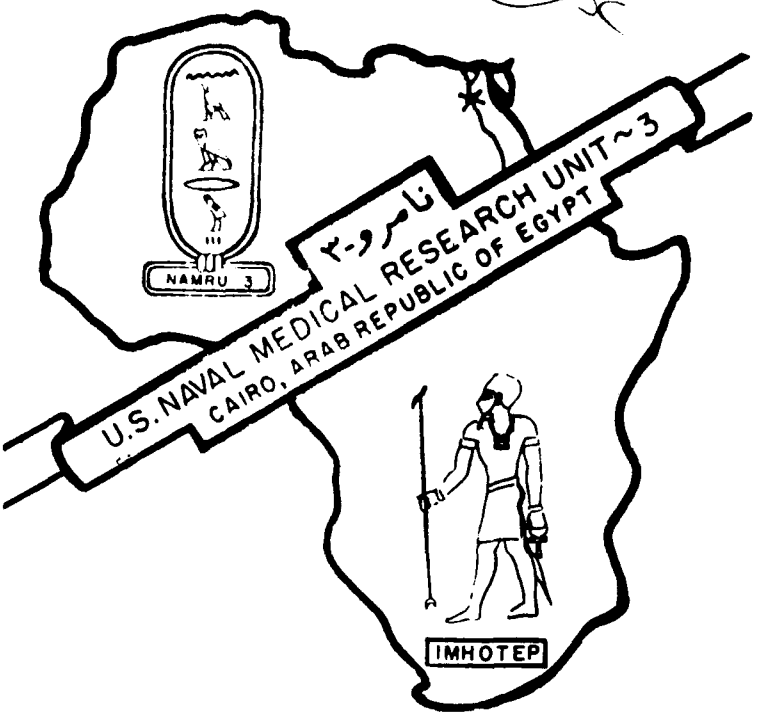

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ACUTE BRUCELLOSIS PRESENTING AS FEVER OF UNKNOWN ORIGIN (FUO)

By

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TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, VOL. 74, NO. 3, 1980

Acute brucellosis presenting as fever of unknown origin (FUO)

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Brucellosis ranks after salmonellosis and tuberculosis as the most important systemic infection causing fever of unknown origin (FUO) in Cairo (HASSAN & FARID, 1974). The cause is nearly always *Brucella melitensis* (see PFISCHNER *et al.*, 1957) but owing to the widespread indiscriminate use of antibiotics in Egypt (FARID *et al.*, 1975), it has become difficult to isolate the organism by blood culture and thus establish a definitive diagnosis. We summarize the clinical data of 16 patients with acute brucellosis presenting with FUO between January 1971 and December 1977 and describe serious complications that developed in three.

Patients' ages ranged from 15 to 54 years (median 38·5); four were women and 12 men. Three were farmers constantly in contact with cattle; the others lived in Cairo and presumably acquired the infection through drinking raw milk. All were seriously ill and reported recurrent attacks of fever with generalized arthralgia and profuse sweating of at least one month duration (range one to 24; median 4·5). All except three had been treated with many antibiotics; 10 with chloramphenicol. All except two (who had positive blood cultures for *Br. melitensis*) had elevated agglutination titres (range 1:640 to 1:5120) denoting an acute infection. *Br. melitensis* was isolated from blood or bone marrow of 13 patients and *Br. abortus* from one. In the two patients with negative blood cultures the Brucella agglutinations were highly positive. In all but two patients, the total leucocyte count was below 10,000/mm^3 (range 3,000 to 13,000; median 5,400). The erythrocyte sedimentation rate (ESR) was elevated in all patients (range 16 to 55mm/hr; median 46, Wintrobe method), again denoting an acute process.

Of the 16 patients, three developed severe complications; all the others responded to treatment with tetracycline and streptomycin and were cured. Oral tetracycline was given in a dose of two grams daily and streptomycin in a dose of one gram intramuscularly daily; both drugs were given for a minimum of three weeks (FARID *et al.*, 1961).

Details of the three patients who developed complications:

Case 1: A 37-year-old manual worker presented with a history of recurrent attacks of fever accompanied by severe arthralgia of nine months' duration. He had been treated with salicylates, butazolidin, chloroquine, chloramphenicol and streptomycin. Physical examination showed a critically ill male with a temperature of 39 C, tachycardia, hepatosplenomegaly and dependent oedema. No heart murmurs were noted. The leucocyte count was 4,970/mm^3; several blood cultures were reported negative but the Brucella agglutination was 1:1260. He was started on oral tetracycline two grams and intramuscular streptomycin one gram daily. On the fifth hospital day the patient's condition deteriorated and a pathologic, high pitched, soft diastolic murmur was heard over the aortic area. He became very dyspnoeic and a diffuse haemorrhagic rash developed over both lower limbs. He became afebrile after two weeks of antimicrobial therapy and appeared to improve clinically but died in congestive heart failure at the end of four weeks of treatment.

Case 2: A 58-year-old engineer was admitted to hospital complaining of recurring episodes of fever, generalized musculoskeletal pains and night sweats of two years' duration. He had been treated with many antibiotics but three weeks before entry to hospital endocarditis was suspected and he was started on intramuscular crystalline penicillin. Physical examination showed a seriously ill male with 2+ pitting oedema and a diffuse petechial rash over both lower limbs. His temperature was 38 C and there was a high-pitched soft diastolic murmur over the aortic area; leucocyte count 3,050 mm^3, ESR 25 mm/hr, and Brucella agglutination 1:1260. Several blood cultures were reported negative but a bone marrow culture was positive for *Br. melitensis*. He responded to tetracycline and streptomycin and became afebrile after four weeks of treatment; but the heart murmur persisted due to the development of irreversible aortic insufficiency.

Case 3: A 42-year-old male clerk was admitted to hospital in July 1976 complaining of recurrent fever, night sweats, arthralgia and weight loss of 17 months' duration. He had been admitted three times to hospital and had received several courses of tetracycline, chloroquine and chloramphenicol. His temperature was 39 C, leucocyte count 4,800 mm^3, ESR 43 mm/hr and Brucella agglutination 1:1260. Blood cultures were positive for *Br. melitensis* and he was treated with tetracycline and streptomycin. In April 1977 he relapsed and was retreated with tetracycline and streptomycin for another three weeks. During the next two years he had three further relapses; on each occasion blood cultures were positive for *Br. melitensis*. In August 1977 he was admitted complaining of fever and cough with haemoptysis. An X-ray of the chest showed bilateral

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Fig. 1. Chest and cervical spine radiographs of Case 3
a. At third relapse in August 1977 bilateral basal opacities can be seen.
b. In November 1978, there is marked narrowing of the intervertebral disc space with destruction of adjacent vertebral bodies of C_5 and C_6.

basal opacities (Fig.). He responded to six weeks' treatment with tetracycline and streptomycin. Seven months later he returned to hospital with severe neck pains. An X-ray of the cervical spine showed early spondylitis of C_5-C_6; his chest X-ray was clear. He was treated for six weeks with tetracycline and streptomycin and went home much improved. In November 1978, he returned complaining of severe neck pains and recurrence of cough with haemoptysis. There was a diffuse petechial rash over the whole body. A chest X-ray showed patchy opacities of the right lower lung field, and an X-ray of the cervical spine showed osteomyelitis of C_5 and C_6 (Fig.). He discharged himself from hospital and died three weeks later in another hospital.

Brucella infection in these three patients had lasted nine to 24 months, yet all were seriously ill and all three had markedly elevated agglutination titres denoting an acute rather than a chronic process. During this period they had received many short courses of various antimicrobials, never adequate to cure but sufficient to suppress the fever and hide the real nature of the infection.

The two patients with infective endocarditis gave no history of previous heart lesions; indeed the first developed a heart murmur after 16 months of illness, only a few weeks before being referred to hospital because his clinical condition had suddenly deteriorated. Brucellosis was undoubtedly the cause of aortic valve disease in both patients. The third patient continued to relapse over a period of observation of 28 months. He developed lung and cervical spine complications (although lumbar spine complications are common in *Br. melitensis* septicaemia (FARID & MIALE, 1964), certainly cervical spine lesions are uncommon) despite adequate antimicrobial therapy. Detailed immunological studies performed in November 1978 showed this patient to have a defect in cell-mediated immunity *which may explain his recurring brucella* septicaemia. The defect appears to have been acquired since a tuberculin test was positive on initial admission but turned negative subsequently. Delayed hypersensitivity skin tests in November 1978 with recall microbial antigens (*Candida albicans*, streptokinase-streptodornase) were also negative. *In vitro* microculture lymphocyte blast transformation assays were also uniformly suppressed (40 to 70 % lower than normal responses). The patient's lymphocytes were tested against the three antigens above as well as to staphylococcal lysate antigen and to the mitogens, phytohaemagglutinin, concanavalin A, and pokeweed mitogen. 10 % autologous plasma further diminished the mitogenic responses by 50 %, suggesting that the suppression observed results from both suppressor cells and soluble plasma factors.

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

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Comparison of IHA test for amoebiasis on serum and filter paper specimens

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Specimens of blood collected and dried on filter paper have been useful in seroepidemiological studies for detection of diseases such as malaria (LOBEL *et al.*, 1976) and Chagas's disease (GOLDSMITH *et al.*, 1978). We have compared indirect haemagglutination titres to *Entamoeba histolytica* on serum and filter paper specimens collected simultaneously from the same person. The study population from El Salvador included patients with proven *E. histolytica* infection, their immediate families and neighbour controls. A total of 110 paired specimens was obtained.

Materials and Methods

Venous blood was collected in vacuum tubes and allowed to clot; serum was recovered by the usual methods. Serum was frozen at −20 C until thawed for testing. For the filter paper specimens, blood was collected in heparinized microhaematocrit tubes (approximately 75μl) by finger prick or from the vacuum tube before it clotted, and was transferred immediately to a 12-mm circle imprinted on a 2·5 × 5 cm rectangle of ROPACO* 1023-.038 filter paper (James River Rochester, Inc., Rochester, Michigan 68063, USA). The blood was allowed to dry at ambient temperature and then was frozen at −20 C. Serum and filter paper blood specimens were transported on dry ice to the Center for Disease Control, Atlanta, Georgia, USA, for processing.

The entire blood spot was cut from the filter paper and transferred to a well of a flat-bottomed tissue culture tray* Flow Laboratories, Catalog No. 76-000-05, and 0·4 ml of phosphate buffered saline (PBS, pH 7·2) was added. The tray was covered with an acetate sheet, and the material was eluted from the papers at room temperature (25 C). After two hours the paper was removed from the well, residual fluid was squeezed out with blunt nosed pliers, and the paper was discarded. Approximately 0·3 ml of dark brown eluate was thus recovered.

* Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health, Education and Welfare.

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Brucellosis ranks after salmonellosis and tuberculosis as the most important systemic infection causing fever of unknown origin (FUO) in Cairo. The cause is nearly always Brucella melitensis but owing to the widespread indiscriminate use of antibiotics in Egypt, it has become difficult to isolate the organism by blood culture and thus establish a definitive diagnosis. We summarize the clinical data of 16 patients with acute brucellosis presenting with FUO between January 1971 and December 1977. Four of these

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