus it appears probable that patients who have already become intolerant clear the drug from their serum less rapidly than do those without intolerance and do not develop intolerance because of a preceding tendency to have higher concentrations.

Although rifampicin dosage in intermittent regimens is known to affect the incidence of adverse reactions, a recent controlled trial has shown that the rhythm of administration of the drug is by far the more important factor.⁴⁻⁶ Thus the incidence of reactions in patients given

rifampicin once a week was significantly higher ($P < 0.001$) than that in patients on the same dosage twice weekly, and the incidence during once-weekly chemotherapy was significantly lower ($P = 0.025$) if the intermittent phase was preceded by two months of daily treatment. Adverse reactions of the type discussed by Dr. Pujet and his colleagues did not occur at all during fully supervised daily administration. A moderate reduction in rifampicin dosage stopped adverse reactions in some patients. However, if it failed to do so a change to a daily rhythm of administration almost invariably succeeded. Of 111 patients with reactions to intermittent rifampicin, for only 11, including three with purpura, was treatment with the drug terminated. These adjustments were made entirely on the basis of the patients' clinical signs and symptoms and without any reference to antibody titres. Similar results have been reported from other centres.^{7,8}

Though the rifampicin-specific indirect antiglobulin reactions obtained with the serum of some patients with adverse reactions to intermittent rifampicin probably indicate the presence of circulating antibodies to the drug, this cannot be assumed.^{9,10} Nor, if such antibodies are present, can it be assumed that they are directly responsible for the reactions.^{2,11} Though the association between the occurrence of reactions and the presence of presumed antibodies has been shown to be close ($P < 0.002$), it is by no means absolute.^{6,10}

The assertion that "antibody titres within 24 hours after administration of the drug must be measured to find when they are lowest . . . and when a further dose may be safely given" is unjustifiable. An association between "antibody" titre and severity of reactions has not yet been clearly demonstrated. Even if it had, such measurements would be quite unnecessary in clinical practice since adverse reactions to intermittent rifampicin, as indicated above, can be managed simply and rapidly on an entirely clinical basis. However high the "antibody" titres in the serum of patients with reactions, rifampicin administration can almost invariably be continued uneventfully and without risk on a daily basis.^{1,6}—We are, etc.,

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Influenza in Families.

SIR,—A large-scale, five-year study of influenza in families in England and Wales began in October 1973 following a pilot trial in the previous winter. The study, organized jointly by the Royal College of General Practitioners and the Public Health Laboratory Service (P.H.L.S.), has nearly 500 volunteer patients. Over 50 general practitioners are taking part, each collaborating with one of 25 P.H.L.S. laboratories. The first winter period (1973-4) has run successfully and it has been decided to enlarge the study. Practitioners interested in taking part are invited to contact Mrs. J. Mant, Epidemic Observation Unit, Royal College of General Practitioners, 14 Princes Gate, Hyde Park, London SW7 1PU by letter or telephone (01-584 6262, ext. 43). At present it is not possible to include more general practitioners in the London area, but doctors from all other parts of England and Wales where laboratories are not already fully committed are welcomed.

Each doctor recruits between two and five volunteer families whose members will agree to provide a 10-ml blood sample in October and April each year (blood samples are not taken from children under 15 years). The families are kept under surveillance and each member is asked to contact the doctor if he develops an illness in which the diagnosis of influenza is even a remote possibility. The doctor or a nurse then records the clinical details and collects a nose and throat swab to be cultured for influenza viruses in the P.H.L.S. laboratory with which the doctor collaborates.

The main aims of the study are: (1) To relate pre-existing immunity, as measured by serological tests, to the influenza attack rate caused by new influenza virus strains as they naturally occur. (2) To study the relationship of pre-existing immunity to the severity of clinical influenza and to occurrence of subclinical infection. (3) To determine how influenza spreads within families.

The findings are expected to be of considerable practical importance. For instance, the results should help to improve the accuracy with which influenza epidemics could be forecast and help to decide when vaccination should take place and which persons should be included.

This is a worth-while study which can be carried out only by the close collaboration of general practitioners with their colleagues in virus laboratories.—I am, etc.,

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Computer Assisted Tomography

SIR,—In your leading article (22 June, p. 623) in which this most promising new method of investigating the intracranial soft tissues is reviewed the following statement regarding its application to the investigation of the orbit is made: "Various contrast media have been used in the past with very qualified success, and the techniques, apart from orbital phlebography, are regarded by most radiologists as being too dangerous since the information provided is limited." In our opinion this is misleading and totally