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CHRONIC URINARY SALMONELLA CARRIERS WITH INTERMITTENT BACTERAEMIA

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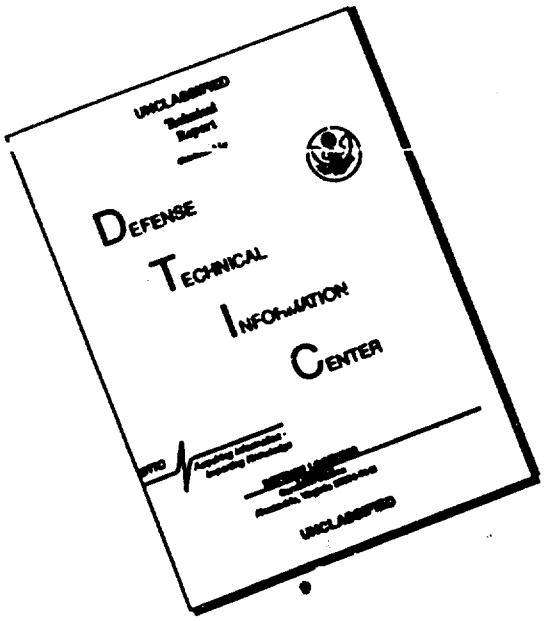

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13. ABSTRACT

Fifteen Egyptian male farmers aged eight to 29 years, known urinary excreters of S. typhi or paratyphi A were observed in hospital for periods varrying between six to 12 months. Blood cultures were performed twice weekly using a Castaneda type two-phase bottle and 10 per cent ox bile. Urine samples were plated on Selenite media directly. Salmonella typhi or paratyphi A were recovered from the blood in every case though the clinical picture did not resemble typhoid fever. These bacteraemic phases were transient and were in some patients accompanied by a low-grade fever with occasional spikes of high fever. All patients were malnourished, debilitated, and had an anaemia refractory to treatment with oral ferrous sulphate. Intravenous pyelography demonstrated damaged urinary tracts caused by schistosomal infection in all patients such as hydronephrosis and hydroureters, bladder modular filling-defects, bladder calcification stricture of the ureters, and reflux.

It is suggested that these patients harbour the salmonella organisms in the urinary tracts from which intermittently they are shed intravascularly. Treatment therefore should aim at relieving the bilharzial obstruction by anti-schistosomal treatment followed by treatment with either ampicillin or chloramphenicol to clear any remaining foci of infection in the kidneys.

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The persistence of viable *Salmonella typhi* in the human body, probably in the reticuloendothelial system, for prolonged periods with intermittent shedding of organisms into the blood-stream has recently been described by Watson (1967) from South Africa, and by Neves *et al.* (1969) from Brazil. Watson (1967) *et al.* (Lancet, 1967; Foster, 1967; Bokkenheuser *et al.*, 1967) suggested that it would be of interest to carry out repeated blood cultures on known excreting carriers to determine whether they are also intravascular shedders.

The incidence of urinary salmonella excretors in Egypt is very high (Miller, 1950). The condition is related to the damaged urinary tracts caused by *Schistosoma haematobium* infection (Miller and Floyd, 1954; Halawani and Badran, 1958; Hathout *et al.*, 1966). During the past five years we were therefore easily able to study over 40 chronic urinary enteric carriers. Fifteen of these were followed-up in hospital for six to 12 months and it soon became evident that these patients not only excrete *S. typhi* or *S. paratyphi A* in the urine but periodically, over months, also shed the organisms in the blood. These recurrent bacteraemic phases were not necessarily accompanied by fever and did not clinically resemble typhoid fever. This paper reviews our findings in these 15 patients.

The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department, the Naval Service at large or the Egyptian Ministry of Public Health.

Materials and Methods

Patients:

Fifteen male Egyptian farmers were from villages in the Nile Delta, mostly within 100 kilometers of Cairo. They were aged eight to 29 years and were observed in hospital for periods of six to 12 months in the period 1966 to 1969. All had haematuria and dysuria of from three to 15 years' duration and all, except four, had received previous antischistosomal treatment. Twelve had active urinary tract infection with *S. haematobium*. Plain x-ray films of the bladder and intravenous pyelography showed that all 15 patients had damaged urinary tracts. Urines and stools were examined routinely and haemoglobin and haematocrits were estimated periodically in every patient. All were repeatedly excreting salmonella organisms in the urine. After deworming with bephenium hydroxynaphthoate all patients were given 5 grains oral ferrous sulphate three times daily.

Bacteriology:

Urine Cultures—Urine was plated directly onto selective medium using a 5 mm platinum loop. In addition, 5 ml of urine was added to an equal amount of Selenite broth (Difco) and incubated for 24 hours before plating on the same selective media. Colony counts were made by spreading 0·01 ml of urine from a calibrated loop onto agar plates of Tryptose blood agar base containing 5 per cent sheep blood and the bacteria per ml of urine counted after 24 hours incubation. Counts of over 100,000 per ml were considered significant of a urinary

TABLE. CLINICAL AND LABORATORY DATA.

Patient No.	Age (years)	Observation Period (months)	Hb g./100ml	Widal "O" Titres	Blood Cultures (multiple)	Urine Cultures (multiple	Intravenous Pyelography
1	14	8	5·0	1/1280	*S. typhi*	*S. typhi*	Bladder nodular filling-defects.
2	15	7	7·9	1/640	*S. typhi*	*S. typhi*	Hydroureters; hydronephrosis; bladder calcification; vesicoureteric reflux.
3	13	7	6·5	1/640	*S. typhi*	*S. typhi*	Bladder calcification.
4	15	6	7·4	1/640	*S. typhi*	*S. typhi*	Hydroureters; bladder calcification.
5	12	6	8·7	1/640	*S. typhi*	*S. typhi*	Hydroureters; hydronephrosis.
6	15	12	9·5	Negative	*S. para A*	*S. para A*	Bladder nodular filling-defects; hydroureters; bladder calcification.
7	20	12	5·7	Negative	*S. para A*	*S. para A*	Hydroureters; hydronephrosis.
8	13	9	9·5	1/640	*S. para A*	*S. para A*	Bladder calcification.
9	16	9	6·3	1/320	*S. para A*	*S. para A*	Hydroureters; hydronephrosis.
10	13	7	8·9	1/640	*S. para A*	*S. para A*	Bladder nodular filling-defects; vesicoureteric reflux.
11	29	6	9·6	1/640	*S. para A*	*S. para A*	Hydroureters; hydronephrosis; bladder calcification.
12	20	6	7·3	1/640	*S. para A*	*S. para A*	Stricture left ureter; bladder calcification.
13	10	6	9·2	1/460	*S. para A*	*S. para A*	Stricture right ureter.
14	30	6	7·1	1/320	*S. para A*	*S. para A*	Bladder calcification.
15	8	6	5·6	1/320	*S. para A*	*S. para A*	Bladder nodular filling-defects.

S. para A=*S. paratyphi A*.

tract infection (Savage *et al.*, 1969). Urine cultures were performed routinely twice weekly and at every fever spike during the entire hospitalization period.

Blood Cultures — Two methods were employed for blood specimen culture, a Castaneda-type two-phase bottle technique (Castaneda, 1947) and 10 per cent Ox bile solution (Kaye, *et al.*, 1966). The two-phase bottle contained a slant of Tryptose Agar W/Thiamine (Difco) and 30 ml Trypticase soy broth (BBL). Three ml blood was introduced into each culture container. Cultures were incubated at 37°C. Subcultures were made from the bile culture after 24 hours incubation and if negative repeated after four to six days incubation. Castaneda bottles were incubated until growth was observed or for a maximum of 21 days before being considered negative. Positive bottles were subcultered onto plating media. Blood cultures were made twice weekly and at every temperature rise over 100°F. During the entire period the patients were under observation.

Stool Cultures — Swab samples of stool specimens were plated on selective media. Swabs were then placed in Selenite broth and treated in the same manner as urine specimens.

Isolates possessing cultural and biochemical characters of Salmonellae were confirmed serologically by testing for "O" and "Vi" antigens in slide agglutination tests.

Routine Widal and brucella agglutination titres were estimated by means of conventional tube test procedures. Serial dilutions of serum were tested against Somatic groups A, B, C, D, and E antigens and flagellar paratyphoid A, B, C, and typhoid H antigens, and only the highest titres reported.

Results

The table summarizes our results.

The presenting symptoms in the 15 patients were those of anaemia-pallor, dyspnoea, weakness, and palpitation on exertions—all had haemoglobin levels under 10 grammes per cent. Their general clinical condition was usually very poor and the majority were malnourished and debilitated. Pyrexia was not a prominant sign and usually these patients were unaware that they were febrile. A few complained of a sudden rise of temperature which lasted for two to three days then settled down again to a niggling 100 to 101°F.—the usual temperature pattern in these patients. This is in marked contrast to the continuous type of temperature usually seen in acute typhoid or paratyphoid fevers. Advanced hepatosplenomegaly was present in only two patients and in the remaining patients the spleen and liver were

palpable approximately 1 to 5 cm below the costal margins.

The Widal titres were usually not markedly elevated. In two patients though the organisms were continuously cultured from blood and urine, the Widal tests were repeatedly negative. In the majority of the other patients the agglutination titres ranged from 1/320 to 1/640. The total white blood count also differed from that usually seen in typhoid and paratyphoid fevers and ranged from 6,000 to 12,000 per c.mm.

Five patients were continually excreting *S. typhi* and 10 patients *S. paratyphi A* in the urine. In all patients the bacterial counts were over 100,000 per ml. of urine signifying a urinary tract infection. Repeated stool cultures in all patients were always negative. Blood cultures obtained from these patients at different times during the observation period grew the same organism as was being excreted in the urine. Repeated blood cultures, however, had to be obtained and usually one out of an average of seven to eight consecutive blood cultures would be positive. A great effort was made to obtain several blood cultures during a temperature elevation, and usually we were more successful in isolating the salmonella during these brief imperceptible periods of pyrexia.

All 15 patients had damaged urinary tracts caused by the schistosomal infection. Bladder nodular filling-defects were observed in four patients. Bilateral hydroureters and hydronephrosis were present in seven patients, and eight had advanced bilharzial bladder calcification. Strictures of either right or left ureters were noted in two patients and vesicoureteric reflux was diagnosed in two patients by micturating cystograms (Savage, *et al.*, 1969).

Though these patients were de-wormed and given a well balanced hospital diet plus 15 grains of ferrous sulphate daily their general clinical condition and marked anaemia hardly improved even though we observed them for over eight to 12 weeks. Following antibiotic treatment, however (chloramphenicol 50 mg. per kg body weight per day or ampicillin 100 mg per kg body weight per day for 14 days) the urine and blood cultures became negative, the refractory anaemia was corrected and their general clinical condition greatly improved. Unfortunately the majority of these patients relapsed both clinically and bacteriologically a few weeks after completing antibiotic treatment. Details of treatment using combined antischistosomal drugs and antibiotics are the subject of a separate paper (Bassily, *et al.* in press).

Discussion

Attention has been drawn to the prevalence in Egypt of urinary typhoid and paratyphoid carriers by Neva (1949), Walton (1949), and Archer, *et al.* (1950). None of these authors, however, reported observing the occurrence of bacteraemia in any of their patients. Fifteen years ago, working at NAMRU-3, Miller and Floyd (1954) treated 15 Egyptian farmers with a urinary carrier history of over 12 months, and though their patients were similar to ours, these authors did not report culturing salmonella from the blood of any of their patients. Later still, Halawani, Abdalla, and Badran (1960) reported treating 36 Egyptian urinary salmonella excretors, but though these authors mention that in none of their patients was there clinical or bacteriological evidence of enteric fever at the time of admission, they did not report obtaining blood specimens for culture during the observation period prior to starting antibiotic treatment. Clearly these earlier workers were unaware of the possibility of bacteraemia occurring in their patients. By observing our patients for long periods and obtaining repeated blood specimens for culture we confirmed Watson's findings (1967) and demonstrated that known urinary excreting carriers may also become intermittent intravascular shedders.

Diagnosis of these patients may be difficult since the clinical picture does not resemble typhoid or paratyphoid fever. A history of urinary schistosomiasis or the presence of *S. haematobium* eggs in the urine in a debilated, sick, and anaemic patient not responding after de-worming to oral ferrous sulphate should arouse suspicion and lead to an active search for salmonella organisms in the urine and blood. A urine bacterial count over 100,000 per ml with a damaged urinary tract evident on intravenous pyelography practically confirms the diagnosis. Repeated blood cultures are then necessary to isolate the organisms from the blood.

We disagree with Hathout, *et al.* (1967) in considering bilharzial hepatic fibrosis to be the cause of the frequently associated septicaemia in these patients; and we cannot agree with Rogers (1968) who refers to these patients as cases of hepatic schistosomiasis comparing them to disseminated salmonellosis in sicklaemia, malaria, and bartonellosis. The Egyptian urinary salmonella excretor is mainly infected with *S. haematobium* which affects the urinary system and rarely causes severe liver fibrosis. These patients have damaged urinary tracts in which the salmonella organisms probably reside

and from which intermittently they are shed intravascularly. We (Bassily, *et al.* In press) succeeded in curing some of these patients by relieving the bilharzial obstructive uropathy by giving antischistomal treatment followed by either ampicillin of chloramphenicol treatment to eliminate remaining foci of infection in the kidneys.

Summary

Fifteen Egyptian male farmers aged eight to 29 years, known urinary excretors of *S. typhi* or *paratyphi A*, were observed in hospital for periods varying between six to 12 months. Blood cultures were performed twice weekly using a Castaneda type two-phase bottle and 10 per cent ox bile. Urine samples were plated on Selenite media directly. *Salmonella typhi* or *paratyphi A* were recovered from the blood in every case though the clinical picture did not resemble typhoid fever. These bacteraemic phases were transient and were in some patients accompanied by a low-grade fever with occasional spikes of high fever. All patients were malnourished, debilitated, and had an anaemia refractory to treatment with oral ferrous sulphate. Intravenous pyelography demonstrated damaged urinary tracts caused by schistosomal infection in all patients such as hydronephrosis and hydroureters, bladder nodular filling-defects, bladder calcification, stricture of the ureters, and reflux.

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