They were resistant to sulphonamide but sensitive to chloramphenicol, streptomycin, tetracycline, and furazolidone.

Discussion

It is generally accepted that the risk to adult handlers of acquiring shigella infection from primates in zoos and laboratories is not great (Ruch, 1959 ; Appleby *et al.*, 1963). However, when the contact is the intimate household fondling of a newly obtained and exotic pet, there is a very real risk of the spread of shigellae to the family from an apparently healthy animal with an unsuspected infection, and the children are especially vulnerable, as shown clearly in this outbreak.

Apart from the index case, who probably had contact with the monkey during a single visit, the other families were in close domestic contact with the animal for two to three weeks. Though the precise incubation period of the disease cannot be determined in this instance, the dates of onset of symptoms in the patients were compatible with the presence of the monkey in the household. Of the 17 persons at risk, seven children developed dysentery, but the single adult infected was symptomless. Two children had severe attacks, but fortunately there were no deaths, unlike the tragedy in Germany reported by Bach *et al.* (1931) in which three children, under 5 years old, died out of 17 human cases following household contact with five guenons brought from West Africa as pets. In that incident the infecting organism was also *Sh. flexneri* Y.

The significance, if any, of the monkey's presence on board to the outbreak of diarrhoea among the ship's crew cannot be assessed, as it is not known when the animal itself was infected.

Conclusions

As the public are probably quite unaware of the danger of monkey pets, both medical practitioners and veterinary surgeons in general practice who are not normally concerned with simian problems should be alert to the potential hazards of the presence of a pet monkey in a household and should discourage families, particularly those with young children, from acquiring monkeys as pets. Whenever an infectious illness occurs within a household having a pet monkey, whether the index case is human or animal, the family should be urged to have the other human and simian members examined by the appropriate practitioner and the necessity explained to them of adopting measures to prevent the spread of disease between human and simian contacts.

Summary

An outbreak of bacillary dysentery is described, involving seven children and one adult out of 17 persons at risk, following household contact with a newly imported pet monkey. *Sh. flexneri* Y was isolated from four children and the monkey. From the other three children *Sh. flexneri* 4a was isolated, and the adult, who remained symptomless, was found to be excreting *Sh. flexneri* Y and *Sh. flexneri* 4a on separate occasions.

All the strains of *Sh. flexneri*, irrespective of serotype, had the rare and epidemiologically useful marker of being catalase-negative. This fact and the known antigenic relation of *Sh. flexneri* Y to *Sh. flexneri* 4a combined with the sequence of the infections following the sojourn of the monkey within the different families are very suggestive that the cases constituted a single outbreak.

The attention of medical practitioners and veterinary surgeons in general practice is drawn to the risks of shigella infections spreading from pet monkeys to their human contacts, and it is urged that the public should be warned of the unsuitability of monkeys as domestic pets, particularly where there are young children in a household.

Our thanks are due to Dr. T. R. Roberton, Medical Officer of Health for Bootle, for his help in obtaining the epidemiological data.

References

Appleby, E. C., Graham-Jones, O., and Keeble, S. A. (1963). *Vet. Rec.*, 75, 81.
Bach, F. W., Fülscher, J., and Harnack (1931). *Veröff. Med.-Verw.*, **34**, 61. Quoted from Ruch (1959).
Boyd, J. S. K. (1938). *J. Hyg. (Camb.)*, **38**, 477.
Carpenter, K. P., and Lachowicz, K. (1959). *J. Path. Bact.*, **77**, 645.
—— and Sandiford, B. R. (1952). *Brit. med. J.*, **1**, 142.
Grunbaum, A. S. (1904). Ibid., **1**, 817.
Ravaut and Dopter (1909). *Bull. Soc. Path. exot.*, **2**, 17.
Ruch, T. C. (1959). *Diseases of Laboratory Primates*, Chap. 3. Saunders, London.

Preliminary Communications

Treatment of Acute Falciparum Malaria with Sulphorthodimethoxine (Fanasil)

Brit. med. J., 1965, 1, 905–907

The effectiveness of weekly doses of 500 mg. of sulphorthodimethoxine in clearing symptomless asexual parasitaemia in East African schoolchildren infected with pyrimethamine-resistant *Plasmodium falciparum* was reported recently (Laing, 1964). The present communication describes the effect of single doses of sulphorthodimethoxine in 25 cases of acute falciparum malaria.

Materials and Methods

Sulphorthodimethoxine is 4-sulphanilamido-5,6-dimethoxypyrimidine, a long-acting sulphonamide known formerly by the experimental number Ro 4-4393, and now by the proprietary name of Fanasil ; it is an isomer of sulphadimethoxine (Madribon) but with a biological half-life of 100 to 200 hours, so that a weekly dosage is sufficient for therapeutic purposes. It was supplied by Roche Products Ltd. in the form of 500-mg. tablets and a liquid suspension containing 100 mg./ml.

The patients were semi-immune Bantu Africans who were suffering from acute attacks of malaria. Fifteen were treated as in-patients at St. Augustine's Mission Hospital, Magila, 10 miles (16 km.) east of Amani in the Usambara foothills, and nine as out-patients at the Amani Institute ; one patient was treated at Muheza Government Hospital, two miles (three km.) from Magila. So far as could be determined no patients selected had received antimalarial drugs prior to treatment with sulphorthodimethoxine.

Thick and thin blood films were taken daily, but this was possible for only as long as a patient would stay in hospital or return for examination as an out-patient. Parasites were

TABLE I.—*Details of 25 Cases of Acute Falciparum Malaria Treated with Single Doses of Sulphorthodimethoxine*

Case No.	Age in Years	Dose Given (Day 1) (mg.)	Dose in mg./kg. Body Weight	Asexual Parasite Counts/per c.mm. on Observation Day No. 1	2	3	4	5	6	7	8	9	10	No. of Days Fever Over 99° F. (37·2° C.)
In-patients														
MAG/1	3	500		100,000	227,000	92,800	48,000	Neg.	Neg.	Neg.	Neg.			3·0
MAG/2	3	250	15	10,400	50,600	14,000	3,900	Neg.	Neg.	Neg.				2·5
MAG/3	3	250	15	60,000	259,000	32,800	< 100	Neg.						1·0
MAG/4	1½	250	37	10,100	7,900	3,600	< 100	Neg.	Neg.					2·0
MAG/5	½	250	37	33,700*	Neg.	Neg.*	Neg.*							1·0
MAG/6	1½	250		100,000	105,600	57,600	12,600	37,200	Neg.					2·5
MAG/7	20	1,000	21	126,000	24,000	5,600	Neg.	Neg.						2·0
MAG/8	20	1,000	18	26,800	7,600	Neg.	Neg.	Neg.						2·0
MAG/9	6	500	31	43,400	21,400	18,000	8,300	600	Neg.	Neg.	Neg.			9·0†
MAG/10	½	250	33	128,000	85,800	80,200	70,000	9,400	4,000	200	Neg.			4·5
MAG/11	1½	250		28,900	22,800	4,120	2,700	Neg.						2·5
MAG/12	½	250S		9,900	4,200	200	< 100*	Neg.	Neg.					1·5
MAG/13	3	250	18	52,800	84,400	70,000	10,400	Neg.*	Neg.*	Neg.*				3·0
MAG/14	5	250	13	19,300	27,800	6,000	800	Neg.	Neg.					0·5
MAG/15	1	250	33	50,200	43,900	< 200	2,600	Neg.						1·0
MUH/1	18	1,000		13,600	5,800	< 100	Neg.	Neg.			Neg.			0·5
Out-patients														
A/2	½	250S		76,000	22,400	1,500	100	< 100	Neg.					
A/4	2	250S	22	1,800	Neg.	Neg.								
A/5	1	250S	32	8,200		800	300	< 200	Neg.		Neg.*			
A/6	8	500S	19	19,200	16,800	3,500	700	Neg.	Neg.					
A/7	5	500S	34	56,000	8,400	< 200	Neg.	Neg.						
A/8	2	250S	23	45,600	40,000	< 100	Neg.		Neg.					
A/9	2	250	22	15,700	5,700	1,200	< 200	< 100*	< 100	Neg.*	Neg.*			
A/11	12	500	13	58,400	53,300	3,400	800	< 100	Neg.	Neg.*	Neg.*			
A/12	1	250S	30	19,200	8,500	8,200	1,300	700	500		< 200	< 100	Neg.*	

* Gametocytes also present. S = Sulphorthodimethoxine in suspension. † "Pyrexia of unknown origin."

counted against leucocytes, the mean total white-cell count being taken as 8,000/c.mm. A blood film was reported as negative if no parasites were seen in 100 thick film fields. Microscopy was done by the regular staff of the Institute.

The doses of sulphorthodimethoxine were given by the medical officer, by the nursing sister, or, at the Institute, by a member of the senior staff. Dosage varied from 250 mg. in children up to 4 years old to 1 g. in adults, given as a single dose.

RESULTS

Details of dosage, parasitaemia, and fever are given in Table I and summarized in Table II. No toxic effects or side-effects occurred among any of the patients treated.

In-patients.—In no case was therapeutic intervention with another antimalarial drug actually required ; in one patient (MAG/9), in whom fever persisted, an intramuscular injection of quinine was given four days after treatment, before it was realized that parasitaemia had already been reduced to a low level (600/c.mm.) and that some other cause was responsible for continuing fever. One patient (MAG/10) had a scanty parasitaemia six days after treatment, but was negative the following day. Excluding these two patients, classed as "failures" in Table II, the average duration of asexual parasitaemia was 2.6 days, and fever 1.8 days. The dosage of sulphorthodimethoxine varied from 13 to 37 mg./kg. Asexual parasite densities prior to treatment ranged from 9,900 to 128,000/c.mm., with an average of 50,200.

TABLE II.—*Average Duration of Asexual Parasitaemia and Fever After Treatment of Acute Falciparum Malaria with Single Doses of Sulphorthodimethoxine*

No. of Cases Treated	No. of "Failures"	Average Duration of Asexual Parasitaemia and Fever in Days (Excluding "Failures")		Average Asexual Parasitaemia per c.mm. Before Treatment (Including "Failures")
		Parasitaemia	Fever	
16 (in-patients)	2	2·6	1·8	50,200
9 (out-patients)	1	3·0		30,400

"Failure" means that asexual parasitaemia was still detectable in the peripheral blood on the seventh day of observation or that treatment with another antimalarial drug was also given.

Out-patients.—One patient (A/12) who had a moderately low parasite count of 19,200/cm. still had scanty trophozoites on the eighth day after treatment ; these, however, had disappeared by the following day. Excluding this case, classed as a "failure" in Table II, the average duration of parasitaemia was three days. The dosage of sulphorthodimethoxine varied from 13 to 34 mg./kg., and asexual parasite densities from 1,800 to 76,000/c.mm., with an average of 30,400. Three out-patients who were treated have not been included: these are A/1, infected with *P. ovale,* and A/3 and A/10, who could not be followed up.

Drug-affected Parasites.—Morphological changes in the appearance of parasites caused by sulphorthodimethoxine were looked for in thin films from some of the patients ; thinning and expansion of the rings, with fragmentation of cytoplasm and in some instances gross distortion of the trophozoites, were seen, but, equally so, perfectly healthy-looking trophozoites were seen in films several days after treatment. Gametocytes appeared to be unaffected by sulphorthodimethoxine.

COMMENT

The results of treatment with sulphorthodimethoxine of the first three patients (one of whom had an ovale infection and is not included in this series) suggested that the action of the drug would be too slow for the treatment of acute malaria (Laing, 1964). Subsequent results, however, showed that this was by no means so, several patients with moderate or heavy parasitaemias responding as rapidly as they would have done had they been treated with chloroquine. It may be that, like diamino-diphenyl sulphone, which also has substantial antimalarial properties (Archibald and Ross, 1960 ; Basu, Mondal, and Chakrabarti, 1962), sulphorthodimethoxine is much less effective against *P. vivax,* a feature common to the older sulphonamides. Nevertheless, the drug clearly has important antimalarial properties and merits further clinical trial.

SUMMARY

Twenty-five Bantu Africans from north-east Tanzania were treated for acute falciparum malaria with sulphorthodimethoxine (Fanasil) in single doses ranging from 250 mg. in young children to 1 g. in adults. Except for three patients, classed as "failures" because of unduly slow response, asexual

parasitaemia subsided on the average within three days, and fever in two days. No toxic effects occurred.

I am indebted to Mrs. D. Bagster Wilson, who as temporary medical officer of St. Augustine's Hospital, Magila, selected, treated, and observed several of the earlier cases for me. My grateful thanks are also due to Dr. L. P. Sitwell, who returned from leave about half-way through the series, and to her staff, for their valuable assistance, especially Mr. Johanna Sekenyee, laboratory assistant, who gave so much of his skill and time for the proper observation of these cases.

A. B. G. LAING, M.B., CH.B., D.T.M.&H.,
East African Institute of Malaria and Vector Borne Diseases, Amani, Tanga, Tanzania.

REFERENCES

Archibald, H. M., and Ross, C. M. (1960). *J. trop. Med. Hyg.*, **63**, 25.
Basu, P. C., Mondal, M. M., and Chakrabarti, S. C. (1962). *Indian J. Malar.*, **16**, 157.
Laing, A. B. G. (1964). *Brit. med. J.*, **2**, 1439.

Medical Memoranda

Acute Poisoning by Cycloserine

Brit. med. J., 1965, 1, 907–908

The antibiotic cycloserine is being used with increasing frequency in infections of the urinary tract. During recent months three patients have been admitted to the Poisoning Treatment Centre, having deliberately taken an overdose of cycloserine; one was treated by peritoneal dialysis. The literature contains no reference to the therapy required to overcome the acute toxic effects of this drug, and the American authority Schreiner (personal communication) has stated that in his experience peritoneal dialysis in the treatment of acute cycloserine poisoning has not been attempted. It was therefore thought desirable that a note on cycloserine and peritoneal dialysis should be recorded.

Cycloserine was first extracted from two fungi of the Streptomycete group in 1954 by Harned *et al.* (1955) and Harris *et al.* (1955). It is bactericidal in its action, unstable in neutral or acid solutions, and compared with most other antibiotic drugs it has a small molecule (molecular weight 102). It is rapidly absorbed when given orally, absorption taking place from both the stomach and the intestine. Peak blood-levels are present about four hours after an oral dose and cumulation occurs for the first three to four days (Welch *et al.*, 1955). Cycloserine is widely distributed throughout the body fluids and tissues; in particular, it enters the cerebrospinal fluid and has been found in ascitic fluid (Anderson *et al.*, 1956; Nair *et al.*, 1956).

In man 64% of an oral dose is excreted in the urine in an unaltered form in 72 hours—40–50% in the first 12–24 hours. The fate of about 35% is not known (Conzelman, 1956). In animals Anderson *et al.* (1956) found that toxicity was of a low order. The acute toxic dose is high in the smaller laboratory animals; consequently the lethal dose in larger animals could not be determined. Toxic doses cause hyperactivity, random movements, convulsions, lethargy, and coma.

In man the drug is more toxic (Katz, 1956), the majority of effects, such as tremor, twitching, muscle spasms, and convulsions, occurring in the central nervous system. McLean (1956) stated that convulsions occur with a plasma cycloserine level of 30 μg./ml. or less; but Lillick *et al.* (1955–6) noted that some patients tolerated 3 to 4 g. a day for up to three weeks with no side-effects, and that some had plasma levels of 90 to 100 μg./ml. without symptoms. Psychotic reactions also occur in patients on cycloserine (Lillick *et al.*, 1955–6), and right ventricular failure has been reported in four patients receiving 1 g. or more daily (Walker and Murdoch, 1957). Other toxic effects are visual disturbances, conjunctivitis, and dry mouth.

CASE HISTORY

In 1961 a woman aged 25 had a right nephrectomy for hydronephrosis and pyelonephritis, and in 1962 started long-term therapy with cycloserine. Prior to admission to the Poisoning Treatment Centre she was taking 0.25 g. on alternate days. After some domestic trouble the patient's husband discovered that she had taken 12 of her cycloserine capsules—that is, 3 g.—and appeared to be asleep in bed. There was no question of her having taken any other drug. She was admitted to the Poisoning Treatment Centre some 11 hours later.

On admission she was acutely ill and semi-conscious, was very pale, and appeared to be shocked. There were no lateralizing signs in the central nervous system, no tremor, and no twitching. The tendon reflexes were exaggerated. Apart from her operation scars no other abnormality was detected. Haematological examination, blood urea and electrolytes, chest *x*-ray films, and electrocardiogram findings were all normal. The plasma cycloserine level was 91 μg./ml. In view of her serious condition peritoneal dialysis was instituted, using Impersol-K with dextrose, 1.5% (*p*H 4.1). An intravenous infusion was also set up.

Three hours after starting dialysis the plasma cycloserine level was 65 μg./ml. and after 10 hours it was 45 μg./ml. By 20 hours the plasma level had fallen to 25 μg./ml., and the dialysis was stopped at 21 hours. After 17 hours of treatment the patient was much better, her level of consciousness had improved, and she was able to answer questions clearly.

DISCUSSION

The chronic toxic effects of cycloserine are well documented (Lillick *et al.*, 1955–6), but information about the acute toxic effects was unobtainable at the time of admission. Peritoneal dialysis was undertaken in an attempt to improve the patient's general condition by reducing the blood-level of cycloserine, thus preventing convulsions and neurotoxic and circulatory complications. This form of treatment was preferable to forced diuresis in view of the possibility of impaired function in her remaining kidney.

Twelve exchanges, each of 2 litres, were carried out in the 21-hour period of dialysis. Analysis of aliquots of the dialysate was undertaken 48 hours later and a total of 0.52 g. was recovered. The small amount of cycloserine obtained was disappointing in view of the rapid reduction in the blood-level and corresponding clinical improvement in the patient. We believe that one reason for the small amount recovered is the fact that cycloserine degrades very quickly in an acid medium, and the specimen was not analysed for 48 hours, during which time the *p*H of the fluid was about 5. Furthermore, the technique used can at present estimate only cycloserine itself and not its degradation products.

The patient did not pass urine until 29 hours after admission. Catheterization was not carried out. This specimen (300 ml.) had a specific gravity of 1033 and no abnormal constituents. The amount of cycloserine in the specimen was not estimated.

CONCLUSION

This patient would most certainly have recovered from her overdose of cycloserine without peritoneal dialysis. However,