

The CENTRAL AFRICAN JOURNAL OF MEDICINE

Dr. DAVID LIVINGSTONE

Vol. 1. No. 4

JULY, 1955

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THE FEVERS OF AFRICA

"Salisbury Fever"

A REVIEW OF A FEBRILE DISORDER
PROBABLY OF VIRUS ORIGIN COMMONLY
OBSERVED IN SALISBURY, S. RHODESIA

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INTRODUCTION

During the past decade it has become increasingly evident in medical practice in Salisbury that there exists a large group of diseases mainly affecting children for which no adequate explanation can be given. Attempts have been made to determine the cause and the clinical picture has been described,^{1,2} but no satisfactory explanation has yet been given. Owing to the absence of local facilities for virus studies, little progress at the present time is being made on this important subject.

It is the purpose of this review to marshal all the available facts concerning the clinical features of this disease and to discuss its probable cause. The opinions and experiences of other workers practising in Central Africa will be welcomed.

The disease is characterised by an acute febrile state which lasts from 3 to 14 days. The patient does not appear to be acutely ill, though temperatures may rise to 104° F. Symptoms are slight, the commonest being complaints of headache, limb and joint pains and general malaise. Physical examination reveals very few signs. The fauces may be slightly reddened. The cervical, axillary and inguinal lymph glands are enlarged. The spleen is sometimes palpable. Laboratory tests invariably give negative results. Relapses are frequent and may continue for long periods varying from some months to two years. No complications have been observed and the patient invariably returns to normal health.

It is obvious that such a syndrome may be accounted for by many well-known acute and relapsing diseases. The main feature, however, has been the uniform failure to find any definite evidence, clinical or pathological, relating these cases to known diseases. The diagnoses offered include glandular fever, abortus fever, rheumatic fever, amoebiasis, bilharziasis, recurrent malaria, metabolic disturbances, etc. If one of these diagnoses is made, it is always prefixed by

"atypical." In view of the constant "atypical" features and the high incidence of this syndrome, it has for some time become apparent that none of these diagnoses are probably correct. It is now our opinion that we are dealing with a new unrecognised disease which is probably caused by one or a group of viruses. As we are unable to find the cause, and as most of these cases have been observed in Salisbury, we propose that this syndrome be called *Salisbury fever*. Our ideas on this disease have crystallised only after many years of examination and follow-up studies. All the cases personally observed have been Europeans.

INCIDENCE

Although such cases were seen sporadically in the pre-war period and were then usually diagnosed as acute malaria with negative blood smears, the syndrome only became frequently observed after 1940. Thereafter the incidence rapidly increased until 1950, since when it has been at times the major cause of acute ill-health amongst Salisbury children.

Both sexes are affected, most commonly between the ages of 4 to 9 years. Similar cases occur in adults, but more rarely. The disease is more frequent in the summer months, but it occurs sporadically throughout the year. At times minor epidemics have been observed.

AETIOLOGY

No causative organism has been isolated. Blood, urine and stool cultures have been negative. During an epidemic of Bornholm's disease in the summer of 1953 many children became ill with an illness greatly resembling that of this syndrome, including splenomegaly. Faeces were taken during this illness and were sent to the South African Institute for Medical Research for virus studies. The first six specimens were found to contain the *Coxsackie B* virus, but negative results were obtained on continuing the investigation. Although it is therefore possible that the coxsackie virus may be responsible for this syndrome, the evidence thus far is insufficient and it is obviously necessary to repeat and extend this avenue of investigation. It is also apparent that the finding of coxsackie virus in the faeces alone does not establish that virus as the cause of the disease and that blood agglutination studies should be made.

Although the evidence implicating the coxsackie group of viruses is inconclusive, the

clinical features and laboratory results clearly favour a virus aetiology. There is usually no significant change in the total and differential white cell counts, and there is no evidence of any constant bacterial pathogen as shown by negative throat, blood, urine and stool cultures. Agglutination tests performed at various stages of the disease against the *Salmonella* group and *Brucella abortus* are in the author's experience always negative. The Paul-Bunnell reaction is usually negative. The failure of the disease to respond to sulphonamides and antibiotics also suggests a virus origin.

CLINICAL FEATURES

Although many mixed forms may be observed, generally two types are recognised. The first type has an acute onset, the fever is high but usually short-lived. The disease lasts from 3 to 14 days and is then followed by a rapid return to normal health. Relapses are common and these commonly take the form of the second type. This type is characterised by a gradual onset of symptoms of general ill-health and a slight febrile reaction. The disease when established may then follow a protracted course lasting sometimes for months. Return to normal health is slow. Again, relapses of either type may occur.

(a) *The Acute Type*.—The onset is sudden, with pyrexia ranging from 102° to 104° F., headache and vomiting. Limb pains and backache may occur, but are infrequent. Sometimes severe joint pains are experienced, the usual joints affected being the ankles and knees. No joint swelling has been observed. A characteristic feature is the usual well-being of the patient at a time when the temperature may be as high as 104° F.

Examination, particularly early in the disease, may be entirely negative. Commonly the fauces are slightly reddened and the cervical lymph glands are palpable. Those affected are usually the tonsillar glands and those of the posterior cervical chain. They are seldom markedly enlarged and vary in size from being just palpable to that of the size of a pea. The axillary and inguinal lymph glands are usually similarly enlarged. The spleen sometimes becomes enlarged, usually later in the course of the disease.

Laboratory tests apart from a raised E.S.R. are usually disappointing. The red cells are unaffected. The leucocytes are within normal limits, but rarely a slight absolute lymphocytosis or monocytosis is found. Early in the disease there may be a neutrophilia, but this finding is very transient, giving way usually to a normal

count. Atypical lymphocytes in small numbers have been noted in these cases, but this finding is very unusual. Myers³ states that these atypical cells are not similar to those seen in classical infectious mononucleosis. The Paul-Bunnell reaction is negative. Agglutination tests against *B. abortus* have been routinely performed with negative results.

Convalescence is often protracted, but no complications have been noted. Relapses are frequent.

(b) *The Subacute Type*.—This is the more usual form of the disease. Its onset is gradual, the child becoming listless, pale, anorexic and irritable. An evening pyrexia of 99° to 100° F. is then noted. Joint pains, headaches and attacks of abdominal pain are frequent. After 2 to 3 weeks the child may become acutely ill, the temperature rising to 103° F. At this stage the child appears ill with a drawn, pale face and sunken eyes, and yet he may have no specific complaint. Physical examination reveals the same findings as described in the acute type of illness. The E.S.R. may be very high, but laboratory tests are again of no assistance. Tuberculin tests, chest X-rays and cardiograms have been frequently performed with negative results.

After a period ranging from a few months to two or more years the attacks become less frequent and finally cease.

TREATMENT

No form of treatment seems to have any effect on this disease. In particular, penicillin and the broad spectrum antibiotics are completely without effect. Salicylates, the sulphonamides and large doses of vitamin C and other types of treatment have likewise failed to alter the course of the illness. Short courses of cortisone have also been tried without apparent benefit.

DISCUSSION

The diagnostic difficulties relating to this group of sick children are apparent. The disease is self-limiting, the affected child is at no time critically ill, no deaths are likely to occur, and the resemblance to other well known acute and relapsing diseases is obvious. An attempt is therefore often made to relate this syndrome to an established disease, to regard it as merely atypical in one or more characteristics and to give appropriate treatment. The absence of complications and subsequent recovery may then be regarded as further proof of the diagnosis.

During the past five years when the incidence of this syndrome had increased greatly it became

apparent that no satisfactory diagnosis had yet been reached. In 1952 Ritchken and Gelfand¹ described a widespread epidemic affecting children in Salisbury. Sixty-five cases were recorded in whom the main characteristic was a prolonged pyrexial state varying from three weeks to four months. Practically the only physical findings reported were slight enlargement of the superficial lymph nodes. All the children had some evidence of recent throat infection and most showed enlargement of the tonsillar lymph glands. Repeated blood counts showed no constant changes, abnormal mononuclear cells were only very infrequently found, and the Paul-Bunnell and other serological tests were invariably negative. The E.S.R. was frequently raised during the acute phase and gradually fell with rest in bed. No complications were noted and all the children finally recovered. It was thought that these children were most probably suffering from a post-streptococcal state. About this time an epidemic had occurred of frequent and severe streptococcal sore throats, scarlet fever, acute rheumatic fever and acute nephritis. In view of the absence of abnormal non-granular leucocytes, the infrequency of raised leucocyte counts and the negative Paul-Bunnell reaction, it was considered that glandular fever could be excluded. The possibility that the disease could have been caused by a virus was mentioned, but as no virus studies had been done this view could not be substantiated.

In 1953 Gelfand⁴ spoke about the unusual fevers that were being encountered in Salisbury. He said: "I think you will agree with me that the nearest diagnosis of the cases I have described is that of glandular fever. Although the picture varies enormously, the main features are the fever, the lymphadenopathy and the occurrence in some of the cases of aberrant monocytes. But I must confess that whatever the causative agent is in our cases, doubt may be expressed because the blood picture is not more striking (as shown by the more usual finding of a normal total leucocyte count and the frequent absence of a monocytosis) and there is an almost constant absence of heterophil antibodies in the blood. One might even say that for these reasons alone the diagnosis of infectious mononucleosis is doubtful."

Meanwhile sporadic cases were almost constantly seen. In the summer of 1954 a very similar syndrome characterised by an acute febrile state, lymphadenopathy and splenomegaly was again frequently observed. At the same time numerous cases of Bornholm's disease were

being met with, mostly in adults. A suggestion was made that the former group were infected by the coxsackie virus which produced in them an illness resembling that of Salisbury fever. Coxsackie B. virus was demonstrated in the faeces of six patients, but on continuing the investigation no virus was found in a further eleven cases. The finding of the six positive cases appeared to be significant, but owing to the prevalence at that time of diseases produced by the coxsackie virus, the findings were probably incidental. It is apparent that further investigation on these lines is necessary.

With continued experience of this disease, and particularly by the careful exclusion of closely related syndromes, it is now our opinion that this disease is a definite and probably new entity. During the past five years a fairly lively discussion has continued in Salisbury regarding its true nature. Clinicians familiar with this syndrome hold three views:

- (a) The disease is a manifestation of glandular fever.
- (b) The disease is brucellosis caused by the *Brucella abortus*.
- (c) The disease is caused by a lymphotropic virus or group of viruses.

(a) *Glandular Fever*.—Until the work of Tidy⁵ in England and Sprunt and Evans⁶ in America, the disease now recognised as glandular fever had been known under a host of different names. These two authorities were mainly responsible for turning chaos into order and in finally establishing the disease as a definite entity. Furthermore, stress was laid on the varied manifestations and atypical features of the condition that may occur. Further clarification followed the demonstration by Paul and Bunnell⁷ in 1932 of the heterophile antibodies in glandular fever. Most workers now agree that the Paul-Bunnell test may be negative in cases which otherwise show typical features. Such cases may occur sporadically or in epidemic form. Tidy⁶ discusses the significance of a negative reaction occurring in an epidemic resembling glandular fever, and postulates that there may be two viruses giving respectively positive and negative reactions. Hoagland⁹ disagrees with this view and states that seronegative cases with protean manifestations are not true examples of infectious mononucleosis. Schubert *et al.*¹⁰ have recently described an interesting epidemic amongst adults. The illness was characterised by a mild upper respiratory infection, abdominal pains, lymphadenopathy and splenomegaly. The lymphocyte count was

above 4,000 in all cases and abnormal mononuclears (10-40%) were found in all of them. The Paul-Bunnell test taken at various stages of the disease was uniformly negative. The authors concluded that this was a different disease albeit probably related to infectious mononucleosis.

The characteristic clinical features of glandular fever are the membranous throat in the anginous type, the large rubbery glands in the glandular type, and pyrexia in the abdominal or febrile type. These features assume great diagnostic importance if allied to an absolute monocytosis and abnormal non-granular leucocytes in the peripheral blood. Under these conditions it would appear reasonable to diagnose glandular fever even though the Paul-Bunnell reaction may be negative. It is also accepted that during some epidemics, particularly in children, some cases may be met with where one or more of the classical signs may be absent.

The aetiology of glandular fever still remains a mystery, no virus or other organism having been isolated in the many animal and human experiments that have been performed. The view has therefore been expressed¹¹ that the disease may represent a hypersensitivity state rather than a specific infection. This new view represents a reversal to one originally held by Continental authors, who furthermore believed that the haemolytic streptococcus was the causative agent. In this connection it is interesting to note that Ritchken and Gelfand¹ reporting in 1952 on 65 cases of the syndrome under discussion, concluded that the condition was probably a post-streptococcal state. At the time, as mentioned above, an epidemic of acute streptococcal diseases was prevalent. If the view can be adopted that glandular fever is not a specific disease, but represents rather an abnormal reaction to a streptococcal infection, the events observed in 1952 would be readily explained.

It is known that in serum sickness and drug reactions, fever, enlargement of the lymph glands and spleen may occur. Atypical lymphocytes have also been observed. The failure to find a causal organism in glandular fever would also favour the allergic theory. Glandular fever could therefore be regarded along with scarlet fever as a specific reaction developed towards a bacterial infection.

It is stated that the strongest argument against the hypersensitivity theory is the fact that numerous epidemics of glandular fever with a very high incidence in any particular group have been reported. The same, however, could be said of scarlet fever.

The exact cause of glandular fever may appear

irrelevant to the present discussion. If the allergic theory of this disease should be established, however, it would be more reasonable to assume that reactions could vary and that many atypical cases would occur. It would also account for the frequent antecedent sore throats which were particularly noted during the 1952 epidemic. The frequency of this syndrome since 1945 could also then possibly bear some relationship to the widespread use of antibiotics in the treatment of sore throats with some resulting disturbance of normal antibody production.

Although this hypothesis is interesting, it is generally thought that glandular fever is a specific virus disease. Classical glandular fever is fairly frequently seen in Salisbury. A sore throat in which the haemolytic *streptococcus* or *staphylococcus aureus* can be isolated is frequently present early in the disease. It is interesting that in these classical cases the finding of abnormal lymphocytes and a positive Paul-Bunnell reaction can usually be anticipated, an observation confirmed by Myers,³ who has had wide experience of this disease.

At the present time, therefore, we consider that cases of Salisbury fever vary sufficiently, clinically and pathologically, to warrant a separate diagnosis. The only pathological finding common to the two diseases is the occasional finding of atypical lymphocytes. It is well known that these may occur in many unrelated diseases such as infective hepatitis,¹¹ during convalescence from measles,¹¹ "three day fever," a coxsackie infection,¹² toxoplasmosis,¹³ Congo Red disease,¹⁴ infections caused by the herpes simplex virus¹¹ and in a variety of allergic diseases.¹¹ This finding must therefore be regarded as a non-specific reaction probably related to reticulo-endothelial activity.

(b) *Brucellosis*.—The researches of Orpen¹⁵ and Bevan¹⁶ in S. Rhodesia proved that cows were commonly affected with *B. abortus* and that human infection was frequent. Since that time sporadic cases have been met, particularly in farmers and in peri-urban dwellers. In acute febrile states in this area, the agglutination test against the *B. abortus* is used routinely. In 1952, the author in an attempt to discover the incidence of this disease went through the records of the Salisbury European Hospital for the past ten years and was only able to find records of a very few proved cases. In private practice during the past fifteen years eight cases of acute brucellosis had been encountered. In these cases diagnosis was established by the clinical findings associated with a high agglutination titre against *B. abortus*.

A group of clinicians in Salisbury believe that the syndrome under discussion is a manifestation of infection by *B. abortus*. They hold the view that because abortus fever is very frequent in the cattle of S. Rhodesia it is also probably common in the human, and argue that diagnosis by cultural methods is difficult and that agglutination reactions even in low titres may be of significance. The author performed agglutination reactions on the majority of a group of 65 children suffering from Salisbury fever. In five cases agglutination in low titres less than 1:100 were obtained, which according to Spink *et al.*¹⁷ are of questionable diagnostic significance. Myers,³ using the procedure outlined by the former workers, performed numerous agglutination tests on this group of children in Salisbury and found the results to be consistently negative.

Apart from the recognised difficulties associated with the diagnosis of brucellosis, it would be reasonable to assume that were these cases suffering from this disease many more cases of acute brucellosis with typical clinical features would be met with. In three proved cases of acute brucellosis personally met with in children in Salisbury over the past fifteen years, the patients were acutely ill in a typhoid-like state and had rigors and severe sweats. Their spleens were fairly large and blood counts showed a marked neutropenia.

From all the available evidence there therefore appears to be no valid reason for regarding the cause of this syndrome to be infection by *B. abortus*.

(c) *A Virus Disease*.—It has already been mentioned that we now regard the disease as being probably caused by a virus infection. We hope that proof of our belief will follow when facilities become available for virus studies on these patients. Reasons for this belief may be grouped as follows:—

- (i) The consistent failure to find any bacterial cause.
- (ii) The type of leucocytic response.
- (iii) The failure to respond to sulphonamide and antibiotic therapy.
- (iv) Its infectious nature, frequently affecting in turn different members of the same family.

Owing to the absence of any specific signs or laboratory tests it is obvious that the utmost care has to be continually exercised in order to avoid diagnostic errors. In an acute case the diagnosis may be suspected during an epidemic, but it is still necessary to exclude other causes of acute febrile illness. Typical features will include a slightly reddened throat, cervical adenopathy,

palpable axillary and inguinal lymph nodes and possibly a palpable spleen. Laboratory tests will be negative and recovery in acute cases ensues usually within 3 to 14 days.

Apart from diseases such as glandular fever, malaria, typhoid, brucellosis, roseala infantum, the coxsackie fevers and others, it is important in Rhodesia to remember the possibility of bilharzial fever. In the latter, eosinophilia, cough and urticaria are usually present, but in the glandular type of bilharziasis confusion may occur. In the chronic relapsing type it is necessary to exclude the post-streptococcal state. In the latter condition there is a history of numerous attacks of sore throat followed after an interval by pyrexial attacks unaccompanied by any evidence of overt sepsis in the fauces. The cervical glands are usually enlarged and the spleen is seldom palpable. Blood counts may be normal, but sometimes a neutrophilia may be evident. The E.S.R. is markedly raised, as is the streptolysin titre. In many cases the differential diagnosis is extremely difficult. Where the tonsils appear to be a source of infection, tonsillectomy will usually result in rapid recovery in cases suffering from a streptococcal state.

In addition to these conditions, care should be taken to exclude relapsing fevers caused by inadequately treated malaria, the prolonged type of bilharzial fever, rheumatic fever, tuberculosis, pyelonephritis, spirochaetal and relapsing fever. At times metabolic disorders such as cyclical vomiting and so-called periodic disease must be considered.

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