mentioned ventriculographic findings, a history of infestation with *Taenia solium*, and the presence of cysticerci in other parts of the body (retina, muscles).

The differential diagnosis must exclude any intracranial space-occupying process, such as cerebral tumours, including tuberculomata and metastases, abscesses, subdural haematoma, and pseudo-tumour cerebri.

The course of the disease, the previous history, the present condition, and the auxiliary tests may establish the diagnosis by itself.

Prognosis and Treatment

The prognosis is poor in generalized, basal, or ventricular cysticercosis. Patients die as a result of raised intracranial pressure or ventricular block. Cortical cysticercosis runs a more chronic course. In cortical cases with only a few cysts there may be spontaneous remissions followed by relapse.

The only non-operative treatment is the administration of anticonvulsant drugs if there are fits. In cortical or ventricular forms, however, the parasites may be excised surgically. In generalized or basal cysticercosis extensive bilateral decompression should be performed to relieve the severe intracranial hypertension.

We operated on 48 of our 65 patients; in 20 cases large decompressive craniotomies were performed, in 7 a decompression according to Cushing's technique, and in 21 the posterior fossa was explored. Wherever possible the cysticerci were excised during the operation. The operations were well tolerated and complications rare. Cerebral oedema was treated by massive dehydration and daily lumbar puncture. In the ventricular form, if collapse occurs after tapping the ventricles the patients must be rehydrated.

In the successful cases the signs of raised intracranial pressure disappeared, as did most of the neurological signs. Convulsions, however, continued. Of the 48 patients submitted to operation 11 died at or within a short time of operation, and two more 1 and 2½ years post-operatively respectively. There was no operative mortality with the 12 cases of cortical cysticercosis; but 2 of the 6 ventricular cases, 4 of the 17 basal cases, and 5 of the 13 generalized cases died after operation.

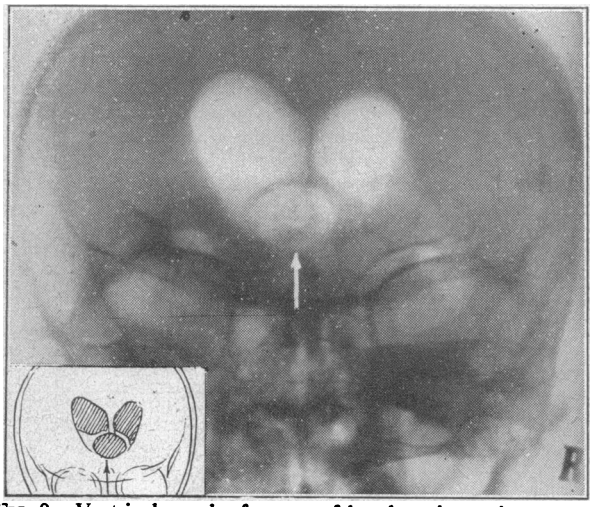

FIG. 9.—Ventriculograph of a case of basal cysticercosis; antero-posterior view. Both lateral ventricles are dilated. The third ventricle is dilated and displaced upward.

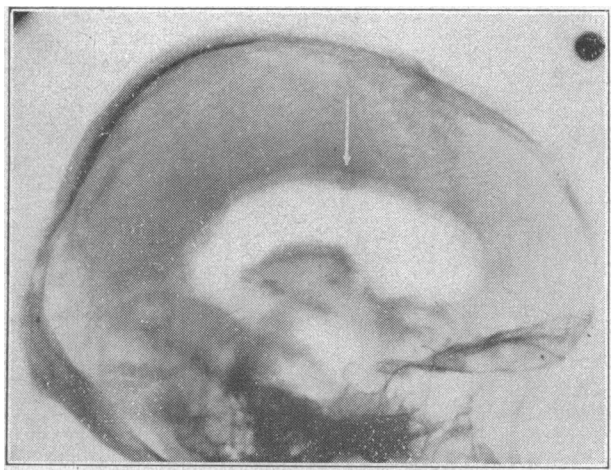

FIG. 10.—Ventriculograph showing a cysticercus attached to the wall of the lateral ventricle.

Summary

A personal series of 65 cases of cerebral cysticercosis seen in Bucharest is presented.

Their clinical features and the results of laboratory and radiological examination are described. Operation was performed in 48.

Differential diagnosis and prognosis are discussed.

PROTEUS INFECTION OF URINARY TRACT, WITH SPECIAL REFERENCE TO TREATMENT WITH NITROFURANTOIN

BY

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Infection produced by potentially pathogenic commensal organisms resistant to the chemotherapeutic agents in general use is becoming prevalent as their more virulent competitors are eliminated by these agents. Among such resistant organisms discussed by Bryer (1955) are members of the *Proteus* group. In the last few years there have been several reports in the American literature on the use of nitrofurantoin ("furadantin") in infections of the urinary tract due to proteus, notably by Richards *et al.* (1955). This relatively non-toxic drug, active *in vitro* against many Gram-positive and Gram-negative bacteria, including the *Proteus* group, is excreted in high concentration in the urine following oral administration, although effective blood and tissue levels are not produced.

The *British Medical Journal* (1955) and the *Lancet* (1955) suggested that it might prove a helpful addition to the established urinary antiseptics, especially in the treatment of proteus infections, but there have been few reports of its use in the British literature. Heffernan *et al.* (1955) and McGeown (1956) recorded only moderately satisfactory results in a small number of cases.

The sensitivity tests performed *in vitro* in this laboratory against *Proteus* strains showed that many were resistant to the commonly used antibiotics but sensitive to nitrofurantoin. A series of patients with a known proteus urinary infection was therefore studied so as to determine whether the response to treatment reflected these observations.

Material and Methods

The series consisted of a group of 58 patients (23 males, 35 females) with a proteus urinary infection. There was no complicating disease of the urinary tract in 12 (21%),

TABLE I.—*Bacterial Sensitivity in vitro*

Organism	No. Tested	Numbers Sensitive to: Penicillin (2·5 u./Disk)	Erythromycin (10 μg./Disk)	Bactracin (10 u./Disk)	Streptomycin (80 μg./Disk)	Neomycin (50 μg./Disk)	Chloramphenicol (100 μg./Disk)	Tetracycline (100 μg./Disk)	Chlortetracycline (100 μg./Disk)	Oxytetracycline (100 μg./Disk)	Polymyxin (500 u./Disk)	Nitrofurantoin (10,000 μg./TAB.)	No. Tested	Numbers Sensitive to: Novobiocin (20 μg./Disk)	Spiramycin (60 μg./Disk)
P. mirabilis	50	11 (22%)	0	2 (4%)	32 (64%)	50 (100%)	44 (88%)	3 (6%)	3 (6%)	6 (12%)	1 (2%)	50 (100%)	14	9(64%)	0
P. vulgaris	3	0	0	0	1	3	2	3	1	1	0	3	1	0	0
P. morganii	2	0	0	0	1	2	2	1	0	1	1	2	0	—	—
P. rettgeri	3	0	0	0	0	3	0	1	2	2	0	3	0	—	—
Providence	2	0	0	0	0	2	0	0	0	0	0	2	1	0	—
Enterococcus	27	8 (30%)	21 (78%)	27 (100%)	4 (15%)	27 (100%)	25 (93%)	13 (48%)	12 (45%)	14 (52%)	0	27 (100%)	0	—	—

though 4 of these had recurrent or chronic urinary sepsis. The remaining 46 (79%) had complicating factors. Of these, 27 (47%) had chronic local disease, which included urethral stricture, prostatic hypertrophy, urolithiasis, hydronephrosis, and automatic bladder; some of these infections were post-operative. Sixteen cases occurred in women during the post-partum period or after operations for genital prolapse, and in the remaining three patients with a normal urinary tract the infection resulted from urethral catheterization. Most of the patients had signs and symptoms of a urinary infection.

Bacteriology

A catheter or mid-stream specimen of urine was examined in all cases before treatment was started, and in many instances both during and after treatment. In each case this confirmed the presence of an infection by revealing protein, pus cells, and organisms. The urine was cultured on blood agar and litmus lactose agar.

The identification of the *Proteus* group was based on the usual cultural, morphological, and biochemical criteria described by Cook (1948), Kauffmann (1954), and Wilson and Miles (1955). The strains isolated were typed biochemically as detailed by Cook (1948), and the *Proteus* group was thus divided into the four species: *P. mirabilis, P. vulgaris, P. morganii,* and *P. rettgeri.* Organisms of the Providence group, defined by Kauffmann (1954), were also included, since they have close affinities with *Proteus* as discussed by Singer and Bar-Chay (1954).

The dried-disk technique described by Fairbrother and Jennings (1955) was used for testing the sensitivity of the strains to penicillin, erythromycin, bacitracin, streptomycin, neomycin, chloramphenicol, tetracycline, chlortetracycline, oxytetracycline, polymyxin, and nitrofurantoin. A few strains were also tested against novobiocin and spiramycin as they became available. Sulphonamide sensitivity tests were not performed. The concentration of antibiotic per disk is recorded in Table I. For comparison a zone of inhibition of growth 10 mm. or more in diameter was considered to indicate sensitivity to the antibiotics, the disks being 5 mm. in diameter. Tablets of nitrofurantoin containing 10,000 μg. were used routinely, and in some instances paper disks containing 100 μg. of the drug were also employed.

Treatment

The series was not a controlled trial, so there was no selection or random sampling of cases for treatment, which was directed by the clinician in charge of the patient. In many instances a lack of response to the initial treatment necessitated a change of drug. Some infections following urinary tract or gynaecological operations were not prevented by prophylactic chemotherapy.

Nitrofurantoin dosage was based on body weight—5–8 mg. per kg. in divided doses in 24 hours. Most patients received 100 mg. six-hourly, and two children were given 25 and 50 mg. six-hourly respectively. With other drugs the dosage was at least that recorded in Table II.

Bacteriological Results

The *Proteus* species isolated initially was identified as *P. mirabilis* in 49 patients (84%), *P. vulgaris* in 3, *P. morganii* in 2, and *P. rettgeri* in 3. One infected with *P. morganii* initially became reinfected with *P. mirabilis* at a later date. A Providence strain was found in one case, and in another one occurred with *P. rettgeri.* In 30 cases (52%) there was a pure proteus infection, but in 28 (48%) other organisms were also present. There was an enterococcus in 27 (47%), *E. coli* in 4, and *Staph. pyogenes* in 3.

The results of the sensitivity tests are detailed in Table I. Although with some species the number of strains tested were few the results suggested that each *Proteus* species has a different antibiotic spectrum. Thus, only *P. mirabilis* was sensitive to penicillin, and the other three *Proteus* species were more sensitive to the tetracycline antibiotics than *P. mirabilis. P. rettgeri* was resistant to both streptomycin and chloramphenicol. Providence strains were particularly resistant to the antibiotics. All the *Proteus* and Providence strains were sensitive to nitrofurantoin and neomycin. The latter two drugs and chloramphenicol were the most effective against the two commonly occurring organisms, *P. mirabilis* and the enterococcus.

The zones of inhibition of growth produced by the 10,000-μg. nitrofurantoin tablet varied from 10 to 20 mm. in diameter (tablet diameter being 7 mm.). Two strains were only partially inhibited, a few less sensitive colonies being present in a larger zone of general inhibition of growth. Thirteen *Proteus* strains were tested against the 100-μg. disk (also 7 mm. in diameter), and the zones of inhibition were

TABLE II.—*Results of Treatment (Four or More Days' Course)*

Drug and Dosage	Average Course of Treatment (Days)	Total Nos. Treated	Cured: Laboratory and Clinical Cure	Cured: Clinical Cure	Cured: Total Cured	Nos. Failed Treatment
Nitrofurantoin (dose see text)	8	23 (12)	12 (6)	6 (2)	18 (78%) (8)	5 (4)
Streptomycin (with mist. pot. cit. *B.P.C.*) 2 g. per day in divided doses	7	23 (13)	7 (3) 1 with nitrofurantoin; 2 with penicillin	3 (0) 1 with penicillin	10 (43%) (3)	13 (10) 2 with penicillin
Sulphonamide (with mist. pot. cit. *B.P.C.*), 2 g. stat., 1 g. 6-hourly	7	22 (13)	2	3	5 (23%) (0)	17 (13) 1 with penicillin
Chloramphenicol, 500 mg. 6-hourly	8	4 (3)	0	1	1 (0)	3 (3)
Tetracycline analogues, 250 mg. 6-hourly	7	10 (7)	3 (3) 1 with nitrofurantoin	3	6 (3)	4 (4)
Penicillin, 1 mega unit per day in divided doses	6	7 (2)	2 both with streptomycin	1 with streptomycin	3 (0)	4 (2) 2 with streptomycin, 1 with sulphonamide
Novobiocin, 500 mg. 12-hourly	7	1 (1)	0	0	0	1 (1)
Mist. pot. cit. *B.P.C.* alone	11	7 (4)	1 (1)	1	2 (1)	5 (3)
Mandelic acid derivative	13	4 (3)	1 (1)	1	2 (1)	2 (2)

Numbers in parentheses refer to cases with chronic complicating urinary tract disease.

from 9 to 14 mm. in diameter, but five strains showed only partial inhibition of growth as described above. These results demonstrated that the 10,000-μg. tablet produced zones of inhibition comparable with the 100-μg. disk, which contained a concentration of the drug nearer the therapeutic level in urine. Sensitivity tests on serial isolations of the organisms from 10 patients who received nitrofurantoin showed no significant change of sensitivity. These included six patients in whom treatment failed after three or more days' administration.

Clinical Results

Table II shows the results of four or more days' treatment with a variety of drugs. This minimal period was not necessarily considered to be optimal, especially in complicated cases, but was adopted for comparative purposes, since a cure had occurred in a number of instances by this time with the most effective drugs. The average course of treatment was seven days or more with most of them. The term "laboratory and clinical cure" in Table II indicates known sterilization of the urine, with cure of signs and symptoms of infection, and without evidence of relapse within seven days of the cessation of treatment. A clinical cure denotes a similar cure of signs and symptoms when the urine was not examined after treatment.

The largest groups of patients were those treated with nitrofurantoin, streptomycin, or a sulphonamide. The numbers in these groups were similar, as were the proportions of patients with a chronic urinary tract complication, the number of mixed infections, and the average duration of treatment. In addition, some patients served as their own control, having failed to respond to one or other drugs. The cures were respectively 78%, 43%, and 23%, and if only patients with chronic complicating urinary tract disease were compared the results were even more divergent: 8 of 12, 3 of 13, and 0 of 13 were cured respectively. Thus, nitrofurantoin was more effective than the other two drugs, especially in complicated cases.

A proportion of the patients who received other drugs were cured, but the numbers treated with each were too small for direct comparison.

The correlation between bacterial sensitivity *in vitro* and successful therapy was not absolute. All the strains eliminated by nitrofurantoin were sensitive, though one was only partially so. In the failures, however, the initially isolated organisms were also sensitive. Eight of the 10 infections which responded to streptomycin were due to a sensitive *Proteus* strain, but so were 5 of the 13 failures. Similar discrepancies were observed in the patients who received other antibiotics.

Twenty-three patients received nitrofurantoin, and 18, including 8 with chronic complicating urinary tract disease, were cured, with bacteriological proof in 12. In 11 of those who responded to treatment, other drugs had failed to eradicate the infection. A course of streptomycin had been given to six of these patients and penicillin with streptomycin to another; oxytetracycline therapy had preceded streptomycin in one of them. One patient had received a combination of sulphadimidine with penicillin, and another chloramphenicol. In two the urine had been rendered alkaline. A known relapse of infection occurred in four complicated cases. The average course of treatment lasted eight days (limits 4–12 days).

The drug failed to remove the infecting *Proteus* strain in five patients. One of them, however, received only four days' interrupted therapy and another complicated case five days' dosage. There were only three failures with more prolonged administration, and all were complicated cases. A nitrofurantoin-resistant *Ps. pyocyanea* replaced the accompanying enterococcus during nine days' treatment in the first patient, who had an automatic bladder. Sulphadimidine had also previously failed. Successive courses of sulphamethizole, streptomycin, 16 days' nitrofurantoin, and chloramphenicol all failed in the second patient, who had renal calculi and abscesses and died of the infection which followed prostatectomy and removal of bladder stones. In the last case a combination of first streptomycin and later oxytetracycline with nitrofurantoin was required to cure the infection which followed a ureteral transplant for carcinoma of the ureter. This patient received a total of 19 g. of the drug in two courses of 31 and 16 days over a period of two months.

The only toxic effect encountered with the drug was vomiting in two patients, but it was severe enough for abandoning of treatment in both. In one the dosage was reduced from 150 to 100 mg. six-hourly without relief. The other had vomited intermittently before treatment as a result of cholecystitis. Two children, aged 3 and 9 years, were treated without ill-effect.

Discussion

The present series of proteus infections of the urinary tract confirmed the findings of Coleman and Taylor (1949) and Erlanson and Jönsson (1953) that *Proteus* strains were uncommon pathogens in acute uncomplicated cases, but occurred frequently in chronic infections, especially after previous antibacterial therapy, following catheterization and instrumentation, and in cases with a chronic urinary tract abnormality or disease. Blahey (1952) also demonstrated that prophylactic chemotherapy during urethral catheterization following gynaecological operations increased the number of proteus infections. Shackman and Messent (1954) similarly found proteus organisms in the bladder urine more frequently after than before prostatectomy. In all such complicated cases the incidence of mixed infections also increased.

The relative frequency of the four *Proteus* species found in this study was similar to that noted by Cook (1948) in isolations from human faeces. The results of the sensitivity tests confirmed the findings of Poole (1954) and Potee *et al.* (1954) that the four *Proteus* species each have an individual and different antibiotic spectrum. Lutz and Hofferer (1955) showed that this also applied to Providence strains. The enterococcus was sensitive to a range of antibiotics similar to that reported by Fairbrother and Jennings (1955).

Garrod *et al.* (1954) found that treatment with drugs in urinary infections was not always successful against organisms sensitive to them, especially when complications were present, and, in contrast, that even resistant bacteria were sometimes removed. Inconsistencies in the correlation between individual sensitivity tests and the results of treatment were also noted in this series.

The poor results with sulphonamides confirmed the opinion of Kass (1955) that such therapy often failed in infections with proteus and the enterococcus, despite a sensitivity *in vitro* of 80% and 30% for the two organisms. He also observed that rendering the urine alkaline or treatment with a mandelic acid derivative were frequently ineffective. With streptomycin acquired resistance was observed in a number of cases in this series and accounted for lack of response, but the low sensitivity of the enterococcus perhaps contributed to other failures. Too few cases were treated with a tetracycline analogue to determine whether the *Proteus* species most sensitive *in vitro* respond clinically. The combination of penicillin with a sulphonamide or streptomycin appeared to add no advantage; perhaps a higher dosage would have been more effective. Only one patient in the series received novobiocin, and without benefit, but some of the *Proteus* strains were sensitive to the antibiotic, as reported by a number of authors in the April issue of *Antibiotic Medicine* (1956).

Chloramphenicol has been found to give inconsistent results in the treatment of urinary infections, and Welch (1954) stated that excretion of the active unconjugated drug is variable and unpredictable. Its routine use is also undesirable because of the occasional complication of fatal aplastic anaemia. The toxicity of neomycin similarly restricts its employment in urinary infections to short

courses. No patient in this series received the antibiotic. The good results with nitrofurantoin confirmed the original bacteriological findings, and in view of its relative lack of toxicity suggest that it is the drug of choice. In one case the infection was cured only when nitrofurantoin was given with an antibiotic. Apart from the value of combined therapy in removing resistant organisms or delaying the emergence of resistance, such combinations would perhaps also be useful in severe pyelonephritis, since effective blood and tissue levels of nitrofurantoin cannot be attained.

The patients were not all observed for a long period following treatment, and the incidence of relapse and reinfection was not determined. In view of this and the consequent criteria accepted for cure it is recognized that perhaps little can be concluded regarding the ultimate effects of therapy. Complicated infections especially are prone to relapse, in addition to their relatively poor response to treatment. However, the object of the investigation was to correlate and compare the relative ability of various drugs in removing infecting *Proteus* strains from the urinary tract with their activity *in vitro*. The results showed that this was in the main achieved. In any case, a final cure in many instances may depend more upon the relief of complicating factors than upon antibacterial therapy alone, and, as McGeown (1956) remarked, a relapse does not detract from the therapeutic value of a drug, but merely indicates the proneness of a damaged renal tract to become infected. Richards *et al.* (1955) observed a relapse of proteus infections which had been treated with nitrofurantoin. However, the relative freedom of the drug from toxic effects and the slow emergence of resistant bacterial strains to it would fit it well for repeated administration or long-term therapy.

Summary

A series of 58 patients with a proteus infection of the urinary tract, of whom 46 (79%) had local complicating factors, were observed in order to compare the results of treatment with sensitivity tests *in vitro*.

The *Proteus* strains isolated were typed biochemically. *P. mirabilis* was the pathogenic species in 49 cases (84%), and in 27 cases (47%) there was a mixed infection with an enterococcus.

Sensitivity tests were performed *in vitro* with nitrofurantoin and 12 antibiotics. All the strains tested were sensitive to nitrofurantoin.

Nitrofurantoin, streptomycin, or a sulphonamide was given to the majority of patients, and these treatment groups were comparable. Nitrofurantoin proved superior to the other two in curing the infection.

There were occasional discrepancies in the correlation between individual sensitivity tests and therapeutic outcome.

Twenty-three patients received nitrofurantoin, and only three failures were recorded with prolonged therapy. The only toxic effect noted was vomiting in two cases.

The results indicated that nitrofurantoin was the most effective drug used, even in complicated cases and mixed infections, and that it is worthy of further trial in a larger series of cases.

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STABILITY OF H. PERTUSSIS VACCINE ESTIMATED BY MOUSE-PROTECTION TEST

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The Whooping-cough Committee of the Medical Research Council (1956) has reported an average deterioration rate of 0.2 log unit per annum for the vaccines used in its trial. This deterioration rate was determined from the results of mouse-protection tests and was not in conflict with the clinical results. In the treatment of the results the Committee regarded the deterioration as a sample value and did not quote the significance of its difference from zero. Moreover, the Committee states that its conclusions are unaltered if the deterioration rate is ignored.

TABLE I.—*Results of Mouse-protection Tests on H. pertussis Vaccine BIV. (Survivors/Total in Group)*

Date of Test	Dose of BIV		
	40×10^6 Cells	200×10^6 Cells	$1{,}000 \times 10^6$ Cells
19/3/51	5/15	9/15	14/15
10/4/51	2/15	2/15	15/15
16/4/51	2/15	5/15	11/12
8/5/51	3/15	4/14	12/15
22/5/51	4/14	9/12	9/14
29/6/51	4/18	5/19	9/10
20/7/51	0/15	7/15	13/15
16/8/51	0/15	3/15	13/15
11/9/51	1/15	6/15	10/15
2/5/52	0/14	2/15	12/15
28/5/52	1/15	4/15	10/20
6/8/52	2/18	9/17	20/20
15/9/52	1/13	1/12	11/15
23/12/52	1/19	1/20	8/18
23/2/53	0/18	2/18	14/18
8/5/53	4/16	7/16	17/20
26/2/54	8/15	10/15	13/14
5/3/54	2/14	3/16	14/16
11/3/54	1/15	2/15	10/13
23/3/54	3/14	5/14	14/15
9/4/54	7/15	11/15	13/15
27/5/54	0/13	7/11	11/15

TABLE II.—*ImD_{50} Values*

Time in Months from January 1, 1951	ImD_{50}	Time in Months from January 1, 1951	ImD_{50}
3	102	19	170
3	350	20	700
4	210	24	560
4	290	26	1,900
5	110	28	180
6	230	38	51
7	240	38	310
8	400	38	490
8	410	39	220
16	510	39	45
17	870	41	200