ENDEMIC TYPHUS FEVER IN DIEGO SUAREZ, MADAGASCAR

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The map showing the recent distribution of the fevers of the typhus group in the Epidemiological Report of the Health Section of the League of Nations, 1936, suggests that these have not been recorded in Madagascar, and the local French public health report, 1940, states that this group of diseases does not occur on the island. It is therefore felt that the following series of cases among Service units, though small, justifies a special record.

The general hospital was functioning with limited equipment in Madagascar for several months after May, 1942. There

were a considerable number of cases with pyrexia of uncertain origin, with and without a rash, to which an accurate label could not be attached, as no agglutinable suspensions were available. Soon after the arrival of the suspensions a patient was admitted to hospital suffering from severe headache, drowsiness, backache, pains in chest, and a productive cough. This case was first diagnosed as bronchopneumonia, but sulphapyridine had no effect, for his fever continued and he remained seriously ill. For this reason, and despite negative blood films, it was thought that he might have malaria as well, and so was given quinine. On the seventh day a macular rash developed, and his bloated appearance with suffused eyes, taken in conjunction with the course of his illness, led to a suspicion that the case was one of typhus (C. G. Baker). This was confirmed by the Weil-Felix test (G. T. L. Archer). Patients in the hospital with indefinite fever—in some cases with a rash and severe malaise, in others only slightly ill, but all from the same unit and area—were immediately examined again, and blood agglutination performed.

The early results of Weil-Felix examination were as follows:

Case 1: OX19, OX2, OXK, 1/100 on 11th day

.. 2: OX19 1/400, OX2=0, OXK=0, on 12th day

3: OX19 1/800, OX2 1/200, OXK 1/100, on 18th day

4: OX19 1/100, OX2 1/100, OXK 1/20, on 12th day

TABLE I.—*Summary and Analysis of Cases*

(On grounds of economy detailed notes of these cases are not included in the report, but are available on request)

	Case 1 Severe Illness	Case 2 Mild Illness	Case 3 Moderate Illness	Case 4 Moderate Illness	Case 5 Moderate Illness	Case 6 Moderate Illness	Case 7 (Complicated) (a) Malaria; (b) Tonsillitis Severe Illness	Case 8 (Complicated) Malaria at Onset Moderate Illness	Case 9 Mild Illness	Case 10 (Complicated) Malaria, M.T. Severe Illness
1. Incubation period (days) ..	?	? 16	?	?	7 to 10	? 2/12	? 1	? 7	? 4 or 5	28
2. Prodromal period (days) ..	0	3	2	2	0	? 2	1	? 7	4 or 5	0
3. Onset ..	Sudden	Gradual; insomnia	Gradual	Gradual	Sudden	Sudden	Gradual; lassitude	Sudden	Gradual	Sudden
Invasion symptom ..	Pain in chest; broncho- pneumonia	Limb pain	Insomnia; vertigo	Backache; pain behind eyes	Headache	Inflamma- tion of old abrasion; headache; backache	Limb and stomach pain	Sweats; headache	Lassitude	Aching; sweating
4. Rigor or shiver- ing ..	Invasion stage {	+	+	+	+	0	+	+	0	+
5. Vomiting ..		0	0	0	+	0	0	0	0	+
6. Headache ..		0	+	+	+	+	+	+	+	0
7. Days of remittent Fever sustained over 102° ..		12	5	12	3	11	10	9	8	13
Total days over 99° ..	17	17 intermittent remittent	14	1/0	16	12	21	11	< 6	18
8. Onset of rash (day) ..	5th	0	0	0	5th or 6th	< 5th	4th	< 9th	0	5th
Duration in days ..	10	0	0	0	6 approx.	< 5	7	< 3	0	0
9. Type ..	Maculo- papular; red fol- lowed by brown stains	0	0	0	Maculo- papular; followed by staining	Maculo- papular; subarticular staining	Maculo- papular	Maculo- papular; subarticular staining	0	Maculo- papular
10. Distribution ..	Generalized; chest, limbs, palm, and soles	0	0	0	Chest and limbs; not face	Generalized	Generalized	Chest and limbs	0	Chest; face very few
11. Blotchy face ..	+	0	0	+	+	+	+	—	0	+
12. Shivering; rigors ..	+	+	0	+	0	0	+	+	+	0
13. Sweating; musty smell ..	+	0	+	+	+	+	+	+	+	+
14. Epistaxis ..	+	0	0	+	0	+	0	0	0	0
15. Conjunctival congestion ..	+	0	0	+	0	+	+	+	0	+
16. Photophobia ..	+	0	0	+	+	+	0	—	0	0
17. Pain on moving eyes ..	+	—	0	—	+	+	+	0	0	0
18. Fatigue; inability to protrude tongue ..	+	+	0	+	—	0	+	+	+	+
19. Frontal headache ..	Attempt painful	+	+	+	+	+	+	+	+	+
20. Occipital headache ..	+	+	+	+	+	+	+	+	+	+
21. Backache ..	+	0	+	+	0	+	+	+	+	+
22. Limb pains ..	+	+	+	+	+	0	+	+	+	0
23. Insomnia ..	+	+	0	+	+	+	+	+	0	+
24. Uncooperative ..	+	0	0	0	0	0	0	0	0	0
25. Amnesia ..	+	0	0	0	0	+	+	0	0	0
26. Drowsiness ..	+	+	+	0	0	0	+	+	0	0
27. Bronchitis ..	0	+	0	0	0	0	0	+	0	0
28. Bronchopneumonia ..	+	0	0	0	+	0	0	0	0	+
29. Cervical adenitis ..	+	0	+	+	+	+	+	0	0	+
30. Axillary adenitis ..	+	0	+	—	+	+	0	0	0	+
31. Splenomegaly ..	+	0	+	0	+	+	+	+	+	0
32. Constipation ..	+	—	—	0	+	+	0	0	+	+
33. Anaemia ..	+	—	+	0	+	0	—	0	+	0
34. Albuminuria ..	+	0	0	0	0	0	0	+	0	0
35. Malaria ..	0	0	0	0	0	0	M.T.	+ M.T.	0	+ M.T.
36. Weil-Felix (see Table II) ..				Otitis externa						

— = No record.

The question of a vector arose. Nothing definite could be deduced from the patients' histories, but within the limited means at our disposal as a stationary hospital some investigations were made, and it was found that:

1. *Lice*.—None of the patients were louse-infested, but all had been bitten, of course, by insects recently.
2. *Fleas*.—Fleas of two puppies which had frequented the location, fleas from rats found in the native huts which were at one time used as sleeping quarters by a few of the men for a short period, and fleas from rats living in an ammunition dump which had been guarded in turn by most of the patients were possible vectors. *Xenopsylla cheopis* and *X. braziliensis* were found on rats caught in the neighbourhood.
3. *Mosquitoes*.—Three cases developed malignant tertian malaria while in hospital.
4. *Ticks*.—Ticks infested almost every dog in the district.
5. An unknown vector remained a possibility.

All respective observations, investigations, and treatment were controlled by medical specialist, pathologist, and officer in charge of the medical division of the unit. The pathologist had only a very limited supply of agglutinable suspensions, so had to choose the time of taking the specimen with considerable care. These three officers are convinced that a fever with a definite clinical picture similar to that seen in cases of the typhus group found elsewhere, supported by appropriate pathological tests, has occurred among people living in the region of Colt's Hill (near Diego Suarez), Sakaramy, and Orangea. In spite of the official views expressed in the first paragraph it may well occur elsewhere on the island.

Incubation Period

This could not be fixed accurately, as most of the patients reached the main site, Colt's Hill, on May 31 but developed their illness at different times (Table I). The dates of insect bites were noted where possible; the incubation period appeared to be 10 days in Case 5, 16 days in Case 2, possibly 2 months in Case 3 (who stated he had not been bitten for that period), and 2 months in Case 6 (who also stated that he had not been bitten recently but had sustained an infected abrasion two months before the onset of the illness). Subtertian malaria infection occurred at the onset of the illnesses in Cases 8 and 9, but towards the end in Case 7. A patient from this site who attended the skin department on account of bites on the thigh and waist region of the abdominal wall, such as most of these patients had had, was admitted and kept under observation to see whether an incubation period between the bite and the fever could be ascertained, but his Weil-Felix reaction never rose above OX19 1/40, OX2 1/20, OXK 1/40.

The *prodromal period* appeared to be about 2 days. It was not present in all cases, being absent in Cases 1, 5, and 10. It was of 1 day's duration in Case 7, 2 days in Cases 3, 4, and 6, 3 days in Case 2, and 4 or 5 days in Case 9. The symptoms during this time were unusual lassitude, fatigue, and sleepiness very early at night, and a headache early in the morning, which gradually passed off during the day but returned in the evening.

Onset of Fever and Illness

This was gradual in half the cases and sudden in the remainder. The invasion symptoms included headache, pains in the chest and epigastrium, severe backache, dizziness and falling to the ground, and rigors or shivering attacks. Severe headache was the most common symptom, starting in the frontal region, then being noted in the occipital region, and finally in the whole head.

The main features of the established illness appeared to be a continuous high fever for about 14 days, temperature varying between 100° and 104° F., and pulse between 80 and 100. Sweating was marked throughout the febrile period and was notable for a characteristic heavy musty odour (quite different from that of patients in hospital at the time suffering from malaria, paratyphoid A, dengue, fevers, etc.). The patients were drowsy, lethargic, and uncooperative; it was an effort to protrude the tongue for inspection. There was puffiness around the orbits, with conjunctival suffusion, blotchy bloated appearance, and sleepy expression. The main ocular symptoms were heaviness of the upper eyelid, pains behind the eyes, pain on moving the eyes to the right or left, and photophobia.

Headaches were very similar, usually starting in the frontal region, spreading to the occipital region and later to the whole head. They were compared with a heavy weight pressing on the head, and were not associated with a marked throbbing or bursting sensation. Early in the morning they were most severe, diminishing during the day but increasing late in the evening, and often keeping the patient awake. Backache was usually in the lumbar muscles, but did not occur between the shoulders. The limb pains were in some ways like those met with in dengue—frequent in the shins and knees and muscles of the upper limbs, biceps and supinator longus being picked out particularly in Case 8. A common finding was a dry mouth and tongue, but sordes was present only in the most severe cases.

A rash appeared in more than half the cases on or about the fifth day. It was noticed on the chest and flanks at first. The full distribution in some included face, limbs, palms, and soles. The rash consisted of small red pinhead-size papules and red macules varying from 1 to 3 mm. in diameter. At first these faded on pressure with a central red point in a few, but after a few days darkened, and on diascopic examination most showed a residual brown pigmentation. The darkening process continued until the lesions were dark brown, and then gradually faded away. Lesions of different colour were present at the same time, and fading ones gave a clear

TABLE II.—Showing Results of Serological Examination

Case		1st Test	2nd Test	3rd Test	4th Test
	Day:	11th	15th	37th	56th
1	OX19	1/100	1/400	1/800	1/200
	OX2	1/100	1/400	1/800	1/200
	OXK	1/100	1/100	1/40	< 1/40
	Day:	12th	14th	38th	56th
2	OX19	1/400	1/400	1/800	1/200
	OX2	0	1/40 tr.	< 1/40	< 1/40
	OXK	0	1/100	1/40	< 1/40
	Day:	18th	40th		
3	OX19	1/800	1/800 +		
	OX2	1/200	1/100		
	OXK	1/100 tr.	1/40		
	Day:	11th	33rd		
4	OX19	1/100	1/400		
	OX2	1/100	1/200		
	OXK	1/20	1/20		
	Day:	7th	27th	47th	
5	OX19	1/100	1/800 +	1/400	
	OX2	1/20	1/40	< 1/40	
	OXK	1/20	1/20	< 1/40	
	Day:	5th	26th	46th	
6	OX19	< 1/100	1/800 +	1/800	
	OX2	0	1/100	1/40	
	OXK	0	1/20	< 1/40	
	Day:	22nd			
7	OX19	1/800 +			
	OX2	1/200			
	OXK	1/20			
	Day:	12th	19th		
8	OX19	—	1/400 +		
	OX2	1/40	1/200		
	OXK	—	1/40		
	Day:	17th	39th		
9	OX19	1/200	1/100		
	OX2	1/40	0		
	OXK	1/200	< 1/100		
	Day:	7th	16th	26th	
10	OX19	0	1/800	1/1600	
	OX2	0	1/400	1/400	
	OXK	1/20	1/20	< 1/40	

impression of subcuticular mottling. The average duration corresponded with the period of high fever, 102° and above, lasting from 7 to 14 days. It was associated with a lineal conjunctival congestion, especially between the cornea and the outer canthus. Epistaxis occurred in 4 cases during the early stages of the fever, and vomiting occurred in 2, but there was no haematemesis.

Chest symptoms and signs were a pronounced feature. Case 1 was first diagnosed as a simple bronchopneumonia, Case 10 had a bronchopneumonia with blood-stained sputum, and in the remaining cases productive cough with signs of bronchial involvement of greater or lesser degree occurred. Involvement of the central nervous system was not marked. Headache and insomnia were common, and the most seriously ill were irrational and uncooperative, with subsequent partial amnesia; but apart from loss of abdominal reflexes and only sluggish tendon reflexes no clinical signs were found. The spleen was palpable in 4 cases in the first week and tender in 1. The lymphatic glands of the neck and axillae were slightly enlarged to the size of a pea in 4 cases and to a greater degree, and particularly in the tonsillar group of cervical glands, in the 2 cases in which there was an associated pharyngitis. Tenderness was absent in most instances, Case 1 being the exception.

Treatment was systematic; morphine was effective.

Pathological findings were as follows. Albuminuria in the severe cases, with red blood corpuscles or casts in deposits, and a secondary anaemia in two cases: Case 3—R.B.C. 3,300,000; W.B.C. 7,200 (polymorphs 60%, lymphocytes 36%, monocytes 4%); Case 4—R.B.C. 3,300,000, W.B.C. 5,200 (polymorphs 68%, lymphocytes 26%, monocytes 5%, eosinophils 1%).

Notes on Table II

The technique used was that of Felix, agglutination in round-bottom tubes at 37° C. The method of reading, however, was modified, after a preliminary examination, by shaking the tubes and observing the end-point of granularity. This was done in view of the fact that many of the tubes in use were not hemispherical at the bottom. Dreyer's technique was not employed, as Dreyer's tubes were not available. On receipt of a few Dreyer's tubes, however, two pairs of tests were carried out in parallel, using the two methods. The results were identical.

The + sign after the titre shown indicates that though the test was not carried further the result on the last tube suggested that the limit of agglutination had not been reached. 0=less than 1/20, the lowest dilution used.

The results, showing comparatively low titres for OX19, with in most cases marked coagglutination for OX2, and, in some, lesser coagglutination for OXK, would appear to indicate a group reaction. They differ from those to be expected in epidemic or endemic (murine) typhus or in mite typhus, while in South African tick typhus the OXK agglutination usually predominates. The results, however, appear to resemble those which occur in the "OX19 Group" of Indian cases (Boyd, 1935).

Vector and Possible Animal Reservoir.—No laboratory investigation was possible on these points, as there were no guinea-pigs available for inoculation experiments with preparations from possible vectors, and the continued shortage of agglutinable suspensions made it impossible to do serological tests on animals.

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TWO CASES OF ANURIA DUE TO SULPHAPYRIDINE CALCULI SUCCESSFULLY TREATED BY URETERIC CATHETERIZATION

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The seriousness of haematuria and anuria complicating sulphapyridine therapy is well recognized, and a number of cases have been reported both in America and in Great Britain. The renal complications of sulphapyridine therapy were well reviewed by Laird (1941) when reporting five cases of haematuria and one of anuria. More recently the literature has been reviewed by Carson and Smith (1942) and by Benson and Percival (1942), who reported respectively the necropsy findings in a fatal case and a case treated successfully by ureteric catheterization.

In the two cases described below relatively small doses of sulphapyridine—9 and 13 g. respectively—were administered, and in both cases haematuria followed by anuria resulted. Both cases were in hospital before haematuria developed, and at first were ambulatory. A high fluid intake was encouraged, but the volume was not measured. Both patients were adult males of good physique, admitted to hospital on account of uncomplicated gonococcal urethritis.

Case I

A man aged 28 was admitted on Nov. 17, 1941. He was given 4 g. of sulphapyridine daily for two days, and on the morning of the third day received 1 g. Soon after the last dose he passed deeply blood-stained urine. Later in the day vomiting and severe renal pain were noted and no more urine was passed. As the anuria persisted he was transferred to the surgical department and cystoscopy was performed after 24 hours' anuria.

The bladder contained a small amount of blood-stained urine. The bladder wall appeared normal except for a well-marked ureterocele on both sides; that on the left side made the passage of a ureteric catheter impossible. A catheter was passed on the right side and the renal pelvis was washed out. On his return to the ward an intravenous drip saline was started, this being continued for two days. A few drops of blood-stained urine drained through the catheter, and 24 hours later he was cystoscoped again. Both ureteroceles were more pronounced, and further attempts to catheterize the left ureter failed; but on catheterizing the right ureter blood and sulphapyridine crystals were seen to escape into the bladder, urine drained through the catheter, and in the subsequent 24 hours he passed 100 oz. of urine through the catheter and per urethram. The catheter was removed after 18 hours. His symptoms rapidly abated, and on discharge from hospital two weeks later his urine was normal. The highest blood urea was recorded on the day of the second cystoscopy, being 72 mg. per 100 c.cm.

Case II

A man aged 27 was admitted on Oct. 14, 1942. He was treated with sulphapyridine, and received a total of 13 g. between admission and 6 a.m. on Oct. 17. At 6.30 a.m. on Oct. 17 he started passing blood-stained urine, 5 oz. being passed between that time and 11 a.m. He then complained of severe pain in both loins and persistently vomited stomach contents containing changed blood. At 7 p.m. his condition had deteriorated, and as he had not passed urine since 11 a.m. he was transferred to the surgical department and cystoscopy was performed. The bladder contained about 1/2 oz. of practically pure blood together with a large amount of sulphapyridine crystals, there were small petechial haemorrhages in the bladder mucosa, both ureteric orifices were congested, and a small pencil of sulphapyridine crystals was seen protruding through the left ureteric orifice. On passing a catheter up the left ureter, crystals, debris, and blood were seen to escape. A catheter could be passed up the right ureter for only about 2.5 cm. On return from the theatre he was started on intravenous drip saline, which was continued for three days till the vomiting ceased. Five ounces of blood-stained urine loaded with sulphapyridine crystals drained from the left ureter and none from the right in six hours, after which the left catheter became blocked.

At 10 a.m. on Oct. 18 both catheters were removed and were found to be blocked with blood and crystals. Fresh catheters were now passed up both ureters, and both ureteric orifices were observed to be more congested. Attempts were made to wash out the renal pelvis with normal saline, but although 5 c.cm. was injected through each catheter no fluid could be withdrawn, presumably owing to oedematous mucosa being sucked into and blocking the catheter orifices. During the next six hours 8 oz. of blood-stained urine drained through the catheters and a further considerable amount leaked around the catheters into the bed. On Oct. 19 5 oz. of slightly blood-stained urine was passed. On Oct. 20 vomiting ceased, and 110 oz. of clear urine was passed. Subsequently the patient recovered rapidly, and on discharge three weeks later he had no symptoms and his urine was normal.

The highest blood urea recorded was 96 mg. per 100 c.cm. on Oct. 21, after which the figure gradually returned to normal.

Discussion

Incidence.—During the last six years one of us has used the sulphonamide group of drugs, and particularly sulphapyridine, in about 4,000 cases. With the exception of the two cases here reported all cases of haematuria have resolved with confinement to bed, cessation of the drug, large quantities of fluid by mouth, and enemata. The incidence is low, but is likely to rise if the less-soluble sulphathiazole replaces sulphapyridine. According to Macartney *et al.* (1942) the relative