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An outbreak of shigellosis in laboratory marmosets and tamarins (Family: Callithricidae)

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SUMMARY

An outbreak of shigellosis due to *Shigella sonnei*, is reported in laboratory maintained marmosets (*Callithrix jacchus*) and tamarins (*Saguinus nigricollis*). The clinical signs and pathological lesions are described and the microbiological findings discussed. Control of the disease was based upon hygiene and antibiotic therapy and the consequences of this approach are described in detail.

INTRODUCTION

Gastro-intestinal diseases are widely recognized in captive primates (Anon, 1967; Ruch, 1959; Taylor, 1972) and bacteria are frequently the cause although such factors as parasites or unsatisfactory nutrition may also be implicated. Both *Salmonella* and *Shigella* species have long been incriminated in the pathogenesis of such diseases (Halloran, 1955) and particular attention has been focussed on these conditions in view of their zoonotic nature (Chaffee, 1973; Fiennes, 1967).

In the case of *Shigella* species, the earliest record traced of shigellosis in non-human primates is that of Ravaut & Dopter (1909). Since that date there have been a number of reports of clinical shigellosis and carriage of *Shigella* species from a variety of species and the subject was reviewed by Cook (1969). Studies on the carrier state are particularly interesting; for example, in a recent survey of South American monkeys, 7 out of 60 animals were found to be excreting *Shigella* species (Kaufman *et al.* 1970). However, it seems highly probable that primates acquire shigellas after contact with man, since a number of workers (Carpenter & Cooke, 1965; Takasaka *et al.* 1964; J. E. Cooper unpublished data) emphasize the failure to isolate the organisms from free-living primates. As Vickers (1973) states 'Minimizing human contact is probably the most important factor in prevention of shigellosis'.

In a previous publication, Needham (1975) described the laboratory investigation of an outbreak of diarrhoea in Rhesus monkeys (*Macaca mulatta*) at this Centre and attention was drawn to the low isolation rate of *Shigella* species and the possible role of commensal organisms. A definite diagnosis of shigellosis was not made.

In this paper we report an outbreak of clinical shigellosis in laboratory-maintained marmosets and tamarins (Family Callithricidae) and discuss its clinico-pathological features, its control and its possible epizootiology.

MATERIALS AND METHODS

The species involved were marmosets (*Callithrix jacchus*) and tamarins (*Saguinus nigricollis*). The colony, numbering approximately 50 animals, is maintained in one room at an ambient temperature of 27° C. and relative humidity of 65%. The animals (hereafter collectively called 'the marmosets') are usually kept in pairs or family groups but the size of the cages varies. The diet consists of mixed fruit, brown bread and a proprietary pelleted diet (Cooper's New World Primate Diet: Cooper Nutrition Products, Witham, Essex). Sterilized bone meal is added regularly to the fruit and a vitamin D3 supplement supplied intermittently in the drinking water.

During the outbreak, clinical examination and treatment of sick animals was carried out inside the marmoset room with both handler and veterinary surgeon dressed in protective clothing consisting of a gown, face mask, cap, gloves and overshoes.

Carcasses were transported to the laboratory for post-mortem examination in two plastic bags, one inside the other, both previously dipped in a hypochlorite solution (Chloros). The necropsy was carried out in an exhaust ventilated laboratory safety hood (Microflow Ltd, Aldershot, Hants.). The nervous system was not examined.

Material for histopathology was fixed in 10% formol-saline, embedded in wax and sectioned. Routine staining was with Cole's haematoxylin and eosin.

Microbiology

Throughout the investigation a total of 1176 samples of faeces was examined. These could be divided into two groups, those obtained during the six weeks acute phase of the outbreak, and those obtained as routine samples in the seven months following the final antibiotic treatment of the entire colony.

During the acute phase of the outbreak every marmoset that died was examined *post mortem*. A portion of faeces was obtained from the caecum and cultured bacteriologically. Fourteen days after the appearance of diarrhoea in the colony three routine faecal samples were taken, from each cage, at weekly intervals.

Samples of faeces were obtained on three consecutive days commencing at days 7 and 14 after the final antibiotic treatment and again at weeks 7–13 inclusive. After week 13, samples of faeces were obtained once a week for two months, after which sampling was carried out fortnightly. During both the acute and chronic phases, all isolations of *Shigella* and *Salmonella* species and enteric commensal organisms were tested for sensitivity.

In an effort to trace the source of the outbreak, faeces were obtained on three consecutive days from all five animal technicians in close contact with the colony and were examined for *Shigella* and *Salmonella* species and enteropathogenic *Escherichia coli*.

Examination of faeces. Faeces were obtained for routine sampling from the tray under the marmosets' cage. Fresh faeces were collected following examination of the tray for signs of blood and mucus. Human stools were brought to the laboratory as soon as possible.

Table 1. *Summary of deaths*

Monkey	Days after start of outbreak
Marmoset (adult)	16
Marmoset (young)	18
Marmoset (adult)	20
Marmoset (adult)	23
Marmoset (adult)	25
Tamarin (baby)	27
Marmoset (adult)	27
3 Marmosets (adult)	29
2 Marmosets (baby)	32
Marmoset (adult)	32
Marmoset (adult)	35
Marmoset (adult)	38
Marmoset (adult)	101
Marmoset (baby)	217
Marmoset (baby)	287

All faeces, from whatever source, were treated bacteriologically in the same way. They were cultured on a deoxycholate citrate agar (D.C.A.) plate and inoculated into Selenite F medium. After 24 hr., sub-cultures of the Selenite F were made on D.C.A. All media were cultured at 37° C. aerobically.

After incubation colonies were identified by standard procedures according to Cowan & Steel (1966). *Shigella* spp. and the strain of *Salmonella irumu* were typed serologically by the Central Public Health Laboratory, Colindale. Colonies of *Escherichia coli* were typed serologically using agglutinating sera (Wellcome Reagents Ltd, Beckenham, Kent).

Sensitivity testing. After identification colonies were sub-cultured on diagnostic sensitivity test agar (with the addition of 7·5% lysed blood) and Multodisks and single antibiotic disks (Oxoid Ltd, Basingstoke, Hants.) were used.

History of the disease

The colony was first established in early 1973. During the following eight months additional animals were introduced; these were mainly obtained from research laboratories and a commercial supplier, both in Britain, but a small number were imported directly from South America.

Although occasional minor illnesses occurred, the colony remained healthy until 20 August 1974 when the first clinical case of dysentery was reported. Further cases followed until, after six weeks, there had been 15 deaths, as shown in Table 1.

Up to the time of writing (August 1975) only two further clinical cases have occurred but regular faecal sampling has continued.

RESULTS

Clinical signs

The disease appeared clinically to be acute or peracute. Affected animals were depressed and lethargic and adopted a rather hunched appearance. On handling there was evidence of dehydration and in the majority of cases the anal region showed signs of diarrhoea or was coated in dry blood. In the terminal stages the buccal mucous membranes were pale, the extremities cold and the rectal temperature low. A number of animals were destroyed *in extremis* with intraperitoneal sodium pentobarbitone.

Blood stained faeces were usually visible on the tray beneath the animal's cage. However, this was also observed in cases where no clinical signs were detectable.

During the course of the outbreak one animal was killed on account of a grossly swollen neck and face. A full post-mortem examination was not performed but sections of the skin of the face showed severe oedema. Another animal, a tamarin, showed clinical signs of head tilting (reminiscent of labyrinthitis) but recovered spontaneously.

Post-mortem findings

Affected animals were usually in reasonable bodily condition with good reserves of internal fat but showing varying degrees of dehydration. The stomach rarely contained food, unless milk had been offered before death, but gas was frequently present. The small intestine usually contained fluid and gas but, as in the stomach, gross lesions were absent. The caecum, however, regularly showed erosions and ulcerations of the mucosa and pinpoint diffuse haemorrhages. The ulcerations ranged from 0·5 to 3·0 mm. in diameter and in severe cases were visible through the serosal surface. They consisted of a white central portion and a red hyperaemic periphery. The lumen of the caecum, colon and rectum contained free blood and fluid faecal material, and there were petechiae and small erosions in the mucosa of the colon in some animals.

The caecal and mesenteric lymph nodes were usually enlarged, oedematous and, in some cases, haemorrhagic. The mesenteric blood vessels were dilated.

Other organs showed only mild lesions, usually restricted to congestion especially of the liver and lungs. One case showed pale white foci (1 mm. diameter) on the surface and in the substance of both kidneys. Another affected animal had a grossly distended bladder, which was full of urine, but the cause of this could not be ascertained.

Pathological results

Histopathology. Histopathological examination was performed on a selection of tissues from certain cases. This confirmed that the main lesions were confined to the large intestine and in particular, to the caecum and proximal part of colon. There were erosions and ulcerations of the mucosa; the ulcers showed haemorrhages on the periphery and the floor was filled with cellular debris. The lamina propria

Table 2. *Percentage of antibiotic-sensitive strains of* Shigella sonnei *and* Salmonella irumu

	Shigella sonnei			*Salmonella irumu*
	During first six weeks of outbreak	After withdrawal of antibiotics		49–63 days After withdrawal of antibiotics
		49–63 days	64–210 days	
Antibiotic	(11)*	(8)	(89)	(3)
Tetracycline	0	0	18	33
Chloramphenicol	92	77	63	100
Cephaloridine	72	77	56	100
Erythromycin	0	0	0	0
Kanamycin	46	44	29	66
Penicillin	0	0	0	0
Ampicillin	0	0	0	0
Streptomycin	9	0	12	66
Tylosin	0	0	0	0
Chlortetracycline	0	0	8	0
Colistin methane sulphonate	46	77	76	100
Furazolidone	92	77	62	0
Neomycin	92	55	71	100
Oxytetracycline	0	0	17	0
Sulphamethoxazole-trimethoprim (Septrin)	36	66	37	66
Carbenicillin	81	88	73	66
Gentamicin	100	88	87	100

* The figures in parentheses show the number of strains tested in each group.

showed a mixed cellular reaction composed of neutrophils and mononuclear cells (Plate 1).

Caecal and mesenteric lymph nodes showed varying degrees of lymphoid hyperplasia and, in some cases, oedema and haemorrhage.

Congestion of the liver was confirmed and some animals showed small hepatic foci of polymorphonuclear cells. The lung lesions were usually areas of congestion and alveolar collapse, with pneumonic changes in a small number of cases.

The pale kidney lesions were not examined histologically. Other kidney sections from affected animals appeared normal. The adrenal glands from one case showed severe cortical haemorrhages.

Bacteriology. During the outbreak 108 isolations of *Shigella sonnei* and three isolations of *Salmonella irumu* were obtained from 1176 samples of faeces. This represented a recovery rate of *Shigella* species of 9·2%. Eighteen post-mortem examinations were carried out: eight (44%) of these yielded *Shigella sonnei*.

Table 2 shows the sensitivity of these strains to antibiotics. During the acute phase of the outbreak 92% of the shigellas were sensitive to neomycin sulphate but immediately after treatment resistance appeared to have increased and only 55% of isolates were sensitive. Over the following seven months 71% of the strains of *Shigella sonnei* proved sensitive to neomycin. All three strains of *Salmonella irumu* were sensitive to this antibiotic.

Table 3. *Serotypes of enteropathogenic* E. coli *isolated*

Number of strains isolated	Serotype
8	O126/B16
2	O128/B12
2	O86/B7
1	O26/B6
1	O114/K90

The isolates of commensal enteric organisms studied for antibiotic sensitivity showed similar results to those described by Needham (1975). After neomycin treatment many of the enteric organisms showed resistance to neomycin.

In addition to the organisms above, five isolates of a *Pseudomonas* species and two isolates of *Arizona* species were obtained from faeces of clinically sick monkeys.

The survey of faeces for the presence of enteropathogenic *Escherichia coli* revealed the presence of 14 isolates from the 28 cages involved. The 14 comprised 5 serotypes as shown in Table 3.

Shigella sonnei was not isolated from any of the animal technicians working with monkeys nor was *Salmonella* or any other enteric pathogen.

Parasitology. Parasitological examination of faeces was carried out on a small number of cases (less than six); in one sample, cysts of an *Entamoeba* species (not *histolytica*) were found. There was no evidence of other parasites.

Control and treatment of the disease

In view of the potential hazard to personnel in adjacent buildings, initial effort was directed at containing the infection. Strict hygienic precautions were taken including the posting of warning notices, the limiting of entry to the room to one member of staff and the movement of cages so that all those infected were grouped together. A formalin footbath was installed outside the door and the members of staff instructed in hygienic procedures to be followed when leaving the room. Whenever possible the technician only entered the room once a day to clean, feed and water the animals. During the course of the outbreak the floor and door handles of the lobby leading to the marmoset room were washed with Chloros disinfectant daily.

Following antibiotic sensitivity tests, neomycin sulphate was chosen for therapy. The preparation was a proprietary one which contained methyl scopolamine as well as neomycin ('Neobiotic P': Upjohn Ltd, Crawley, Sussex) and this was added to the drinking water at a rate of 6 ml. of drug to each 310 ml. of water. All animals were treated and water consumption appeared unaffected (approximately 15 ml. per animal per day). Treatment was continued for 10 days.

A small number of clinically affected animals were given dextrose saline (5% dextrose; 0·85% sodium chloride) orally or subcutaneously. Particularly sick animals were isolated and fed by hand.

The efficacy of the treatment was difficult to assess but mortalities ceased one week after therapy commenced, although three further deaths occurred later as

shown in Table 1. There was also no evidence of spread outside the room to other monkeys.

DISCUSSION

The outbreak of disease described killed 18 animals and a further small number showed morbidity as indicated by clinical signs of diarrhoea or dysentery. A diagnosis of shigellosis was not made immediately because the first four cases yielded *Pseudomonas aeruginosa* and this organism was thought a possible cause of the diarrhoea. It was only later, when *S. sonnei* was isolated from classical lesions of the large intestine, that the diagnosis of shigellosis was confirmed. The failure to isolate *Shigella* species earlier may have been due to the masking effect of the large number of commensal organisms present, of which the predominant one was *Pseudomonas aeruginosa*. It is known that this organism can effectively overgrow *Shigella* when cultured from faeces (E. J. Stokes, personal communication).

Salmonella irumu was isolated on three occasions after the withdrawal of antibiotic therapy. The failure to isolate this organism earlier was possibly attributable to its inhibition by the normal commensal enteric organisms. Also isolated from routine faecal samples was an *Arizona* species. The isolation of this organism was not associated with any clinical signs of disease although Arya, Verghese, Agarwal & Pal (1973) referred to *Arizona* species causing death in Rhesus monkeys (*Macaca mulatta*).

The survey of enteropathogenic *E. coli* showed that 50 % of the monkeys carried such strains. Schiff *et al.* (1972) in a survey of laboratory animals, isolated strains of enteropathogenic *E. coli* from Rhesus monkeys (*Macaca mulatta*) but with a lower percentage recovery (10 %). It is possible that in the present survey *E. coli* might have been responsible for some of the cases of diarrhoea.

The clinical signs and pathological lesions in the marmosets were similar in many ways to those described in shigellosis in humans (Davidson, 1965) and in other species of monkey (Hartley, 1968; Lindsey, Hardy, Baker & Melby, 1971). The mortality rate in the marmosets was high, more so than in humans where *S. sonnei* usually produces only mild disease which may even escape detection. However, it must also be remembered that a clinical diagnosis of shigellosis in monkeys can rarely be made until the disease has progressed in severity and treatment may then prove of no avail.

Treatment was introduced only reluctantly. Although it was hoped to do all possible to save the marmosets, great concern was felt over the danger of antibiotic resistance. Development of a degree of resistance was considered inevitable; in recent years *S. sonnei* isolated from humans has shown an increasing resistance to three or more antibiotics (Davies, Farrant & Uttley, 1970) and Lindsey *et al.* (1971) showed development of resistance in Rhesus monkeys. It is known from other studies (e.g. Brown *et al.* 1970) that the symptomless excretor rate is likely to be higher when antibiotics are administered.

As has been shown, these fears proved justified. Before treatment started, 92 % of *Shigella sonnei* strains were sensitive to neomycin but after 10 days of

treatment only 55 % of those tested were sensitive. In general those that proved resistant to neomycin also proved resistant to the other antibiotics used in the test. It appeared therefore that the development of resistance to antibiotics was not specific for neomycin. However, the incidence of resistance appeared to decline after the cessation of treatment.

Throughout the outbreak it was essential to continue the breeding programme. This meant that monkeys were moved between cages and this led to the isolation of *Shigella sonnei* from cages that had previously not yielded the organism. It also resulted in an interesting case. The last monkey to die (Table 1, day 287) was a baby marmoset. Cultures of its faeces taken at post-mortem examination yielded *Shigella sonnei*. A search of the laboratory records showed that while its mother was pregnant there was a history of *Shigella sonnei* excretion although no clinical signs were apparent. After birth, cage faecal samples were tested twice without the isolation of this organism. When the organism was obtained from the baby, faeces of the parents were again cultured and *Shigella sonnei* was isolated.

The source of the *S. sonnei* is a matter for conjecture. Before the outbreak 218 faecal samples from the colony had been examined microbiologically but no *Shigella* or *Salmonella* species had been isolated. We believe, therefore, that the organism originated from either a human carrier, or a recently introduced animal. The third possibility, that of a carrier animal within the colony, seems improbable in view of the number of faecal samples tested – but it is a theory that cannot be discounted completely. There is evidence from elsewhere that *Shigella* species may not be detected in routine faecal sampling; Tokura & Matsubayashi (1973), for example, described shigellosis in monkeys in Japan despite triple faecal sampling during the quarantine period.

No routine screening of staff is performed at the Centre and therefore information is not available on the intestinal bacterial flora of the technicians responsible for the husbandry of the various species of monkey. The small faecal survey of these technicians mentioned above did not yield *Salmonella* or *Shigella* species. The marmosets' food was prepared by another group of technicians from whom faeces were not sampled but it seems unlikely that they were the source of the *S. sonnei* since other monkeys in the building receiving the same food had remained unaffected and their faeces yielded no *Shigella* species on culture.

The second hypothesis, that of entry with a recently introduced animal, could not be pursued. However, approximately five weeks before the outbreak 25 animals, from three different suppliers, entered the colony. During this five week period only one faecal sample per animal was examined and thus a symptomless excretor may have remained undetected.

A possible clue to the source of infection was provided by Carpenter (1968) who demonstrated that in Britain 98 % of *Shigella* strains isolated were *S. sonnei* and only 2 % *Shigella flexneri*. This suggests that this *S. sonnei* infection may have originated in Britain rather than in the country of origin of the monkeys.

As far as is known, this is only the second recorded description of shigellosis in captive laboratory marmosets. Kingston (1972) mentioned an outbreak of disease in 1967 from which *Shigella* was isolated but did not give any further details. The

outbreak described in this paper illustrates the possible outcome if the organism enters a marmoset colony, and the consequences to research. It also emphasizes the importance of screening and quarantine or isolation procedures in the detection of infections and of full clinical and laboratory investigation in diagnosis and control. In this outbreak emphasis was laid upon control, rather than therapy, although the latter has been well documented (see, for example, New, 1966).

At the time of writing, eight months after the acute outbreak, the remaining marmosets and tamarins appear clinically well and breeding is in progress. The colony remains a potential threat, however, since shigellas continue to be isolated sporadically and use of the animals for research is curtailed for fear of initiating clinical disease. It can be concluded that every effort should be made to prevent the entry of *Shigella* species into a primate colony by appropriate quarantine procedures.

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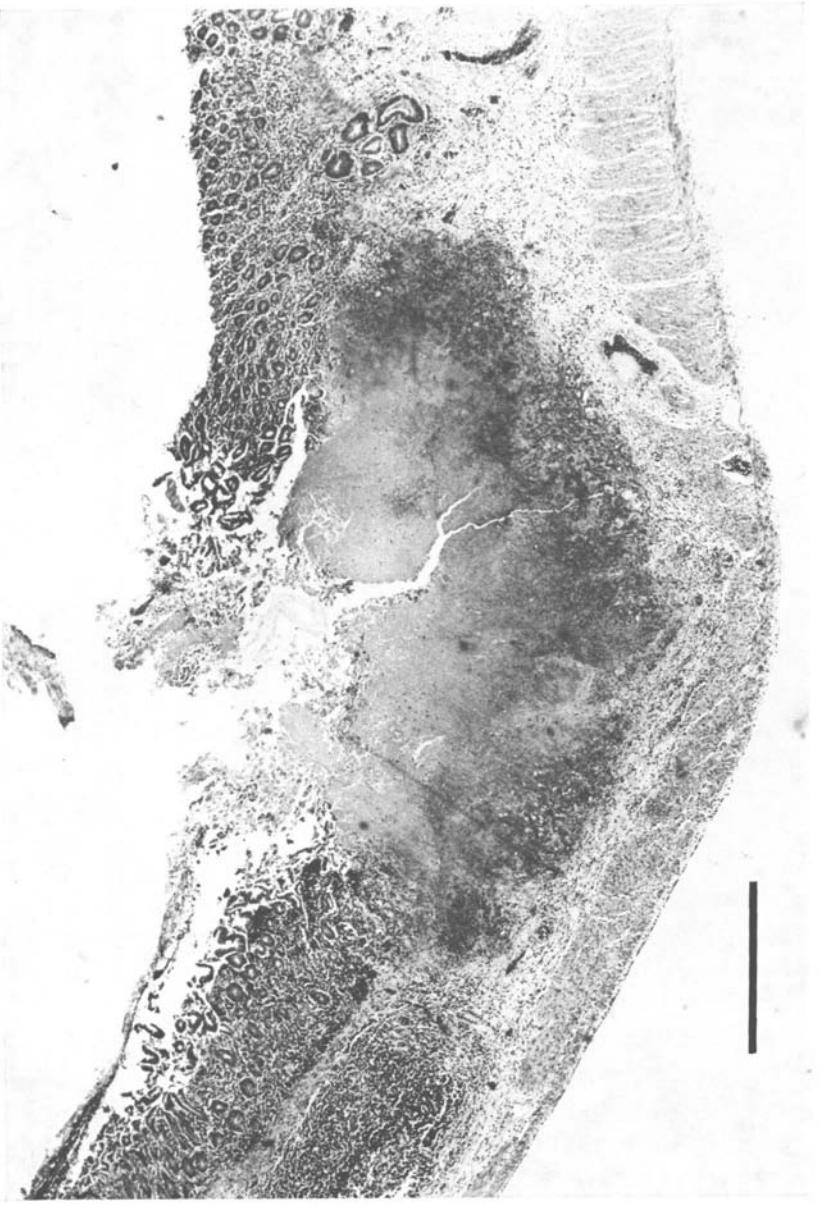
EXPLANATION OF PLATE

Section of caecal wall of marmoset showing deep ulcer extending into the submucosa and partly involving the muscular layer. Stained with Cole's haematoxylin and eosin. The black line = 500 μm.



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