4. Ampicillin appears to be a most valuable antibiotic for urinary tract infections but courses of the drug should probably be for a minimum of 10 days with adequate laboratory follow-up studies.

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AMPICILLIN IN BACTERIURIA AND PYELONEPHRITIS OF PREGNANCY

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ASYMPTOMATIC bacteriuria is present in about six per cent of pregnant women and about half these women develop pyelonephritis of pregnancy. Kass (1960, 1962) findings suggested that pyelonephritis of pregnancy could be virtually eliminated by treatment of bacteriuria, because no pyelonephritis occurred in his non-bacteriuric patients or in those receiving treatment for bacteriuria. He also found that the high incidence of prematurity and perinatal mortality in his bacteriuric patients was reduced by treatment. Because of the important implications of these observations and because other findings had not been entirely in agreement with those of Kass (Kaitz and Hodder 1961, Turck, Goffe and Petersdorf 1962, Turner, 1961) we instituted a double blind controlled trial of anti-bacterial drugs in pregnancy bacteriuria.

Our own findings in a pilot study like those

of Kass (1960) suggested that continuous administration of an anti-bacterial drug was necessary to control bacteriuria. In selecting a drug for continuous administration during pregnancy, ampicillin seemed a good choice in that it was effective in urinary tract infections and being a penicillin was unlikely to have serious toxic effects on mother or foetus. Sufficient supplies were not available, however, and ampicillin was therefore used only in infections resistant to sulphonamides, sulphamethoxydiazine being used to control the bacteriuria in most patients.

Methods

Bacterial counts by a spread plate technique were done on mid-stream urine specimens collected at the first ante-natal visit in 4,000 women. Six per cent of these showed bacteriuria (> 100,000 organisms/ml.). Patients with bacteriuria were allocated at random to placebo or treatment and seen at monthly intervals in a special clinic for clinical, bacteriological and biochemical assessment. In addition to bacterial counts, quantitative leucocyte counts were performed on urine specimens.

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TABLE I
Symptomatic Urinary Tract Infection (Pylonephritis)

	Total No.	Symptomatic Infection	Percentage
No bacteriuria at first antenatal visit	4,000	48	1.2
PLACEBO GROUP			
Bacteriuria at first antenatal visit	60 (47)	19 (19)	31 (40)
TREATMENT GROUP			
Bacteriuria at first antenatal visit	64 (55)	1* (1)	1.5 (1.8)

() Patients with Bacteriuria on two occasions
* Persistent Bacteriuria

Ampicillin in a dose of 500 mg. thrice daily was used for the treatment of bacteriuria.

For the treatment of pyelonephritis in pregnancy or the post-partum period a two-week course of 500 mg. ampicillin four times a day was given. Before treatment was started a urinary bacterial count and leucocyte count was performed and this was repeated three days after the treatment was stopped. Thereafter the urine was examined one week, six weeks, and six months after delivery.

Results

Treatment of Bacteriuria

Our results have confirmed that there is a high incidence of pyelonephritis of pregnancy in patients with bacteriuria and that this can be prevented by treatment (Table I). The one patient who developed pyelonephritis while on an anti-bacterial drug was receiving ampicillin, her original bacteriuria had been replaced by a different organism resistant to ampicillin shortly before the symptoms developed.

We have not been able to diminish the high incidence of prematurity, foetal loss and pre-eclamptic toxæmia which occurs in bacteriuria by treatment with an appropriate anti-bacterial drug.

Figs. 1 and 2 show the urinary bacterial counts and leucocyte excretion rates in 11 patients who were allocated to ampicillin treatment because their bacteriuria was resistant to sulphonamides. The bacterial count and leucocyte excretion rate usually fell sharply when treatment was started and remained normal for the rest of pregnancy, in about 25% of patients however the bacteriuria persisted in spite of treatment. Among the 11 cases receiving ampicillin, in three, the bacterial count was still over 100,000 organisms per ml. a month after treatment was started and as might be expected the organism was now resistant to

ampicillin. One of these three patients developed the clinical features of pyelonephritis.

Intravenous pyelograms done in the post-partum period showed that 50% of all bacteriuric patients had radiological renal abnormalities (Table II). Of the 11 patients in whom the bacteriuria was treated with ampicillin, six had an underlying abnormality. Failure to respond to treatment and a persistently high leucocyte excretion rate were particularly liable to occur in patients with an underlying calculus or chronic pyelonephritis (see p. 23).

There was a defaulter rate of 23% and most of these were due to failure to take tablets continuously. In five of 13 defaulters initially allocated to ampicillin, side effects of the capsules (vomiting in four and rash in one) were directly responsible for the failure to take tablets. A further two patients initially allocated to ampicillin treatment had to be changed to another drug because of vomiting. Thus 24% of patients allocated to ampicillin had to stop taking it because of side effects. One foetal abnormality was observed in patients who had taken ampicillin during pregnancy. However, this patient had only taken two doses of ampicillin at approximately 20 weeks and there was certainly no causal relationship between this and the grossly malformed foetus which was born four weeks later.

Treatment of Pyelonephritis

Twenty-four patients with signs and symptoms of acute pyelonephritis of pregnancy were treated with ampicillin. Seven of these patients were subsequently shown to have underlying chronic renal disease. The results of treatment are shown in Table III. Two

FIG. 1—Urinary bacterial count in eleven patients with bacteriuria before and after one month of treatment with ampicillin 500 mg. thrice daily. Relevant findings on the intravenous pyelogram are given in six cases. C.P.N. = Chronic pyelonephritis. Two of the three patients in whom bacteriuria persisted in spite of treatment had no demonstrable abnormality on the intravenous pyelogram. The organism in these three and in one patient with a bacterial count of 15,000 organisms per ml. and an underlying renal calculus were resistant to ampicillin at the time of the second urine examination.

FIG. 2. — Urinary leucocyte excretion rates per hour in eleven patients with bacteriuria before and after one month of treatment with ampicillin 500 mg. thrice daily. The leucocyte excretion rate fell to below 400,000 per hour in all but three cases. Two of these three had chronic pyelonephritis (C.P.N.). In the third with no radiological abnormality the leucocyte excretion rate rose from a normal figure of 100,000 cells per hour up to 600,000 when paracolon bacillus was replaced by a proteus infection resistant to ampicillin.

FIG. 3.—An intravenous pyelogram done in the post-partum period in a patient who presented with asymptomatic bacteriuria and in whom a high leucocyte excretion rate persisted for the remainder of pregnancy. A large left uretic calculus was present and there was very poor function and hydronephrosis on the left side. After removal of the calculus the function of the left kidney on an intravenous pyelogram was very much improved.

TABLE II
Radiological Lesions
IVP in 134 of 200 cases

	No.	%
Normal	67	50
Chronic pyelonephritis	13	9.7
Calyceal abnormalities including papillary necrosis	11	8.2
Localised scar probably chronic pyelonephritis (5 also with > 2 cm. difference in length)	11	7.5
Renal calculi	10	7.5
Duplex system (3 with localised chronic pyelonephritis)	6	4.5
Miscellaneous (marked hydronephrosis tuberculosis > 2 cm. difference in length)	16	11.9
TOTAL	134	100

patients were unable to take ampicillin because of vomiting and one failed to show any clinical or bacteriological response and the organism apparently became resistant to this drug.

Two of the 21 patients who showed an initial response relapsed a week after treatment had been stopped. One of these had a ureteric calculus, but the intravenous pyelogram was normal in the other.

Six patients did not attend for post-partum follow-up, but of the remaining 18 patients five developed urinary tract infection in the early post-partum period and in three other patients asymptomatic infection was present six months after delivery. Only one of these three showed a radiological abnormality.

Treatment of Post-partum Pyelonephritis

Eleven patients who developed pyelonephritis in the first three months after delivery were treated with 500 mg. ampicillin four times a day for two weeks.

Nine of these 11 patients had radiological evidence of an underlying chronic renal lesion.

TABLE III
Ampicillin in Pyelonephritis of Pregnancy

	No.	%
Total cases (7 with I.V.P. abnormality)	24	
Unable to take ampicillin (vomiting)	2	8.3
Initial response, bacterial count normal 3 days after ampicillin stopped	21	87.5
Failed to respond. Resistant organism appeared	1	4.1
Relapse within a week	2	8.3
Follow-up post-partum	18	75.0
Urinary infection in early post-partum period	5	27.7
Urinary infection 6 months post-partum	3	16.6

The results are given in Table IV. In spite of an apparent initial clinical response to treatment in ten of the 11 patients, four showed persistent infection while still receiving ampicillin. In two patients the organism appeared to have become resistant to ampicillin and in the other two a different infection resistant to ampicillin had appeared. In the patient who failed to show any clinical response, the organism had apparently become resistant to ampicillin. In all these patients infection recurred within the next six months.

Discussion

In the patients in whom asymptomatic bacteriuria in pregnancy was treated with ampicillin, 54% had a radiological abnormality demonstrated in the intravenous pyelogram. Garrod, Shooter and Curwen (1954) showed that only 60% of patients with a demonstrable urinary tract abnormality will develop a sterile urine following treatment. We obtained a satisfactory response in 72% of this small group of bacteriuric women. However the second bacterial count was done while the patient was receiving ampicillin and the findings must be interpreted with caution as the ampicillin in the urine could have been bacteriostatic in some cases.

Patients who developed a frank attack of pyelonephritis of pregnancy had a much lower incidence (29%) of demonstrable renal abnormalities and 87% of these were bacteriologically free of infection three days after stopping treatment.

The group of patients in whom we studied the effect of ampicillin on post-partum pyelonephritis had a very high (81%) incidence of demonstrable radiological abnormalities and as might be expected only 54% of these

TABLE IV
Ampicillin in Post-Partum Pyelonephritis

	No.	%
Total cases (9 with I.V.P. abnormality)	11	
Initial response, bacterial count normal 3 days after treatment stopped	6	54.5
Clinical response but infection reappeared while patient on treatment	4	36.3
Failed to respond clinically or bacteriologically	1	9.0
Recurrence during next 6 months	11	100

patients had a bacteriological response to treatment.

Thus our experience with ampicillin in bacteriuria and pyelonephritis of pregnancy suggests that it is an effective drug which can be given with safety in pregnancy. Side effects, particularly vomiting, were common.

Summary

Ampicillin has proved satisfactory for the treatment of bacteriuria and pyelonephritis in pregnancy. Vomiting was a troublesome side effect.

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