with these problems a poor prognosis provided that the disorder is treated in a reasonable way.

Summary

Of 111 children referred to hospital with enuresis who were comprehensively evaluated, 93 were followed up after a period of five years. It was possible, therefore, to determine the number who remained wet five years after initial investigation and treatment and to ascertain the time of cessation of bed-wetting in those who had become dry.

At initial evaluation no single causal factor accounted for enuresis. A positive family history of the condition was frequent and abnormalities in the electroencephalogram were present in 84%. The majority of the children came from stable homes and most of them did not show marked emotional disturbances.

At follow-up 93 children were traced and interviewed: 37 (60%) of the 62 boys and 23 (74%) of the 31 girls had become "dry." Age was more strongly associated with cure than any other factor. A greater percentage of those entering the survey at 10+ years had become "dry" more frequently than of those investigated earlier. Half the series

were dry by the age of 12 years and three-quarters by 14-15 years.

Children whose bed-wetting persisted after puberty tended to be duller than those becoming dry earlier, but no correlation was shown between persistence of enuresis and deprivation, maladjustment, or abnormalities of the bladder neck.

The study has failed to reveal a constant, single cause of bed-wetting, nor has it indicated any particular factor among those commonly considered which is associated with the persistence of enuresis. At present, therefore, it is reasonable to regard enuresis as a delayed development or loss of bladder control which may be affected by many factors, physical and psychological.

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"COLOMYCIN" TREATMENT OF KLEBSIELLA AEROGENES INFECTION OF URINARY TRACT IN PARAPLEGIA

BY

E. W. COLLEY, M.R.C.S., L.R.C.P., D.Path.

Registrar in Clinical Pathology

H. L. FRANKEL, M.B., B.S., M.R.C.S., L.R.C.P.

Senior Registrar, National Spinal Injuries Centre

Stoke Mandeville Hospital, Aylesbury

Recently introduced into this country, "colomycin" (colistin methane sulphonate) is an antibiotic isolated by Koyama *et al.* (1950) in Japan as a fermentation product of *Bacillus colistinus*. In chemical structure and antimicrobial activity it closely resembles the polymyxins, but no serious toxic effects have been reported (Schwartz *et al.*, 1959-60; Wright and Welch, 1959-60). Colomycin is effective in many Gram-negative infections, mainly those due to the *Pseudomonas* and *Klebsiella* groups (Petersdorf and Hook, 1960; Yow *et al.*, 1961; Carroll and Malette, 1961).

Traumatic paraplegia results in an initial period of complete retention of urine, when some form of catheterization is necessary. In the National Spinal Injuries Centre intermittent catheterization is employed as the method of choice in the immediate and early stages following the onset of paraplegia, and is continued until automatic micturition begins and the residual urine is less than 100 ml. Many patients remain free from infection for many weeks during this period of intermittent catheterization, and only a certain number develop an infection of the urinary tract. In the absence of complicating factors, such as stones in the urinary tract, hydronephrosis, or bladder diverticula, treatment with the appropriate antibiotic is generally effective in eliminating the infection and rendering the urine sterile again. An exception is infection due to *Klebsiella aerogenes*, which is often resistant to all the routine antibiotics and is found relatively frequently in this centre. The trial reported here was carried out to determine the effectiveness of colomycin in the treatment of *K. aerogenes* infection of the urinary tract in paraplegia.

Material and Methods

Eighteen male paraplegic patients were selected, all of whom had had persistent *K. aerogenes* infection of the

urinary tract for varying periods from 2 to 60 weeks, the organism having been isolated in pure culture on at least three separate occasions immediately preceding the trial. All patients had persistent pyuria and bacilluria, but were afebrile and free from toxic symptoms. Other antibacterial drugs, such as penicillin, nitrofurantoin, tetracycline, sulphadimidine, and streptomycin, had previously been unsuccessfully tried in all cases. Residual urine in each patient was less than 100 ml. All patients had normal renal function as judged by a normal blood urea at the beginning of treatment and a urinary protein level of less than 10 mg./100 ml.

During the trial no patient was catheterized. Midstream specimens of urine were carefully taken from each patient daily during the course of treatment and at least twice during the week following the end of treatment. All specimens were cultured on blood agar and MacConkey agar, examined microscopically, and tested for protein. The viable bacteria in the urine were counted on the day before treatment began and daily throughout the course of treatment, using the method of Miles *et al.* (1938). Each specimen of urine was examined within one hour of being taken from the patient.

A blood urea estimation was carried out on each patient during the week before onset of treatment and again within a week after conclusion of treatment. Capsular typing of the organism was carried out in each case, and also on any *K. aerogenes* isolated during treatment and the period of follow-up. The minimum inhibitory concentration of colomycin for growth of *K. aerogenes* freshly isolated from each patient was determined before treatment, using doubling dilutions of colomycin in broth. Colomycin blood levels were measured in five patients and urinary levels in eight. The levels were determined by serial dilu-

tions in broth, using as test organism a strain of *Escherichia coli* of known colomycin sensitivity.

All cases were followed up for varying periods from 3 to 22 weeks and the urine was cultured weekly during this period.

Dosage.—Nine patients were treated with 80 mg. (1 million units) of colomycin eight-hourly. Two patients received only two doses each owing to the occurrence of side-effects. The remaining seven patients received the full course of five days' treatment. Nine other patients were given 160 mg. (2 million units) eight-hourly for five days. All doses were administered intramuscularly.

Results

Sensitivity of *K. aerogenes* to Colomycin.—The minimum inhibitory concentration of colomycin for all the freshly isolated *K. aerogenes* strains lay within the range 2–16 $\mu\text{g./ml.}$

Capsular Typing.—All except three of the organisms were of capsular type 25, which is indigenous to this hospital. One was of type 7 and two were of type 54. In the five cases in which *K. aerogenes* infection persisted or recurred the capsular type remained the same. These included four cases of type 25 and one of type 7.

Blood Levels.—In five patients a single dose of 80 mg. resulted in blood levels of 8 $\mu\text{g./ml.}$ after one hour. After seven hours blood levels of 8 $\mu\text{g./ml.}$ were present in three patients and 16 $\mu\text{g./ml.}$ in two.

Urinary Levels.—Urinary colomycin levels were measured in eight patients receiving 80 mg. of colomycin eight-hourly. One hour after the initial dose there was no detectable colomycin in the urine. Six hours later the colomycin concentrations were in the range 128–512 $\mu\text{g./ml.}$ Daily assay showed that these levels were maintained.

Therapeutic Effect.—*K. aerogenes* persisted throughout treatment in one case. In the other 17 patients the urine was free of *K. aerogenes* at the end of the second day of treatment, including the two patients who received only two doses of colomycin. In 11 cases the *K. aerogenes* was immediately supplanted by other resistant organisms. These were *Proteus mirabilis* in five cases, *Proteus rettgeri* in two, *Providencia* in two, and *Streptococcus faecalis* in two. In six patients the urine was sterile at the end of treatment. In 13 of the 18 patients there was no recurrence or persistence of *K. aerogenes* infection throughout the period of follow-up. In three cases *K. aerogenes* infection recurred within a few days of ending treatment, in one case infection recurred after five weeks, and in one case *K. aerogenes* infection persisted.

Bacterial Counts.—Viable bacterial counts before treatment varied from 10^6 to $10^9/\text{ml.}$ The lowest counts occurred on the second and third days of treatment, when in five cases the urine was sterile and in 10 cases the counts were in the range 10^2 to $10^3/\text{ml.}$ In three cases there was no reduction in bacterial count. In those cases where a resistant organism appeared on the second or third day of treatment, and in the one case where *K. aerogenes* infection persisted, the viable counts gradually increased and by the fifth day of treatment were near pre-treatment levels.

Side-effects.—Side-effects possibly due to colomycin occurred in two patients, both of whom were treated with the lower dosage. In one case severe headache with vomiting developed three hours after the second dose. The symptoms subsided four hours after onset. In the other patient nausea and a severe burning upper abdominal pain developed one hour after the second dose. Symptoms sub-

sided after three hours. No more colomycin was given in either case. No evidence of renal toxicity was encountered. There was no increase in casts or protein in the urine of any patient nor was there any rise in blood urea.

Discussion

Assessment of these results on the basis of elimination of the infecting organism from the urine indicates that colomycin is an effective antibiotic in the treatment of *K. aerogenes* infection of the urinary tract. Some of the patients had been continuously infected for many months, but in only five cases did *K. aerogenes* recur or persist during the period of follow-up. An interesting feature in 11 of the 18 patients treated was the appearance on the second and third days of treatment of organisms completely resistant to colomycin. The early appearance of these resistant organisms suggests that they were already present in the urinary tract but that their growth was suppressed by the dominant *K. aerogenes*.

Results were better in the nine patients treated with the higher dosage of 160 mg. eight-hourly. In five patients the urine was sterile at the end of treatment, and *K. aerogenes* recurred in only one patient, five weeks after the end of treatment. In the patients treated with the lower dosage of 80 mg. eight-hourly *K. aerogenes* persisted or recurred in four patients. The urine was sterile in only one patient of this lower dosage group at the end of treatment, but the presence of bladder diverticula in four cases may have encouraged the growth of resistant organisms. The capsular type of the organism remained the same when *K. aerogenes* infection recurred, suggesting a recrudescence of persistent infection rather than a reinfection.

In one case the *K. aerogenes* persisted throughout treatment although there were no complicating factors in the urinary tract. The organism was inhibited *in vitro* by a colomycin concentration of 4 $\mu\text{g./ml.}$, but, except for an initial decrease, it persisted in the urine in unabated numbers despite a urinary colomycin level ranging from 128 to 512 $\mu\text{g./ml.}$ Blood levels, however, were 8 $\mu\text{g./ml.}$, which is only marginally above the *in-vitro* sensitivity of the organism. Similar cases are reported by Petersdorf and Hook (1960).

Summary and Conclusions

Eighteen male paraplegic patients all with chronic *K. aerogenes* infection of the urinary tract were treated with colomycin. Assessed on the basis of elimination of *K. aerogenes* from the urine, the antibiotic was moderately successful. An undesirable feature was its ineffectiveness against some other urinary pathogens, mainly of the *Proteus* group, which replaced the *K. aerogenes* during treatment in 11 of the 18 cases. In one case *K. aerogenes* persisted throughout treatment. In six cases the urine was sterile at the end of treatment, but in three of these *K. aerogenes* recurred within a few days. There were no serious toxic complications, but minor side-effects occurred in two patients.

ADDENDUM.—Since this trial was completed nine similar patients have been treated with colomycin 160 mg. eight-hourly. Bacterial counts were not performed. In one patient the antibiotic had to be discontinued on the third day of treatment owing to severe burning abdominal pain, vomiting, headache, and facial paraesthesiae. The symptoms subsided within 24 hours. Six other patients remained free of *K. aerogenes* infection for a minimum of four

weeks after treatment and in two patients the urinary *K. aerogenes* infection persisted throughout treatment. In both these cases the organism showed the same *in-vitro* sensitivity before and after treatment.

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Preliminary Communications

Thymectomy in Systemic Lupus Erythematosus

Thymectomy is a recognized therapeutic measure in myasthenia gravis, especially for young female patients with severe disease of recent onset. This is of interest in relation to the possibility that myasthenia gravis is an autoimmune disease, since circulating autoantibody against muscle components is frequently detectable (Strauss *et al.*, 1960). Moreover, the thymus is abnormal in most cases; hyperplasia with pronounced germinal-centre formation is present in 50-60% of cases, and thymomas, usually of lympho-epithelial character, make up most of the remainder. Burnet and Holmes (1962) drew further attention to the possible relationship of the thymus to autoimmune disease by their recognition of thymic lesions in the mouse strain NZB/BL, the only experimental animal model of spontaneous autoimmune disease. These thymic lesions, which are basically similar to those seen in myasthenia gravis, appear in 90% of mice around 5 to 7 months of age. Experiments with the NZB/BL strain of mice have indicated that thymectomy in early life delayed but did not prevent the appearance of a positive Coombs test, which is the main serological evidence of the development of the autoimmune condition in this strain.

In view of the uncertain prognosis in classical systemic lupus erythematosus in young women, and the possibility that thymectomy might remove an important source of abnormally active lymphoid cells, we undertook thymectomy for the treatment of this condition. The patient was a 20-year-old woman whose disease had been poorly controlled despite maintenance corticosteroid therapy.

CASE REPORT

A housewife aged 20 was referred in December, 1961, with classical systemic lupus erythematosus. The past history included transitory non-arthritic "rheumatic" pains for one year, and a scaly itchy rash on the hands, face, and back six months previously. Her admission illness, of six weeks' duration, consisted of recurring chills and shivers, malaise, migratory joint and muscle pains, and thereafter an erythematous papular rash on the face and trunk. The major physical findings were mild tonsillar infection, rash, and fever (temperature 38-39° C.).

The laboratory investigations fully supported the diagnosis of lupus erythematosus: these included an elevated erythrocyte sedimentation rate (E.S.R.) of 46 mm./hour (Westergren), an elevated gamma-globulin level of 2 g./100 ml., consistently positive L.E. cell preparations, and highly elevated serum titres, up to 1/512, in the autoimmune complement fixation (A.I.C.F.) reaction with liver and kidney antigens (Gajdusek, 1958). Prednisolone treatment induced prompt remission, but cessation

of this treatment in February, 1962, precipitated another relapse with pronounced fever, rash, and pneumonitis. Thereafter treatment with prednisolone was continued, the dosage being reduced to a maintenance level of 10 mg. daily.

However, in August there was a further relapse with fever, muscle pains, pneumonitis, and delirium. The prednisolone dosage was maintained at 10 mg. daily, and in September thymectomy was performed. The thymic excision was thought to have been complete.

A vertical incision was made from the suprasternal notch almost to the umbilicus, and the whole length of the sternum was split vertically. The extraperitoneal tissues and the anterior mediastinum were entered and the split edges of the sternum were retracted. The body of the thymus was situated in the neck and the two poles extended down, anterior to the innominate vein, to the level of the aortic arch. The entire thymus was very small; the body was yellow, and the lower poles were very pale. Small arteries entered the thymus from the inferior thyroid arteries, and two very large veins entered the innominate vein from the posterior aspect of the thymus. Neither pleural cavity was opened. The mediastinum was drained by a long Portex tube with multiple side holes which was connected to an underwater drainage system.

Macroscopic examination of the resected thymus showed it to be of normal shape but small, weighing only 5 g. (Fig. 1). Microscopical examination showed pronounced atrophy (Fig. 2). There was no cortex. The medulla showed islands of cells, some of which were epithelial in character and others were spindle-shaped, resembling fibroblasts. Varying-sized collections of lymphocytes were present adjacent to these cellular areas, but plasma cells were scanty. Hassall's corpuscles were scanty and atrophic. There were neither discrete lymphoid follicles nor structures resembling germinal centres. A characteristic histological abnormality was not identified in this thymus: the appearances could well be accounted for by a prolonged period of corticosteroid treatment.

Manifestations of active disease persisted, necessitating increase of the prednisolone dosage to 60 mg. daily on the tenth post-operative day. Convalescence was temporarily interrupted by a minor staphylococcal wound infection, staphylococcal bronchopneumonia, and loss of 10 kg. in weight, but after eight weeks she improved and resumed her normal activities, although still receiving a maintenance dose of prednisolone ranging from 20 to 10 mg. daily. The post-operative changes in the laboratory indices of disease activity are shown in Fig. 3.

FIG. 1.—Photograph of the two lobes of the resected thymus, weighing 5 g.