cases seen here suggest that a time-interval of weeks, or even months, may occur between the exanthem and the detection of frank thrombocytopenic purpura.

It seems likely that, among virus infections, rubella may have a special importance in the causation of some cases of "idiopathic" thrombocytopenic purpura, and, if this is so, its importance is surely belied at present by the scarcity of available information on the incidence of this serious complication.—I am, etc.,

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Evaluation of Phenoxypenicillins

SIR.—The carefully controlled blood-level study of the clinically available phenoxypenicillins by Dr. J. Ilian M. Bond and her colleagues (October 19, p. 956) rightly draws attention to the pitfalls attendant upon carrying out this type of work. Since, however, much attention is drawn to previous work from the Research Division, Pfizer Ltd., we crave your indulgence for the following remarks:

(1) In the original paper on the laboratory assessment of propicillin¹ the amount of the phenoxypenicillins present in the sera from volunteers given the antibiotic was determined not only in terms of penicillin G (a method described by Kunin *et al.*² for the tetracyclines and adapted to the phenoxypenicillins by Williamson *et al.*³) but also in terms of itself. This fact has been ignored by Dr. Bond and her colleagues.

(2) When the laboratory work reported by Williamson *et al.*³ was carried out, Bunn and Knight⁴ had not published their findings regarding the ideal concentration of bovine albumin that could be used as a diluent in the assay of penicillins in human serum. Grove and Randall⁵ recommend a 7% solution of bovine albumin as a diluent, and the use of 6% bovine albumin as a diluent by Williamson *et al.*³ was, as stated under "Methods," the outcome of previous experimentation. In this context attention is drawn to the use of 3% bovine albumin by Knudsen and Rolinson⁶ for the assay of phenethicillin, and of 4% bovine albumin by Knudsen *et al.*⁶ for the assay of ampicillin. Dr. Bond and her co-workers place no emphasis upon the use of bovine albumin by these workers whilst drawing attention to the possible errors in our work following the use of this diluent.

Carefully controlled developmental work upon the technique of large plate assay has led us to adopt the principle that the vehicle for the antibiotic standard must be identical to that of the body fluid whose content of antibiotic is to be determined. Each individual's premedication fluid is the ideal vehicle, but where this is inconvenient then a pool of fluid from at least six individuals appears, in our hands at least, to give reliable results in the test systems employed. Our belief is substantiated by Bunn and Knight,⁴ who

state "normal pooled human serum probably is the only diluent that can be used for accurate and dependable measurement of any penicillin, new or old, in human serum." All studies upon the distribution and concentration of antibiotics in body fluids undertaken by us in the last two years have been carried out using as vehicles for the antibiotic standard either pooled human serum, pooled human urine, or a pool of whatever fluid was appropriate.

(3) In our technique both the standard, dispensed in 100% pooled human serum, and test sera are treated in an identical manner. Three serial dilutions of the standard and of the test sera are made in such a way that all dilutions have a final concentration of 33% serum in phosphate buffer at pH 7. Using this test system Jackson and Williamson⁷ obtained the following average blood-levels (see Table) in a controlled cross-over study involving 35 volunteers given 250 mg. phenoxymethylpenicillin, phenethicillin, and propicillin. It is pertinent to mention that the values for the test sera at all dilutions were almost identical, thereby showing that the dose/response curve was linear.

Total Levels of Antibiotic in Serum ($\mu\text{g./ml.}$) After a Single Dose of 250 mg. of a Penicillin

Penicillin	Hours after Administration			
	$\frac{1}{2}$	1	2	4
Phenoxymethylpenicillin K	3.42	2.33	0.72	0.04
Phenethicillin K	4.88	4.93	1.72	0.15
Propicillin K	9.04	7.86	2.89	0.36

It is to be noted that the values obtained for phenoxymethylpenicillin and phenethicillin are almost identical to those reported by Dr. Bond. However, the values obtained for propicillin are considerably higher and in keeping with those reported by Williamson *et al.*³ and with those obtained by us on several occasions.

(4) Finally, whilst on the subject of microbiological assay, it should be pointed out that the technique used by us to obtain the results quoted above enabled an assessment of the parallelism and linearity of the assay results obtained from individual plates to be made. Knowledge of both these factors is of fundamental importance in the evaluation of the validity of an assay. The technique described by Lighthown and Sulitzeanu⁸ and used by Dr. Bond does not allow these two factors to be evaluated for individual assays or groups of assays.

(5) The results of extensive experiments in these laboratories upon the effect of 100% pooled human serum upon the minimum inhibitory concentration of the phenoxypenicillins for *Staphylococcus aureus* are in agreement with those of Dr. Bond. However, since we have not obtained the low serum levels of total propicillin reported by Dr. Bond and her colleagues we cannot accept their low rating of this antibiotic.

—We are, etc.,

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Enuresis

SIR.—Dr. I. G. Wickes and Dr. T. H. Gillison (November 9, p. 1200) both strongly advise the buzzer and would seem to imply that it is likely to be a straightforward easy procedure in the majority of cases. The following occurrences are taken from 15 consecutive cases where the buzzer was used: (1) The bell rang seven times one night. (2) Five members of the family were awakened by the bell; the patient slept through. (3) A father on discovering that the boy had turned off the bell and wet his bed threatened him with a severe caning. The bed was dry thereafter.

It would seem that one of the effects of the buzzer may be to mobilize a considerable number of family tensions any of which may affect the individual, his sleep, and his habit. Our original article (September 28, p. 787) indicated that there had been isolated a group who remained "wet." The buzzer was offered to all those who lived within easy travelling distance of the hospital. Nine accepted the offer—three girls and six boys. After a further two years only one is fully dry; two have given up the buzzer, settling for one wet night in six; one remains wet after two prolonged trials; another is improving after a third trial; four proved to be uncooperative and when last heard of were all wet. As a group they tended to ignore letters and not keep appointments. This suggests that for some adolescents either the "cure" is more distasteful than the symptoms or that their "non-cooperative" attitude is now well ingrained.

In our article we wrote: "The doctor's role need not necessarily be entirely passive, and intervention designed to aid the learning process (conditioning devices, bladder-training) or to remove anxiety and unhelpful parental attitudes may be successful." Undoubtedly the buzzer can function satisfactorily in some cases, but it may also arouse considerable anxiety and is certainly not the answer in every case.—I am, etc.,

Bristol 8.

R. F. BARBOUR.

SIR.—The symptom nocturnal enuresis must tax all medical practitioners who see children, yet its aetiology is obscure and its treatment haphazard. Of 399 children referred to our school and family psychiatric service last year 27% presented this symptom, so I have followed with interest the articles and correspondence on the subject in your pages (November 9, p. 1199 and preceding).

The "buzzer" we have found effective, if used properly, in most physically fit chil-