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CYCLOSERINE IN TREATMENT OF INFECTION OF URINARY TRACT

BY

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Cycloserine, first isolated in 1954 as a fermentation product of *Streptomyces orchidaceus* (Harned *et al.*, 1955), has been extensively investigated in the treatment of tuberculosis. Toxicity in patients given large doses for prolonged periods is the major disadvantage of such therapy (Walker and Murdoch, 1957). Nevertheless, lower oral dosage for short periods is virtually non-toxic provided renal function is good. Under these circumstances much higher urine than plasma concentrations are achieved (Welch *et al.*, 1955). Cycloserine has therefore been used to a limited extent, with encouraging results, in patients suffering from infections of the urinary tract caused by a variety of organisms (Herrold *et al.*, 1955; Hughes *et al.*, 1958). *In vitro* studies have also suggested that concentrations of cycloserine sufficient to inhibit the growth of some strains of coliform organisms are attainable in human urine (Welch *et al.*, 1955; Garrod, 1959). We report here the results of a detailed study of the use of cycloserine in a small number of patients with severe infection of the urinary tract by coliform organisms who have been observed for periods of two to seven months.

Materials and Methods

Clinical

Five female patients have so far been selected for study. Three were diabetic subjects who had suffered severe and repeated attacks of urinary infection characterized by malaise, frequency of micturition, nocturia, and dull loin pain for many months. Treatment with courses of sulphonamides, chloramphenicol, tetracyclines, and streptomycin had failed to relieve the symptoms or to render the urine sterile for an appreciable length of time. Renal biopsy was successfully performed in two of these three patients and histological evidence of pyelonephritis was demonstrated in both. Kidney tissue was not obtained from the third patient. The two remaining patients, who were not diabetic, had acute infections causing severe illness with high fever, rigors, dysuria, and oliguria of short duration. Renal biopsy was therefore not performed because of the delay involved in preparing for this procedure. Similarly, pre-treatment laboratory studies were also curtailed. Individual details of the patients are shown in Table I.

Treatment consisted of the daily oral administration of cycloserine in doses of 250 mg. eight-hourly for 14 days. Each patient was instructed not to drink excessively during this time. Daily observations of the temperature, pulse, and respiration rates and of the urinary volume were made. The patients were questioned and examined daily in respect of the subsidence or otherwise of their disease. Subjective and objective signs of drug toxicity, such as drowsiness, personality change, myoclonus, and epileptiform phenomena, were especially sought.

Bacteriological

As repeated catheterization carried with it the risk of introducing further infection, the following method of obtaining " clean " mid-stream specimens was devised. Patients were instructed to bathe in the early morning, washing the ano-genital region thoroughly with hexachlorophane soap. Urine was voided at 9 a.m. and discarded. Chlorhexidine cream was applied to the labia at 10.45 a.m. At 11 a.m. the patient, in the erect posture, with the labia separated by a sterile gloved hand, voided urine. The mid-urinary flow was collected in a wide-mouthed sterile jar and delivered immediately to the bacteriologist. Three such specimens were obtained on successive mornings before treatment was begun in Cases 1, 2, and 3. Only one such specimen was taken in Cases 4 and 5.

The pretreatment specimens from all patients were examined by standard laboratory procedures—namely,

TABLE I.—*Pretreatment Clinical Observations*

Case No.	Age and Sex	Duration	Temp. Rise	W.B.C. Cells/ c.mm.	E.S.R. Westergren	I.V.P.	Renal Biopsy
1	27 F	12 months	97–100° F. (36·1–37·8° C.)	6,000	50 mm.	Normal	Failed
2	55 F	3 ,,	97–98·6° F. (36·1–37° C.)	7,000	42 ,,	,,	Acute pyelonephritis
3	38 F	12 ,,	97–99° F. (36·1–37·2° C.)	7,500	93 ,,	,,	Chronic pyelonephritis
4	24 F	1 month	99–105° F. (Rigors) (37·2–40·6° C.)	17,200	45 ,,	—	—
5	20 F	3 weeks	99–102·4° F. (37·2–39·1° C.)	10,600	45 ,,	—	—

microscopy of stained centrifuged deposit, culture on blood-agar and MacConkey-agar plates.

Microscopy showed the presence of large numbers of pus cells and Gram-negative bacilli. The cultures yielded pure and heavy growths of *Escherichia coli* in all five cases.

The antibiotic sensitivity pattern of these organisms was determined by the disk-diffusion method (Bowie and Gould, 1952). The minimum concentration of cycloserine required to inhibit the growth of these strains of *E. coli* was determined in the following manner. A standard solution of cycloserine was prepared by dissolving 100 mg. of the drug in 100 ml. of meat-extract broth. This was diluted appropriately, with broth, to give concentrations of cycloserine ranging from 1,000 to 25 μg./ml. 0.5-ml. aliquots of these solutions were inoculated with 0.02 ml. of a 1 in 250 dilution of an overnight broth culture of the organisms under test. The concentrations of cycloserine required to produce growth inhibition were noted after 18 hours' incubation at 37° C. (see Table II).

TABLE II.—*Resistance Pattern and Minimum Inhibitory Concentration of Cycloserine for the Causative Organism*

Case No.	Causative Organism	Disk Sensitivity Pattern					M.I.C. Cycloserine (μg./ml.)
		Su	P	Str	C	T	
1	E. coli	R	R	S	S	S	100
2	,,	S	R	S	S	R	125
3	,,	S	R	S	S	R	100
4	,,	R	R	S	S	S	100
5	,,	S	R	S	S	R	75

Su=Sulphonamide. P=Penicillin. Str=Streptomycin. C=Chloramphenicol. T=Tetracyclines. M.I.C.=Minimum inhibitory concentration.

The viable organisms in the three pretreatment specimens in Cases 1, 2, and 3 were enumerated (Miles and Misra, 1938).

During treatment, mid-stream specimens of urine from Cases 1, 2, and 3 were obtained on alternate days and submitted to the full laboratory procedures already described. In Cases 4 and 5 standard laboratory cultures were performed twice weekly.

Biochemical

The following studies of renal function were made on each patient on a number of occasions before and after cycloserine administration: (*a*) creatinine-clearance test, and (*b*) blood-urea nitrogen determination. The results of these studies are summarized in Table III.

During treatment cycloserine concentrations were measured (Jones, 1956) in plasma and in 24-hour collections of urine, every second day.

Results

All five patients responded dramatically to treatment. Within three days they were afebrile and free from all urinary symptoms, the most striking feature being the disappearance of nocturia. Patients 1, 2, and 3 had their first nights of uninterrupted sleep for many months. Patients 4 and 5, who had high swinging fever, sweating, and prostration, became afebrile within 48 hours after the start of treatment, and rapidly regained their appetite and feeling of well-being. All patients have remained completely well since stopping treatment, the follow-up periods ranging from two to seven months.

TABLE III.—*Renal Function Tests Before and After Treatment*

Case No.	Mean Blood-urea Nitrogen (mg./100 ml.)		Serum Creatinine (mg./100 ml.)		Creatinine Clearance (ml./min.)	
	Before	After	Before	After	Before	After
1	19 (3)	20 (3)	1·1 (2)	0·7 (2)	50 (2)	64 (3)
2	15 (4)	15 (2)	0·75 (4)	0·7 (2)	102 (4)	77 (2)
3	41 (2)	55 (2)	1·8 (1)	1·5 (2)	33 (1)	40 (2)
4	16 (2)	—	0·7 (2)	0·6 (1)	92 (2)	64 (1)
5	14 (1)	9 (1)	0·6 (1)	0·6 (1)	45 (1)	144 (1)
Normal ranges ..	8–20		0·6–1·2		80–130	

Figures in parentheses indicate the number of determinations from which each mean value was derived.
Urea-nitrogen determinations by the manometric Van Slyke technique.
24-hour creatinine-clearance determinations by the method of Owen, Iggo, Scandrett, and Stewart (1954).

With one exception there was no evidence, either subjectively or objectively, of any toxicity attributable to cycloserine in the dosage employed. The patient (Case 3) who showed a mild personality change, characterized by phases of depression alternating with mild confusion, previously had impaired renal function (see Table III) and in consequence had much higher plasma cycloserine levels than the other patients in the series. These toxic effects, however, rapidly disappeared at the end of treatment and were never severe enough to warrant withdrawal of the drug.

Figs. 1, 2, and 3 illustrate the bacteriological progress in Cases 1, 2, and 3 respectively, in relation to the urine and plasma concentrations of cycloserine achieved during treatment. They also illustrate that the urinary concentrations attained equal or exceed the minimum inhibitory concentrations of cycloserine required for the strains of *E. coli* isolated from these patients. Cases 4 and 5 achieved urine cycloserine concentrations of 113 and 172 μg./ml. respectively, and these substantially exceeded the minimum inhibitory concentrations for their respective strains of *E. coli*. (see Table II).

In every case microscopical evidence of pyuria disappeared when the urine became sterile. Follow-up studies at approximately monthly intervals have shown no bacteriological evidence of relapse (see Figs. 1–3).

There has been no marked change in the results of the renal-function tests during the period of the study, with the exception of Case 5. In this instance the marked increase in creatinine clearance probably reflects an improvement in fluid balance rather than a change in glomerular filtration efficiency.

Discussion

The treatment of recurrent infection of the urinary tract in women is notoriously difficult, and even after apparently successful treatment relapse is common. The incidence of such infections in female diabetic patients is much higher than in the general population (Barnard *et al.*, 1953) and, like any infection in the diabetic subject, is apt to complicate the control of their disease. The three diabetic women included in this study were seriously ill on account of urinary infections which had proved resistant to multiple courses of sulphonamide and antibiotic treatment. In contrast, a single course of cycloserine, 250 mg. thrice daily for 14 days, gave a prompt and lasting remission of the infection, with consequent striking improvement both in their general health and in the state of their diabetes. The two

young non-diabetic women had fulminating and very alarming illnesses due to coliform infection of the urinary tract, which was rapidly and completely controlled within 48 hours of starting treatment with cycloserine.

The strains of *E. coli* encountered in the present series have all shown similar sensitivities to cycloserine *in vitro*, though much more resistant strains have been reported by other workers (Hughes *et al.*, 1958). In part at least, this discrepancy may be attributable to differences in technique for determination of minimum inhibitory concentrations. The levels of the drug found in the plasma in the present study are considerably below those required for effective *in vitro* inhibition, and it may be that only as a result of concentration of the drug in the renal tubules is an effective bacteriostatic or bactericidal concentration attained. If this is so, infections due to *E. coli* elsewhere in the body may respond less satisfactorily than those in the urinary tract.

It is noteworthy that the patient (Case 3) whose renal function was most seriously impaired attained urinary sterility more slowly than the others, and this was associated with a slower rise in urinary concentration of the drug and with a much higher plasma level. For these reasons, cautious administration is advised in the presence of established renal damage.

It seems likely that *E. coli* infections of the urinary tract, which do not commonly respond completely to existing chemotherapeutic regimes, will often yield to cycloserine therapy. The results of this small study are, in our opinion, encouraging enough to justify a more extensive trial of cycloserine in a larger series of patients with infection of the urinary tract due to *E. coli* and other coliform organisms. This study is at present proceeding.

Summary

Five patients with severe urinary infection due to *E. coli*, three of whom were diabetic subjects, were treated with cycloserine, 250 mg. thrice daily for 14 days. Complete clinical and bacteriological remission was achieved, without subsequent relapse during a follow-up period of from two to seven months.

Mild toxicity, encountered in one patient with impaired renal function, did not interfere with treatment.

We acknowledge a generous grant from Messrs. Eli Lilly and Co. Ltd. for equipment, and also for supplies of cycloserine. We thank Dr. J. S. Robson and Dr. Mary McDonald for carrying out the renal biopsy studies.

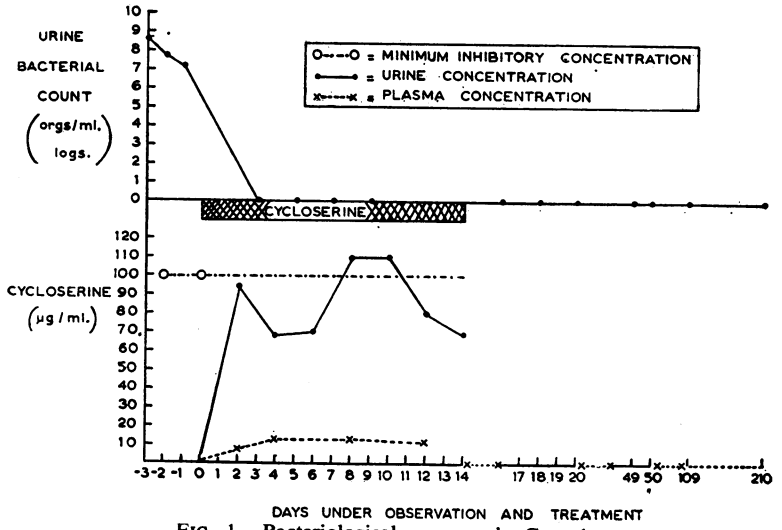

FIG. 1.—Bacteriological progress in Case 1.

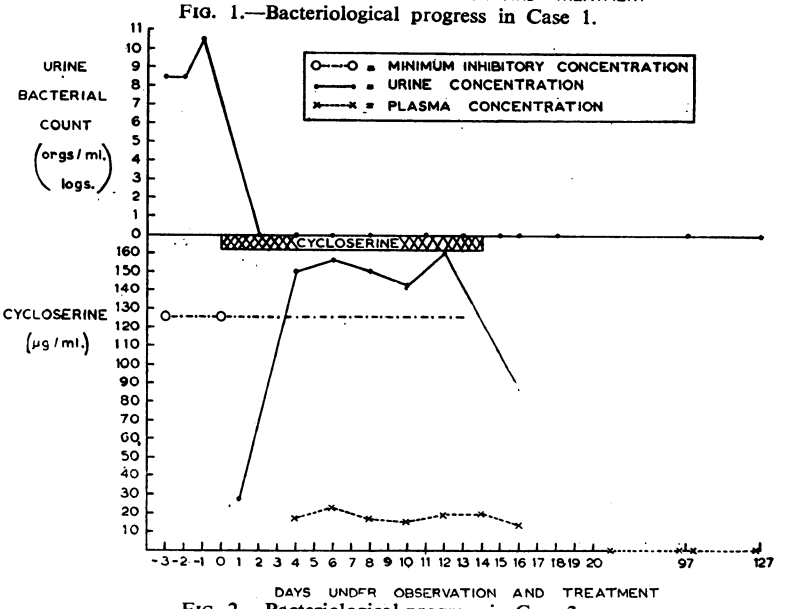

FIG. 2.—Bacteriological progress in Case 2.

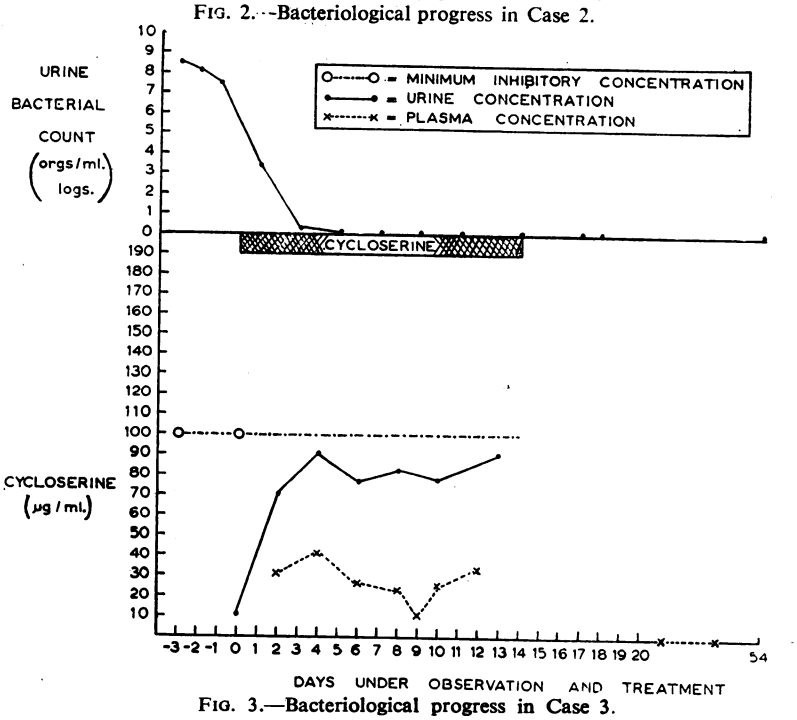

FIG. 3.—Bacteriological progress in Case 3.

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CAESAREAN SECTION SCAR SAFETY

BY

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After a caesarean section, the question "Once or always?" still remains most pertinent, the answer to which verges on gambling. There is no clinical test for the estimation of scar safety in a subsequent pregnancy or labour short of the practical experience. Radiology is capable of providing guidance in some cases.

A recent specimen of a uterus previously subjected to a lower-segment caesarean section and later removed because of fibroids shows quite clearly the typical appearance of a healed transverse incision in the lower segment (Fig. 1). On opening all uteri which have previously been subjected to lower-segment caesarean section a larger or smaller depressed scar will always be seen. That this scar is at the site of the previous caesarean section can be confirmed by inspecting Fig. 2. A hysterogram prior to opening this particular uterus shows a sound in the external scar and the typical internal depression at the same level (Fig. 3). Histopathological evidence (Fig. 4) adds further confirmation in that this thinned area, with both an external and an internal depression, consists entirely of fibrous tissue.

Now this finding, far from being unusual, is present after all lower-segment caesarean sections. Poidevin and Bockner (1958) previously reported the results of a

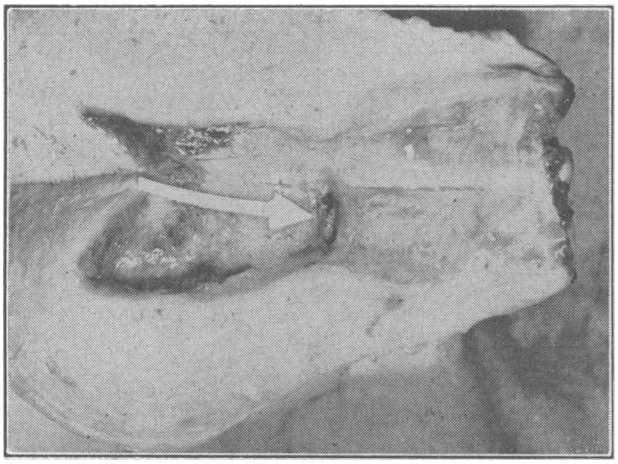

FIG. 1.—Arrow points to the typically seen scar of a previous lower-segment caesarean section.

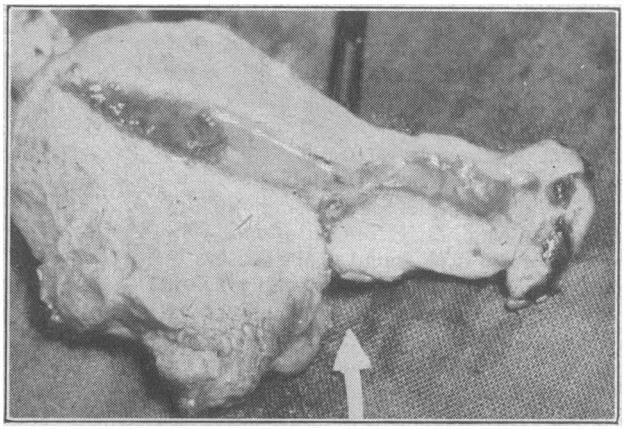

FIG. 2.—Arrow points to the external scar of a previous lower-segment caesarean section shown at the same level as the internal scar.

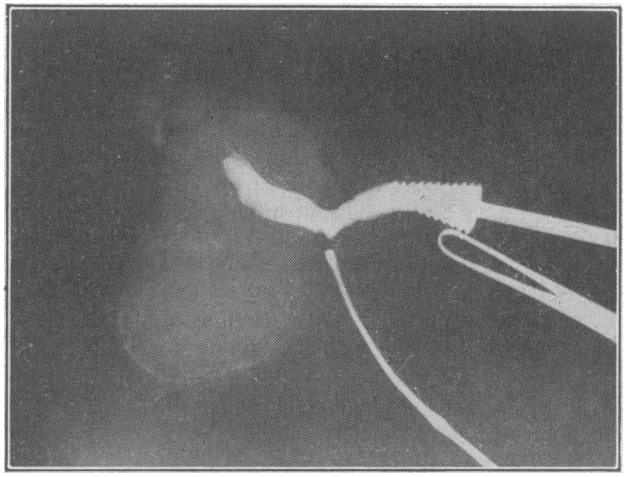

FIG. 3.—Hysterogram of same uterus, as in Fig. 2, before opening. The sound is in the external scar, and the internal scar is shown by a typical wedge-type deformity.

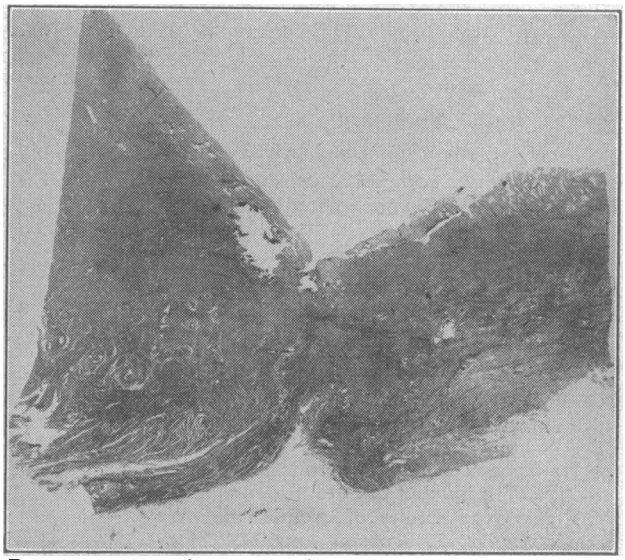

FIG. 4.—Section of scar area from same uterus as in Figs. 2 and 3.