pictures, or renal functions, despite one patient receiving as much as 150 g. of fucidin over three months. No hormonal effects could be detected. Many patients complained of nausea and epigastric pain during the first few days of treatment. This was reduced to a minimum by administering fucidin just before meals or after a dose of aluminium hydroxide suspension. One patient vomited profusely after fucidin, and complained of dizziness, blurring of vision, and itching of the skin. Fucidin had to be stopped and her symptoms quickly disappeared. Another patient who vomited when given fucidin in gelatin capsules was able to tolerate the drug in enteric-coated capsules.

Of particular interest has been the effectiveness of fucidin in the presence of large collections of pus, despite the fact that it is known to be bound to a considerable degree to plasma proteins.

I would like to thank the many consultants under whose supervision these patients have been treated, and the nursing

staff who have cared for them so well. Advice and technical assistance have been willingly forthcoming from the medical and technical staff of Broadgreen Hospital Laboratory. I have drawn quite freely on Dr. A. Darragh's extensive knowledge of the pharmacology of antibiotics. Leo Laboratories have provided generous supplies of fucidin, often at short notice, through the efficient liaison of Mr. J. Kelly.

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A TRIAL OF XENALAMINE

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Recently published reports suggested that a new synthetic antiviral agent xenalamine (*p*-[α -ethoxy-*p*-phenylphenoxyamido]benzoic acid) might be of value in the treatment of measles infections. De Mattia and Rapellini (1961) treated 32 children and 28 adults and reported that in the adult cases xenalamine exerted a beneficial effect. Magni (1961) reported that the drug was of benefit in 10 out of 13 patients treated. On the other hand, Nordio and Massimo (1961) treated 20 patients with xenalamine and found no evidence that the drug had any effect on the illness. Baldini and Vaccari (1961) also failed to find any evidence of chemotherapeutic action in their small series of five treated cases. Rasi (1961) treated 94 patients, and suggested that xenalamine might be of value in reducing the severity of the disease if given early enough. The dosage employed by all workers was 50–100 mg./kg./day. No toxic effects of the drug have been reported.

Measles is a severe disease in Nigerian children, affecting mainly those under 3 years of age, and causing an estimated 4% case mortality (Gans *et al.*, 1961). The main cause of death is bronchopneumonia. Clearly a drug which would reduce the severity of the disease and the incidence of bronchopneumonic complications would be of great value.

In view of the conflicting reports in the literature, it was decided to undertake a controlled trial to establish whether xenalamine, given in a dose of approximately 50 mg./kg./day, would prove of value in the treatment of measles under local conditions.

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Methods

A preliminary clinical study was made on 30 consecutive Nigerian children attending the out-patient department of the University College Hospital, Ibadan, who were suffering from early measles. The children were examined daily, and unless complications supervened were given only a linctus and chloroquine, the latter because of the possibility that malaria was also present. Of the 30 children, 28 were over 6 months and under 3 years of age, one was 3 years, and one 4 years old.

By this means an accurate picture was obtained on the natural history of the disease in Ibadan, thus assisting the statistical design of the present trial. A detailed description of the natural history of measles in Nigerian children will be the subject of a further communication by one of us (K. C.).

In view of the age incidence found in the preliminary study, the trial was limited to children in the age-group 6 months to 3 years. As it is unusual for measles to be diagnosed in the prodromal stages in Nigeria, cases selected for the trial were restricted to those in whom the rash had appeared within 24 hours of first attendance at the out-patient department. Any children showing complications at this stage were excluded.

It was decided to use a sequential design of restricted type (Armitage, 1961) for the trial. Analysis of the preliminary series of 30 consecutive untreated cases of measles showed that respiratory complications occurred in 11, conjunctival injection in 20, and diarrhoea in 19. Bacteriological examination of the stools from those children with diarrhoea revealed a recognized pathogen (*Shigella*) in only one case. It was decided to design the

trial to estimate the effect of xenalamine upon the incidence of all three of these events independently; observations would also be made of the duration and severity of pyrexia and of any complications other than respiratory ones.

The quantity π_1 , the proportion of cases required to show absence of the particular complication or sign under consideration, was arbitrarily fixed at 0.95. π_2 , the proportion expected to be free from the particular sign or complication, was calculated from the data on the preliminary series of 30 untreated cases. Values for ϕ (the expected proportion of untied pairs, θ_0 (the proportion of untied pairs expected to show positive preferences), and N (the maximum number of preferences required) were computed from Tables 3.7, 3.8, and 4.1 in *Sequential Medical Trials* (Armitage, 1961).

For the effect of xenalamine upon the incidence of respiratory complications, a closed design with 2α (the significance level)=0.05; $1-\beta$ (denoting the sensitivity of the experiment)=0.95; θ_1 ($=1-\theta_0$)=0.9; ϕ =0.365; and N =19 pairs, was adopted.

For the effect upon the duration of conjunctivitis a closed design with 2α =0.01; $1-\beta$ =0.95; θ_1 =0.95; ϕ =1 and N =16 pairs was adopted. The value of ϕ was selected as 1 in this case, since a comparison was to be made of the duration of conjunctivitis in the treated and "untreated" cases, rather than setting an arbitrary time limit on the observations: in this case it is clear that if both members of the pair were untreated there would be a 50% chance of patient A having conjunctivitis for a shorter time than patient B, or vice versa.

For the effect upon the incidence of diarrhoea, a closed design with 2α =0.01; $1-\beta$ =0.95; θ_1 =0.95; ϕ =0.635; and N =16 pairs was adopted.

Patients were paired for age and sex in the following groups: 6-11 months, 12-14 months, and 24-35 months.

In order to ensure unbiased assessment of the clinical condition of the patients, the drugs for the treatment of each pair (xenalamine and inert tablets of similar appearance) were placed separately in small numbered packets enclosed in a larger envelope. Allocation of cases to the treated or control group was made according

to a table of random numbers. On accepting a patient into the trial he or she was allotted a number, and the big envelope containing the packets for the patient and the other member of the pair was opened, and the tablets from the appropriately numbered inner packet were used to treat the patient. When a patient suitable for pairing was found the other packet was opened, and the enclosed tablets were used to treat that patient. Thus in each pair one patient received xenalamine and the other received inert tablets. The physicians responsible for the clinical examination of the patients (K. C. and H. J.) did not know which child was receiving xenalamine and which was receiving placebo. All the patients were seen initially by one of us (K. C.). Where there was any doubt about the development of a complication the patient was seen by both physicians.

To ensure that the tablets were actually taken by the children the dose was administered in the clinic. Before going home the children waited for 30 minutes, to check that the drug was retained. They returned each day for examination and treatment, which lasted for five days. As in the preliminary series, a linctus and chloroquine were given to each child, to be taken at home.

Since Nigerian children in the age-group chosen might be expected to weigh between 7 and 15 kg., it was decided to use a standard dose of 500 mg. of xenalamine a day for each child.

Results

The results are expressed in Figs. 1-3 and in the Table. It will be seen from the figures that on the criteria used there was no significant difference between xenalamine and the placebo tablets. The Table also shows that there was no significant difference between the two groups with regard to either duration or severity of the pyrexia in uncomplicated cases.

All the complications noted developed during the course of treatment: the majority occurred on the third day after dosage started.

Discussion

In order to ensure that the child actually received his treatment, a single daily dose of 500 mg. of xenalamine

FIG. 1.—Incidence of bronchopneumonia. $2\alpha=0.05$; $1-\beta=0.95$; $\theta_1=0.9$; $\phi=0.365$; $N=19$ pairs.

FIG. 2.—Duration of conjunctivitis. $2\alpha=0.01$; $1-\beta=0.95$; $\theta_1=0.95$; $\phi=1$; $N=16$ pairs.

FIG. 3.—Freedom from diarrhoea. $2\alpha=0.01$; $1-\beta=0.95$; $\theta_1=0.95$; $\phi=0.635$; $N=16$ pairs.

Duration of Fever in Uncomplicated Measles Patients

Xenalamine Group				Placebo Group			
Case No.	Duration (Days) of Fever from Start of Treatment	Max. Temp.		Case No.	Duration (Days) of Fever from Start of Treatment	Max. Temp.	
		F.	C.			F.	C.
6	1	100.2	37.9	2	4	103.0	39.4
11	3	103.0	39.4	5	2	101.6	38.7
23	2	101.4	38.6	8	1	103.0	39.4
28	2	103.4	39.7	13	4	103.8	39.9
31	2	103.0	39.4	15	1	100.8	38.2
34	2	104.0	40.0	17	4	103.8	39.9
				*24	4	101.0	38.3
				25	3	101.0	38.3
				33	2	103.2	39.6
				50	4	102.4	39.1

Xenalamine group: Mean duration = 2.0 ± 0.3 days.

Placebo group: mean duration = 2.8 ± 0.4 days.

Xenalamine group: Mean max. temp. = 102.5° F. (39.17° C.).

Placebo group: Mean max. temp. = 102.4° F. (39.11° C.).

Temperatures were taken rectally: "Fever" was taken as a reading of 101° F. (38.3° C.) or over.

* This patient developed bronchopneumonia on the seventh day, after the temperature had fallen to normal.

was given in this trial. While it is possible that this may not be the best method of administration, Liu and Ferlauto (1961) found that a single daily dose of xenalamine was effective in treating experimental influenza infections in mice.

According to earlier reports, the viraemic stage in measles probably extends from some time during the prodromal period until about 24 to 30 hours after the appearance of the rash. The children in this trial were therefore given xenalamine only when the viraemic stage was subsiding or had ended, and large numbers of cells would be infected by the virus. It is at present difficult to judge exactly how great an effect this might be likely to have on the results of treatment with xenalamine; Liu and Engle (1961), working with influenza virus, showed that there was a direct virucidal action of xenalamine *in vitro*, but felt that this was probably not its main mode of action *in vivo*, since it could also be shown that it reduced the yield of virus from cells of a CAM preparation already infected before the drug was added. If this was also true of measles virus, it might be expected that the drug, if active, would reduce the severity of the disease even if given after the viraemic stage had subsided. Under local conditions it is most unlikely that measles will be diagnosed or treated prior to the appearance of the rash: thus one is likely to require a drug which exerts a true "virustatic" effect rather than one which is active only against unabsorbed virus. It should, however, be borne in mind that our present results may not indicate the possible activity of xenalamine given prophylactically or during the prodromal period.

This trial was designed to test the efficacy of xenalamine in reducing the observed incidence of diarrhoea (63%) and respiratory complications (37%) to an incidence of 5% in both cases, and in reducing the period of conjunctivitis in 95% of patients. Under the conditions chosen for the trial, it was found that there was no significant difference between xenalamine and placebo tablets in these respects; nor did xenalamine appear to shorten or lessen the severity of pyrexia. The respiratory complications appear to be due to secondary bacterial invasion, and if treated early respond well to penicillin. It is, however, clear from our results that xenalamine given after the appearance of the rash has no influence on the development of this serious complication.

Summary

In a trial based on Armitage's method of sequential analysis no difference was found between groups of children suffering from measles who were treated either with xenalamine or with inert tablets, in respect to the incidence of complicating respiratory infections, duration of fever, duration of conjunctival injection or incidence of diarrhoea. Xenalamine was administered at a dose level of approximately 50 mg./kg./day for five days, commencing within 24 hours of the appearance of the rash.

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EFFECT OF MENSTRUATION ON SIMPLE REACTION AND MOVEMENT TIME

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The significance of the menstrual cycle in accident proneness has been discussed by Whitehead (1934) and demonstrated by Dalton (1960). The latter surveyed 124 women who were hospitalized because of accidents, and found that for a significant number of those with regular cycles the accident had occurred during menstruation or the four days prior to it. She suggested that these accidents were the result of the increased lethargy which impairs judgment and slows reaction time. Noack (1960), after a study of German sports-women, also reported that the pre-menstrual woman is, in general, less efficient than the post-menstrual. However, Bilhuber (1927) conducted a longitudinal study of 14 women aged 17 to 22 and concluded that menstruation does not affect motor ability; Youngen (1956) found no change in the speed of arm movement or simple reaction time of 122 college women as a result of menstruation; and Bausenwein (1960) points out that many a woman athlete's best performance has been achieved during menstruation, even to the extent that records have been established and Olympic medals won.

It was the purpose of the present study to investigate the effects of the menstrual cycle on simple reaction time and movement time. A secondary consideration was the relationship of reaction time and movement time.