

Laveran's discovery of the parasite. Manson, Ross, Grassi, and others, after years of labour, worked out the complicated development of the parasite in these insects. Then, on Manson's suggestion, a party of research workers from England lived for several months in the most unhealthy part of the Roman Campagna, among the malaria-soaked peasants. Taking no precautions against infection except that before dusk they retired to a mosquito-proof hut and stayed under

cover until daylight. All remained healthy. Finally, mosquitoes fed on malaria patients in Italy were sent to London, where they were fed again on volunteers who had never been abroad. These developed typical malaria, and the diagnosis was clinched by the demonstration of malaria parasites in their blood. Thus the complicity of the mosquito as the vehicle of infection passed from the realm of speculation to that of established and proven fact.

TUBERCULOUS ARTHRALGIA

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Manifestations of a high degree of sensitivity to the presence of tuberculous infection within the body are usually seen shortly after the primary infection, often pulmonary, has been acquired. These manifestations occur in the immediate post-primary infective period and are an expression of a high degree of allergy which has been built up, certain parts of the body becoming highly sensitive and reacting to the tuberculous infection. Such lesions are comparable to the secondary stage of syphilis, where the whole system becomes highly sensitive to the *treponema pallida*, and reacts accordingly, the skin lesions being usually highly characteristic. However, in syphilis the skin lesions often contain large numbers of spirochaetes, whereas the expressions of tuberculous skin sensitivity do not contain tubercle bacilli. Other examples of this allergic state which may be cited, are serum sickness, and the syndrome complex of rheumatic fever, the latter being due to sensitisation to the Haemolytic Streptococcus. It is not generally possible to differentiate allergy from sensitivity in the case of tuberculosis.

When due to tuberculosis, these allergic reactions are to be viewed in the light of warning signals. Not in themselves of serious import, they indicate that a primary infection has occurred and that a severe post primary infection may result later unless the condition is taken seriously and complete isolation from further infection achieved. For example, a child with erythema nodosum due to a primary tuberculous infection may be dead from tuberculous meningitis within a year, although no direct evidence of any tuberculous infection other than a strongly positive Mantoux Test was present at the time.

The following allergic manifestations are usually described:

1. Erythema nodosum.
2. Pleurisy with effusion.
3. Phlyctenular conjunctivitis.
4. Rheumatism, including arthralgia.

It will be seen that these are not specific for the tubercle bacillus—erythema nodosum may and often does occur as a manifestation of acute rheumatism. Bearing in mind that poly-arthralgia and erythema nodosum may occur concurrently as reactions to either rheumatic fever or tuberculosis, it is easy to appreciate that it may be extremely difficult or even impossible to distinguish rheumatic fever from tuberculous allergy. Moreover, cardiac manifestations, other than sinus tachycardia which is often merely febrile in origin, may be absent in a child or adult suffering from rheumatic fever with florid joint manifestations, while pericarditis with effusion and pleurisy with effusion may complicate either condition. In some cases the appearance of typical rheumatic nodules and choreiform movements on the one hand; or the radiographic appearances of a primary tuberculous infection in the lungs and a strongly positive Mantoux test, on the other, may decide the issue.

The following account of a case of arthralgia complicating renal tuberculosis in an adult who gave a previous history highly suggestive of rheumatic fever, but no history suggesting primary tuberculosis, may be of interest. Tuberculous rheumatism while by no means uncommon in children

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is not usually recognised in adults, and I have never seen it in conjunction with renal tuberculosis.

Case Report

Mrs. X, a well-developed married woman of 34 years was admitted to hospital on February 3, 1946, complaining of pain and swelling in the right ankle. The history was as follows:—

History.—Eight years previously, while in Persia, she had an attack of "influenza," possibly accompanied by a sore throat, which was followed by profuse sweating and pain in all her joints, which involved each one consecutively, but in no definite order of progression. The pain flitted from joint to joint, and she remembered swelling of both ankles and of her fingers. No record is available of the treatment she received or the final diagnosis made, but after a short time the condition resolved and she was able to resume her normal activities which included exhibition dancing. Until the present time she had had no further joint involvement whatever. There was no history of typhoid or dysentery at any time and she had never had a vaginal discharge. There were no children and she had suffered no miscarriages. There was no evidence from her past history that she had ever had any form of primary tuberculosis, such as cervical or mesenteric adenitis. There was no history of contact with known tuberculosis and no family history of tuberculosis or rheumatism of any sort.

While passing through Cairo, on her way to Persia in December, 1945, she developed a sore throat, cough, sweating and intermittent pyrexia. She was able to continue the journey, but shortly after arriving in Persia, she began to feel tired and noticed stiffness in both knees and both ankles. Two of her fingers swelled but were not painful. This was followed by profuse sweats at night and painful swelling of the right ankle. In the preceding month or so, she had lost some weight. No cough, dyspnoea on exertion or haemoptysis. Menstruation regular, no amenorrhoea. No frequency of micturition or dysuria.

On Examination.—A pale woman with no obvious loss of weight. Rather nervous, with moist hot skin and tachycardia of 100/minute. No evidence of hyperthyroidism. Tongue furred, throat reddened, no enlarged lymphatic glands, no rheumatic nodules felt. Heart was normal in all respects; there was a faint systolic murmur at all areas, functional in origin. Blood pressure 130/90. Abdomen normal. Mucous membranes did not show evidence of anaemia and there were no purpuric spots seen. All joints were normal except the ankles. The right ankle was considerably

swollen with some pitting oedema. There was an effusion present and movements were limited and painful. The skin was red, hot and tender. Left ankle—full movements, slight swelling, but no demonstrable effusion; skin warm but not red. Dorsalis pedis arteries pulsated strongly. Central nervous system—normal. No phlyctenular conjunctivitis, no tubercles seen on the choroid. There were no signs of chorea and no evidence of erythema nodosum. Vaginal examination normal. No evidence of gonorrhoea.

The following investigations were performed:—

<i>Blood Count:</i> W.B.C.	16,000 per cu. mm.
Haemoglobin	85 per cent Sahli
Polymorphs	80 per cent
Lymphocytes	18 per cent
Hyalines	2 per cent
B.S.R.	38 mm. in one hour.

Throat swab revealed non-haemolytic streptococci. Blood culture was negative.

Coagulation time 7 min. 45 sec.—Platelets 273,000 per cu. mm.

W.R. negative. Blood uric acid—3.9 mgms. per 100 cc.

Agglutination to brucella abortus and brucella mellitensis were negative.

Urine showed a faint trace of albumen, many pus cells and red cells, but no casts.

These findings appeared to support the clinical diagnosis of rheumatic fever, the polymorphonuclear leukocytosis being sufficient to exclude undulant fever. She was treated by absolute rest in bed in a sitting position, splinting to the affected joint and 120 grs. of Sodium Salicylate daily for 3 days. Analgesics were given as required. After 3 days, the right ankle was considerably less swollen and tender, and movements were nearly full. Salicylate was reduced to 60 grs. daily for a further 2 days and then discontinued. Two days after this, the right wrist joint became involved, being swollen, hot, painful and tender and Salicylate was commenced again, causing the joint to return to normal after a further 3 days. By this time the temperature was normal and it was decided to repeat the examination of the urine, this time with a catheter specimen to ensure that there should be no contamination. This examination revealed the persistence of a faint trace of albumen, together with some red cells and pus cells. The urine was acid. Culture of the urine was sterile. It was now felt that such changes could no longer be explained by a simple febrile nephrosis as was suspected after the first specimen.

In view of the sterile acid pyuria demonstrated, the possibility of tuberculous infection of the renal tract was considered. A 24 hours specimen of urine was examined and found to contain large numbers of typical acid alcohol fast bacilli. Three subsequent 24 hours specimens contained acid fast bacilli also. A guinea pig was inoculated, but up to this time has shown no signs of tuberculosis. Culture on to a glycerine-egg medium was negative. It was not possible to determine whether the infection was human or bovine. There were still no urinary symptoms, the joints were all normal, and the patient felt quite fit, although the temperature rose to 99° F. at night. W.B.C. were now 14,000 per cu. mm., Polymorphs 81 per cent, Lymphocytes 19 per cent, and B.S.R. 44 mm. in one hour. There were no signs of carditis.

X-ray of the chest showed no abnormality of heart or lungs; no primary tuberculous complex was seen. The blood urea was 31 mgms. per 100 c.c. Urea concentration test showed 100 per cent renal function. Mantoux test with 1:10,000 Old Tuberculin gave a positive result.

Intravenous pyelogram: Plain Films: showed no opaque calculi and no calcified shadows. Concentration of dye was good, excretion rate normal. The right kidney appeared slightly enlarged, a pelvic hydronephrosis being present and the upper pole calyces appeared to be depressed and overlying the pelvic shadow: they also were probably hydronephrotic. There was early clubbing of the lower pole calyces. The right ureter could not be seen at any point. The left kidney appeared to be rotated, so that the ureter was seen emerging from the lateral aspect of the calycine formation and the pelvis was obscured. This might be a congenital mal-position of the kidney with lateral rotation, or possibly a partial "horseshoe" type. From the available films it was not possible to be certain whether or no tuberculous disease was present in the left kidney. The left ureter and the bladder appeared normal.

Cystoscopy by Mr. E. R. Davies revealed a mild non-specific trigonitis. Both ureteric orifices were clear and there was no evidence of tuberculosis. The right ureter, however, was not excreting, and a ureteric catheter could not be passed up the ureter for more than half an inch. The left ureter was seen to be excreting and permitted the passage of a catheter with ease. This suggested a stricture of the right ureter, possibly due to a congenital valve, but presumably due to tuberculous involvement with consequent fibrosis, which would explain the pelvic hydronephrosis.

Since any form of renal damage is a contra-indication to remaining in a hot climate, the patient was repatriated to the United Kingdom for further

investigation. During the four weeks spent in hospital at complete rest she was completely asymptomatic after the first ten days, and her blood sedimentation rate fell to 19 mm. in one hour.

Discussion

Although the possibility of coincident acute rheumatism and renal tuberculosis cannot be ruled out, it seems reasonable in this case to suppose that the arthralgia was due to sensitisation of the joints to the tubercle bacillus. Possibly the original attack of polyarthritides was due to rheumatic fever, which left the joints in a state of partial sensitisation, requiring only a stimulus to provoke another attack. In the later instance the trigger mechanism was renal tuberculosis.

Lehmann, in a preliminary communication published recently, describes the treatment of tuberculous abscesses following thoracoplasty with 4-aminosalicylic acid (p-aminosalicylic acid), and records definite clinical improvement. Two other cases were also treated, one of exudative pulmonary phthisis and one of bilateral tuberculous pleural effusions, with marked clinical improvement. Both cases were given 14 grammes daily for 8 day periods, with weekly intervals between courses. The usual effects of salicylate therapy—tinnitus, etc.—were not noticed.

Bernheim in 1940 showed that salicylic and benzoic acids increase the oxygen consumption and carbon dioxide production of the tubercle bacillus. He concluded that these acids were oxidised as metabolites. Lehmann has investigated more than fifty derivatives of these substances for their inhibitory effect on the growth of tubercle bacilli (competitive enzyme inhibition) and found para-aminosalicylic acid to be the most effective.

In the case described in this article it is interesting to note that rapid resolution of the arthralgia was achieved by the administration of sodium salicylate, while the renal tuberculosis was apparently unaffected. However, it is well known that rheumatic manifestations commonly improve with salicylate therapy.

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