postulated. The first suggests that there is a temporary secretion of pitressin by the cells of the median eminence and posterior lobe of the hypophysis, while the second theory states that there is a release of stored anti-diuretic hormone (A.D.H.) from the degenerating posterior lobe. Mudd *et al.* (1957) have shown that sectioning of only the hypothalamic-hypophysial pathway results in diabetes insipidus with interphase, whereas the interphase does not occur if all the vasopressor-secreting tissue is removed—that is, sectioning of the hypothalamic-hypophysial tract with hypophysectomy. Lipsett and Pearson (1956) believe that, at equal solute loads, the severity of the diabetes insipidus depends on the level of stalk section and a preservation of a variable portion of the pars nervosa.

In the case presented here, the symptoms were characteristic: polydipsia was outstanding, as is usual in children. They have been seen to drink water from flower bowls or their own urine to relieve their thirst. Enuresis may occur as the first symptom in children where bladder control has been previously established. In adults the polyuria and the need for fluid may be so great as to interfere with work and sleep. If fluid is withheld in these cases, dehydration rapidly ensues, with headache, fatigue, irritability, muscular pains, weight loss, and tachycardia. Cardiovascular collapse may result. The urine is pale, the specific gravity being between 1001 and 1008 and rarely above 1010. The renal-function tests are usually within normal limits, but the effective plasma clearance may be decreased. This is thought to be due to an impairment in the excretory function of the tubular cells which is restored under the influence of repeated administration of posterior pituitary extract (Winer, 1942). The diagnosis of diabetes insipidus was confirmed by the typical response to standard quantities of hypertonic saline and pitressin. Fig. 2 shows the continued excretion of excessive quantities of urine (failure of the hypophysis to liberate A.D.H.) and the decrease following pituitrin which excludes renal disease (or pitressin-resistant diabetes insipidus). The tuberculous nature of the meningitis was indicated by the active tuberculous focus in the chest, development of tuberculin skin hypersensitivity, and a suggestive cerebrospinal fluid, despite the failure to isolate the mycobacteria. The excellent response to antituberculous therapy, with complete resolution of the meningitis and the subsequent demonstration of calcification in the hilar glands, established this aetiology. The lesion produced by the meningitic process is likely to be situated in the hypothalamic-hypophysial tracts or in the hypothalamic nuclei. It seems unlikely that a lesion occurring in the region of the pituitary gland would produce total destruction of the posterior lobe without affecting the anterior lobe as well. The absence of any signs of hypopituitarism in this patient excludes the latter possibility.

This case exhibits an unusual feature in that the glucose-tolerance test showed a low fasting sugar and an extremely low curve; the usual result is a normal curve or one resembling that of diabetes mellitus. Gibson *et al.* (1927), investigating blood-sugar curves in seven cases of diabetes insipidus, showed persistently increased blood sugars with curves similar to those of diabetes mellitus in six, while only one had an abnormally flattened curve. Bauer (1954), however, in a general survey of hypothalamic disease, found 3 patients out of 10 with flattened curves, and 3 who had a delayed return of the blood sugar to normal. There

has been no evidence of malabsorption, and the cause of the flattened curve is not fully understood.

Summary

A case of diabetes insipidus associated with tuberculous meningitis in a child of 5 years is reported. Treatment with nasal insufflation of powdered posterior pituitary extract successfully controlled the patient's polyuria.

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CLINICAL TRIAL OF FURAZOLIDONE IN TREATMENT OF DIARRHOEA

BY

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Medical practice in Bombay is not always comparable with that in the United Kingdom. The standard of living and the conditions under which patients have to be treated are very different from those seen in Western countries. Because of these conditions gastro-enteritis looms large as one of our main therapeutic problems. Another factor is that the continuous advances in the treatment of infectious diseases have produced diverse problems, prominent amongst which is the appearance of extremely virulent pathogenic bacteria which have become resistant to all antibiotics and sulphonamides. The West Bengal Government has warned medical practitioners against uncontrolled or inefficient use of antibiotics, which, if not checked, would increase the incidence of resistant strains of bacteria still further.

Apart from the expense and inconvenience of administering antibiotics and sulphonamides I have found resistant strains develop very readily. This is especially so with *Micrococcus pyogenes* and *Micrococcus aureus*. *Candida albicans*, *Pseudomonas aeruginosa*, *Proteus*, and enterococci are also involved. The necessity for finding a drug which does not produce bacterial resistance and is cheap and easy to administer

has become paramount, particularly in the conditions under which we in India usually have to work.

It is necessary to be aware of the local conditions whenever a clinical trial of a new drug is instituted. Laboratory investigations of stools may be difficult and the follow-up of patients even more so. When, however, a new chemotherapeutic agent which is available for trial appears to be active *in vitro* and *in vivo* against a wide variety of bacteria encountered in intestinal diseases, it must be welcomed and trials begun. The assessment of the results is also a problem, and clinical impressions may sometimes be all that we can offer. In relation to the wide experience we have in the treatment of gastro-intestinal disease a clinical impression may nevertheless be of great assistance in the evaluation of a drug.

A new chemotherapeutic agent, furazolidone ("furoxone"), has been suggested for the treatment of gastro-intestinal infections. It is one of the nitrofurans derivatives, of which group we have previous experience; and the reports of its effects *in vitro* have shown that it is active against a wide variety of organisms. Preliminary clinical trials have already shown that it is effective against, and does not produce resistance in, the organisms commonly encountered in infection of the gut. Furazolidone is bactericidal in low concentrations and has not predisposed to monilial and staphylococcal overgrowth in the faeces. Its effectivity is not apparently inhibited by the presence of mucus, pus, or organic matter, and this is a great advantage in the treatment of enteritis (Yurchenco *et al.*, 1953; Rogers *et al.*, 1956; Ponce de Leon, 1957).

Method and Material

In the latter part of 1958, 58 patients suffering from gastro-intestinal disease were treated with furazolidone. In spite of the difficulties mentioned above, bacteriology of the stool was done in every case. The patients were given tablets each containing 100 mg. of furazolidone, and the usual dose was one tablet four times in 24 hours. No other treatment was given at this time, but the patients were encouraged to drink as much fluid as possible and to eat only if they felt the desire for food. Some of the patients were severely ill, being prostrate and confined to bed. Others were not so ill, and were ambulant while under treatment.

The assessment of improvement was based on the average number of stools on the first day, the average number of stools on the fourth day, and the average number of days for obtaining a complete clinical cure.

On occasion it was difficult to obtain accurate figures for the number of stools on the first day of treatment, and the figures shown in this column of the Table must be regarded as approximate and conservative. Figures for the number of stools on the fourth day were certainly accurate. The clinical cure was assessed on the basis that the patients returned to normal work and the number of stools was reduced to that normally passed by each patient before the onset of the infection.

Results

The Table presents the results obtained in the 58 patients investigated. The ages varied considerably, but in almost every case the patient had received 400 mg. of furazolidone each 24 hours. All patients presented in an acute attack, the main complaint being diarrhoea. In 11 patients no growth of pathogenic bacteria was obtained in the stools. All in this group were regarded as clinically cured at the end of four days' treatment. In 47 patients it was possible to obtain pathological evidence of noxious organisms in the stool. Of the 12 suffering from salmonella infections, 11 were cured within four days. In one patient suffering from *Salmonella typhimurium* infection, the stools were still positive, although the patient was clinically cured, after five further days' treatment. In the nine shigella-infected patients, seven were cured at the end of the course of treatment. In two it was still possible to obtain bacterial growth from the stools in the follow-up even after they were clinically cured. In 9 out of 10 patients with *E. coli* growth in the stools clinical cure was obtained in three days; one patient, not cured, still had a positive growth in the stool at the follow-up investigation. Four patients suffering from amoebic dysentery had normal stools within 8 to 12 days of treatment, and *Entamoeba histolytica*, previously present in the stools, was no longer demonstrable. Similarly, seven patients with *Giardia lamblia* in the stools were also clinically cured within four days of treatment and the stools were normal.

Illustrative Cases

Case 1.—A patient 42 years of age had suffered for five days with violent diarrhoea, blood and mucus in the stool, nausea and vomiting, and a temperature of 105° F. (40.6° C.). Haemolytic *Staph. aureus* was grown from the stool. The organism was resistant to tetracycline, chloramphenicol, streptomycin, and penicillin. It was found to be sensitive to furazolidone. This patient was given 150 mg. of furazolidone every four hours for seven days. Within 48 hours the temperature dropped to normal and remained there. Within six days the diarrhoea and all the other symptoms gradually subsided. Follow-up examination of the stool was negative.

Results of Furazolidone Treatment of 58 Patients Suffering from Diarrhoea

Organism in Stool	No. of Patients	Average No. of Stools		Clinical Cure		Failure to Cure No. of Patients	Follow-up Stool Examination	
		1st Day	4th Day	No. of Patients	Average Days		Pathogens Eradicated	Pathogens not Eradicated
<i>Salmonella anatum</i> ..	1	6	2	1	3	—	1	—
<i>Derby</i> ..	4	10	2	4	4	—	4	—
" <i>Newport</i> ..	1	7	1	1	3	—	1	—
" <i>typhimurium</i> ..	6	9	2	5	4	1	5	1
<i>Shigella dysenteriae</i> ..	5	12	3	4	5	1	4	1
<i>flexneri</i> ..	3	11	2.5	2	8	1	2	1
" <i>sonnei</i> ..	1	14	3	1	6	—	1	—
<i>Staphylococcus aureus</i> ..	3	9	2	3	4	—	3	—
<i>Streptococcus faecalis</i> ..	2	6	2	2	3	—	2	—
<i>E. coli</i> ..	10	8.5	3.5	9	3	1	9	1
<i>Entamoeba histolytica</i> ..	4	8	2.5	4	12	—	4	—
<i>Giardia lamblia</i> ..	7	4.5	1.5	7	4	—	7	—
No growth obtained ..	11	8	2	11	4	—	—	—
Total ..	58			54				

Case 2.—A patient aged 34 was suffering from severe pain in the right side of the thorax, which radiated into the right hypochondrium. X-ray examination revealed no pulmonary lesion, but the right dome of the diaphragm was raised and moved imperceptibly with respiration. A diagnosis of sub-diaphragmatic disease, most probably amoebic hepatitis, was made, and examination of the stools revealed the presence of *E. histolytica*. After five days' treatment with 400 mg. of furazolidone per 24 hours the chest pain disappeared and the diaphragm was moving almost normally. After a further five days' treatment the patient was very much improved, and no amoebae could be found on repeated examination of the stools. The curative value of furazolidone in this case is certainly not established, and investigations are still in progress.

Discussion

Of a total of 58 patients suffering from diarrhoea due to various causes, 54 were restored to normal within a week of being treated. There is no doubt that some patients may have been cured without chemotherapy, particularly those in whom no growth of pathogenic bacteria could be obtained from the stool before beginning treatment. In my experience the rate of cure for all the patients was most satisfactory and compared favourably with the results previously obtained with antibiotics and sulphonamides.

Twelve patients suffering from salmonella infection responded most promptly to treatment, and within a day or two there was great relief from the muscular aches, fever, diarrhoea, and tenesmus with which this infection is associated. Some of these patients had previously been treated with other measures to which they had not responded. Nine patients with shigella infections were passing characteristic dysenteric stools with mucus and blood when treatment was begun, and a gratifying response was noted within 8 to 10 hours of beginning therapy. Clinically, the patients soon felt very much better, and within 24 hours the stools began to lose their liquid character and developed a more normal colour and consistency. On the average, within three days most patients were subsequently very much better, and once the stools had been reduced to a normal number each day the patients were much improved, but still very weak. It must be stressed that treatment does not cease with the relief of symptoms. Patients require subsequent management with adequate diet and fluids before they are able to return to full employment. This is a common finding with most acute illnesses in my practice, and is certainly due to the normal physical condition of the patients even when no dysenteric infection complicates their living conditions.

It is interesting that seven patients suffering from *G. lamblia* infection responded most satisfactorily to furazolidone after other measures had failed. The four patients suffering from *E. histolytica* infection responded satisfactorily to the treatment, but it is, however, most common to find that in cases of amoebiasis a superimposed infection with a dysentery-producing organism is present. It is clear that furazolidone will readily control the superimposed infections in amoeba-infested patients. Case 2, with the presumed diagnosis of amoebic hepatitis, responded extremely well to furazolidone, as did the other three patients with amoebic colitis. It is far too early to comment on the possibilities of furazolidone in the control of amoebiasis itself, and investigations are being continued. I have no information to offer on sigmoidoscopic examination of the intestinal wall of these four

patients, and it is essential that a detailed investigation into this disease should be made.

The side-effects of treatment with furazolidone are said to be nausea and vomiting. It is very difficult to know how serious these may be, because most of my patients presented initially with nausea and vomiting as symptoms of the infection. Only one patient was unable to take the tablets, but none of the others complained of any untoward effects which could be attributed to the drug in question. The results in a group of patients where the pathology is not always simple have encouraged me to continue with this work, and I hope to report later in more detail on certain aspects of what is one of our major problems—amoebiasis.

Summary

58 patients suffering from diarrhoea due to a variety of causes were treated with a new preparation, furazolidone.

The results have shown that furazolidone is a convenient and valuable addition to the drugs available for the treatment of these conditions.

The possibility of the value of furazolidone for the treatment of amoebiasis is being pursued.

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TUBEROUS SCLEROSIS ASSOCIATED WITH SPONTANEOUS HYPOGLYCAEMIA

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Tuberous sclerosis is a rare familial disease of protean manifestations, involving primarily the skin and the nervous system. The characteristic sclerotic patches, to which the disease owes its name, were first described by Bourneville in 1880, and the classical triad of epilepsy, mental retardation, and adenoma sebaceum which characterizes the disorder has been recognized since 1908 (Vogt, 1908). Until then no certain diagnosis had been made in life.

While tuberous sclerosis is often referred to as one of the neuro-cutaneous syndromes, other tissues are often involved. Since the term tuberous sclerosis refers primarily to the changes in the brain, a broader term—"tuberous sclerosis complex" (Moolten, 1942)—is employed to denote the coexistence of tumour-like formations in other organs, notably the skin, heart, kidneys, retina, thyroid, breast, duodenum (Russell