HUMAN BRUCELLOSIS IN SOUTH AFRICA

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Brucellosis could well be termed 'the forgotten disease'. When faced with a patient with pyrexia of obscure origin, the medical practitioner often places brucellosis near the end of his list of alternative diagnoses. He may even forget its very existence until an unexpected positive result emerges from the battery of tests submitted to the laboratory.

A constant awareness of the prevalence of this infection in Southern Africa will be rewarding to the observant clinician in both general and specialist practice, since its protean manifestations cause diagnostic problems in many fields of medicine.

An investigation into the incidence and clinicopathological features of brucellosis was undertaken when I noted that a small, but fairly constant, proportion of positive reactors to the brucella agglutination test was found among the 4,000 - 5,000 specimens of serum submitted annually for this test to the Johannesburg laboratories of the South African Institute for Medical Research.

In a survey conducted intermittently between 1956 and 1959, approximately 250 questionnaires were sent to the medical attendants of patients with possible brucellosis, requesting information about their clinical features. A limited field study was also carried out in the Sekukuniland region of the North East Transvaal to establish the rate of positive reactors among apparently healthy Africans in an area where brucellosis is believed to be relatively common.

HISTORICAL REVIEW

Human brucellosis has been recognized in Southern Africa for many years, under a variety of names. Strachan[1] quoted a Dr. Leister's unpublished report that he had observed cases of undulant fever in the Orange Free State and Basutoland as early as 1894. Strachan[2] also referred to Dr. Simon Fraser, the district surgeon at Gordonia, who in 1898 reported seeing 40 cases of what he believed to be Mediterranean fever occurring in the North West Cape. This fever was well known in Malta during the 19th century, its aetiology being established in 1887, when Bruce isolated *Micrococcus* (later *Brucella*) *melitensis* from the spleen of a human case.[3] The incrimination of the island goats as the chief source of the infection followed in 1905.[4]

Towards the end of the last century numerous undiagnosed cases of fever occurred on the Kimberley diamond fields. These were known by various names, such as camp fever, Kimberley fever, 'slepende koorts', and 'zinking koorts'. Many of these patients presented features indistinguishable from Mediterranean fever, which by this time was widely known as Malta fever.

Strachan, who was the district surgeon at Philippolis in the Orange Free State from 1902 to 1911, saw 298 clinical cases during that period, 231 being proved by serological or cultural tests to be *Brucella melitensis* infections.[2] Positive agglutination tests also identified several cases of camp fever as Mediterranean fever. Strachan made extensive epidemiological studies in man and the local goat population, and campaigned vigorously in favour of boiling all milk for human consump-

tion. The success of his efforts is shown by the sharp decline in the numbers of cases in that region to a total of 3 in 1914.

In 1911, Garrow[5] reported on the high incidence of undulant fever in Steytlerville, in the Cape Province. He noted that the handling of infected goats and the swallowing of contaminated kraal dust were probably responsible for many human cases. The widespread distribution of the disease in other parts of the African continent was emphasized in a contemporary speech by Sir David Bruce in which he said that more than 1,000 Africans in a certain part of Uganda had died of Malta fever (cited by Garrow[5]).

Several human cases of *Brucella abortus* infection in Southern Rhodesia were described by Bevan in 1921.[6] This was the first evidence that man could become infected by the cause of contagious abortion in cattle. In fact, it was only 3 years earlier that Alice Evans had shown that Bang's bacillus (its earlier name) was closely related to *Brucella melitensis*.[7] Bevan also gave an accurate description of the epidemiology of this condition in Southern Rhodesia, and its relationship to the drinking of milk from infected cows.

In more recent years, several case reports and limited surveys have appeared in the medical literature of South Africa and the neighbouring territories. Among these have been papers by Sacks and Neser[8] (a case of undulant fever), Eales[9] (a case of brucellar arthritis), Wright *et al.*[10] (analysis of 70 cases in Kenya, confirmed by culture), Jones[11] (orthopaedic aspects of brucellosis in Rhodesia), Manson-Bahr[12] (approximately 100 annual notifications of brucellosis in Kenya), Christie[13] (several hundred cases in Rhodesia traceable to infected milk), Ipp[14] (2 cases of brucellar spondylitis in Johannesburg), Lewis[15] (10 cases in the Krugersdorp area), and Kirsten[85] (brucellosis in South West Africa). Reference to further publications will be made below, in a discussion on serological surveys.

DIAGNOSIS

On purely clinical grounds the diagnosis in man is rarely unequivocal. Conditions for which brucellosis is frequently mistaken include malaria, typhoid fever, tuberculosis, rheumatic fever, influenza, and rickettsial infections. Whatever the diagnosis, such antibiotic therapy as may be given is usually in too low a dosage to cure brucellosis. Under these conditions, a patient will often progress to a state of low-grade chronicity which is very refractory to further treatment. It is thus of the utmost importance to identify the disease at an early stage, when adequate treatment can produce a complete cure, and an early diagnosis cannot be made with certainty without the help of the laboratory.

Before discussing the laboratory aspects of diagnosis, it may be of interest to review briefly the main clinical and pathological features of the infection.

Brucellosis can be classified broadly into 2 clinical types: the active (acute, subacute, and chronic), and the inactive.

Active Acute and Subacute Phases

In the typically untreated active case, the patient undergoes an incubation period of from 1 to 10 weeks, depending on the route and the size of the infecting dose. The acute phase follows, in which pyrexia, headaches, profuse nightsweats, rigors, pains in the muscles and joints, and lassitude are prominent symptoms.

The symptoms abate to some extent after a week or two, re-appearing after intervals of 1 - 3 weeks. Continued remissions and relapses of this nature produce the well-known subacute clinical picture conveyed by the term undulant fever. The spleen is often enlarged at this stage.

The usual route of infection is the alimentary tract, following ingestion of infected milk. A slightly enlarged, tender liver, possibly with a mild degree of jaundice, will often reflect the production of hepatic granulomata and micro-abscesses as part of the primary complex involving the gastro-intestinal tract.

The skin may be the site of introduction, as occasionally happens in veterinary surgeons, farmers, and abattoir workers. These patients may show an initial localized granulomatous lesion progressing to a nodular rash, usually on the forearms, which may eventually cause gross thickening of the skin.

A respiratory infection is not uncommon in laboratory workers, owing to the inhalation of infective aerosols. In this type, the primary complex consists of a focal pneumonitis with hilar adenopathy, characterized by a persistent non-productive cough, in addition to the usual systemic features of active brucellosis.

Another unusual route of infection is *via* the conjunctiva. This has been reported in several veterinary workers following syringe accidents while vaccinating cattle with low-virulence living strains of *Br. abortus*.[16]

Regardless of the manner in which the organism gains entry into the body, the acute and subacute phases are characterized by an intermittent brucellar bacteraemia, which probably coincides with the periodic exacerbation of symptoms, and provides the source of later complications by seeding out in various tissues throughout the body. In this connection, Ganado and Bannister[17] recorded very little correlation between pyrexia and bacteraemia, in contrast to the views held by other workers, e.g. Dalrymple-Champneys.[18a]

The typical picture may be modified considerably by treatment with broad-spectrum antibiotics, which will generally produce a remission of symptoms. Even in the absence of specific treatment, a proportion of patients will recover at this stage, but some of these may later show evidence of latent or inactive brucellosis, even after an interval of many years.

Active Chronic Phase

In the active chronic phase (6 - 12 months after the first appearance of symptoms), the disease settles down to a state of prolonged remissions with occasional low-grade pyrexial episodes which may be brought on by intercurrent infections or exposure to cold. These relapses tend to be more frequent and severe in infections with *Br. melitensis* than with *Br. abortus*.

The patient now develops one or more of the innumerable localized complications described in brucellosis. The commonest of these is probably due to involvement of the vertebral bodies, intervertebral joints, or soft tissues surrounding these joints, leading to the prominent symptom of low backache. Strachan[2] observed that 61·9% of 268 patients complained of 'lumbago'; Dalrymple-Champneys' series of 1,500 patients included 54·8% with pain in the back and limbs;[18b] and Spink[19a] referred to spondylitis as being the most frequent complication of brucellosis of the bones and joints.

Synovitis or suppurative arthritis of the knee, hip and wrist are common. There may also be involvement of the kidneys, liver, intestine, central nervous system, or cardiovascular system. Peery[20,21] pointed out how closely brucel-

losis can mimic rheumatic fever, and claimed that endocarditis is the commonest cause of death in fatal cases of brucellosis. Orchitis, which is particularly common in infected animals, is occasionally seen as a complication in man. Psychical disturbances such as severe depression may occur, which, together with anorexia, loss of weight, and vague aches and body pains, often lead to a diagnosis of neurasthenia.[19b,22] Active brucellosis as such may run a protracted course of years.

Inactive Stage

The inactive stage is an ill-defined entity, presumably representing the burnt-out chronic case in which the body defence mechanisms have controlled the spread of the infection by healing and fibrosis, but in which hypersensitivity phenomena play a dominant role. This is somewhat analogous to the condition of healed tuberculosis.[23] The patient is afebrile, but still complains of backache, joint pains, anorexia, lassitude, and mental depression. This is the typical picture of one variety of 'chronic brucellosis' as described by Spink.[24] Such cases are characteristically refractory to treatment with antibiotics, but may show considerable improvement after desensitization with a vaccine prepared from killed *Brucella* organisms.[25]

Many patients fail to present the typical pattern of brucellosis described above. It is not uncommon to stumble upon the diagnosis in a person complaining of little more than vague ill-health of long standing and who has never had a preceding acute illness.

LABORATORY DIAGNOSIS

With regard to the laboratory diagnosis of brucellosis, concrete evidence of the infection can be provided only by the isolation and culture of the causative organism. Blood culture is rarely successful in this country, owing partly to inadequate laboratory facilities in the rural areas, where brucellosis usually occurs, with consequent delay in transit to the larger centres.

Repeated blood specimens should be collected over several days because of the sparse and intermittent nature of the bacteraemia. Under the best conditions, it is found that only a small proportion of blood cultures will yield positive results. Bone-marrow culture has been claimed to give better results than culture of peripheral blood,[26] but since it is a procedure unsuited to frequent repetition, a positive isolation can probably be obtained equally well by multiple blood samples collected at intervals of 6 - 12 hours, preferably during pyrexial periods. Infected material removed at operation should be cultured, since this is often successful with specimens of synovial membrane, fluid, or pus.[11,27]

Under South African conditions, the agglutination test is the most valuable of the laboratory procedures. In spite of transport delays of up to 7 days, the specimens rarely show sufficient deterioration to interfere with the test. Negative reactions may be obtained in the first week or two of the infection as well as in the late chronic form, yet no other single test for brucellosis gives as high a proportion of true positive results.[28]

Almost every case of brucellosis develops a positive agglutination test at some stage during its course. Typically, the titre is low when first detected, rising steeply during the early weeks of the disease, so that a four-fold or greater increase in titre over a period of 7 - 10 days may be taken as diagnostic. Levels of 1 : 6,400 or higher may develop in the first few months of an active infection. Some individuals never show titres of this magnitude, and may even fail to develop agglutinins at any time.[29]

Agglutinins in low titre (less than 1:100) may be present in the absence of clinical brucellosis. This could be due to repeated subclinical infections, as seen in persons exposed by reason of their occupations (e.g. butchers, veterinarians, farmers, laboratory workers), or following the continued drinking of raw infected milk. It is probable that the majority of such patients would have had an acute illness initially, followed by spontaneous recovery. False-positive reactions in low titre occur in tularaemia,[30] and after vaccination against cholera,[31] neither circumstance being significant in South Africa. Braude *et al.*[32] produced experimental evidence to show that the swallowing of killed *Brucella* organisms, e.g. in pasteurized milk, can give rise to low levels of agglutinating antibodies, although others have been unable to confirm this.[33] It can thus be presumed that all positive reactions in this country must indicate exposure to organisms of the *Brucella* group, either by infection (recent or past) or by ingestion.

The presence of agglutinins in a titre of 1:100 or higher, is generally accepted as being of diagnostic significance, particularly in a patient with clinical evidence of brucellosis.[15c] With active infections, early antibiotic treatment leads to a drop in titre within 3 - 6 months, followed by residual levels of the order of 1:100, which gradually disappear over a period of several years.[34]

In brucellosis there is a marked tendency for incomplete (indirect) antibodies to appear, which cause the 'blocking', or 'prozone' phenomenon.[35] This interferes with the reading of the agglutination test, occasionally to the extent of giving a negative result. The antiglobulin test (modified Coombs') avoids this difficulty, and should be considered in every patient giving a negative agglutination reaction where brucellosis is suspected. Since it is carried out at a lower serum dilution than the standard agglutination test, a greater proportion of positive results will be obtained in a given population. The qualitative modified Coombs' test thus has limited value as a screen test, in that a negative result virtually excludes brucellosis, while a positive result probably has no more significance than the ordinary agglutination test at the same dilution. However, a strongly positive Coombs' test, or a high titre if the test is done quantitatively, suggests a level of antibodies which would be significant if accompanied by other evidence of brucellosis.

The *Brucella* skin test, in which an extract of the bacteria is injected intradermally, is of some diagnostic value. A positive allergic reaction of the delayed type, similar to that of the Mantoux test, indicates past or present infection. The test may be positive for many years after a complete cure, and gives little information about the activity of the infection. An interesting problem is raised by the possible induction of antibodies in unexposed persons by this test, leading to a positive agglutination reaction at a later stage.[36] In a patient previously showing low-level agglutinins, a marked rise in titre after the skin test may be of diagnostic significance.[37] In spite of its deficiencies, the test can provide confirmatory evidence in active brucellosis, and has definite value in field surveys for judging the exposure rate of a population. The skin test is negative in the first 6 - 10 weeks of a fresh infection, and occasionally fails to become positive at any stage.

The blood picture in brucellosis is fairly constant. In the first few weeks there may be a moderate leucocytosis, but this is soon replaced by a neutropenia with a relative lymphocytosis.[38] Anaemia may be a prominent feature in the chronic case.

The procedures of splenic puncture, liver biopsy, and lymph-gland biopsy enable the pathologist to carry out bacteriological and histological studies on tissues from the reticulo-endothelial system. They are rarely required in the routine diagnosis of brucellosis, but may give valuable information in obscure cases.

To quote Castaneda,[39] 'no single test is, by itself, sufficient to detect all cases of human brucellosis, and it is therefore advisable to use as many tests as possible, in the hope that one at least may lead to a diagnosis of *Brucella* infection'.

SEROLOGICAL SURVEYS

In 1906, a survey carried out by Strachan[1] showed clinical evidence, with some serological support, of cases in many areas of the northern part of the Cape Province, the southern part of the Orange Free State, the Eastern Transvaal, and Basutoland, but not in Natal. He concluded that undulant fever was widely distributed in South Africa, where it had been endemic for many years. Although a number of reports

TABLE I. SEROLOGICAL SURVEYS IN SOUTHERN AFRICA

Author	Year	Region	Total tested	Source	Agglutination titre	Percentage positive
Alves[40]	1936	S. Rhodesia	1,000	WR*	1 : 50	0·1
Campbell[42]	1937	Cape Town	661	PUO**	1 : 100	9·4
Barnetson[43]	1939	Johannesburg	1,900	Widal and *Brucella*	1 : 50	5·7
Lewin[44]	1948	Johannesburg	200	Blood donors	1 : 40	1·5
Coetzee[45]	1956	Pretoria	400	Random patients	1 : 40	1·5
					1 : 40 (Coombs')	11·0
Coetzee[45]	1956	Pretoria	67	Occupational	1 : 40	19·4
					1 : 40 (Coombs')	61·2
Zoutendyk[46]	1958	Johannesburg	300	Random	1 : 5 (Coombs')	5·0
Zoutendyk[46]	1958	Johannesburg	2,100	PUO etc.	1 : 5 (Coombs')	20·6

*Sera submitted for Wassermann reaction.

**Patients with pyrexia of unknown origin.

on the incidence of the disease have been published since then, the surveys have usually been confined to selected groups in limited geographic areas, with reference to the proportion of individuals giving positive agglutination reactions.

In 1936, Alves[40] found 0·1% positive to *Br. abortus* at a dilution of 1:50 in more than 1,000 African sera submitted for the Wassermann test in Southern Rhodesia. This contrasts with 3·3% in Tanganyika (also 1:50 against *Br. abortus*), as reported by Wilson.[41] In Cape Town, Campbell and Greenfield[42] found 9·4% to be positive at a dilution of 1:100 among 661 pyrexial patients, after excluding cases of typhoid fever, malaria, tuberculosis, and influenza. This figure is of limited significance in view of the high degree of selection in this group.

Barnetson,[42] working at the South African Institute for Medical Research in Johannesburg, reported 109 reactors at 1:50 among 1,900 sera received over a period of 2 years for routine Widal and *Brucella* agglutination tests. This represents 5·7% of a group of persons presumed to be suffering from undiagnosed pyrexial conditions. He indicated that this figure was influenced by the high proportion of positive reactors among sera from South West Africa (24·9% of 249 specimens). Lewin *et al.*[44] found only 3 reactors at 1:40 in 200 healthy blood donors from the Johannesburg area.

Coetzee[45] observed 1·5% reactors to the standard agglutination test at 1:40 or higher in 400 non-brucellosis hospital patients in Pretoria, but this figure rose to 11·0% when the same individuals were tested by the modified Coombs' antiglobulin test at the same dilution. In a group of 67 workers exposed to *Brucella* by virtue of their occupations, the figures were 19·4% and 61·2% respectively. Zoutendyk[46] found 5% of 300 random individuals in Johannesburg to be positive at 1:5 by the modified Coombs' test. Out of approximately 2,100 pyrexial patients in whom brucellosis was suspected clinically, 20·6% were positive to the same test.

Table I summarizes the published figures. It will be noted that the reactor rate in the pyrexial and occupational groups ranges from 5·7% to 61·2%, while the 'random' groups, although not acceptable as such from a strict viewpoint, show far fewer reactors (0·1 - 11·0%).

The significance of these findings is difficult to assess in view of the varied conditions under which the surveys were done. The results are greatly influenced by such factors as the choice of the minimum agglutination titre, and the criteria for selecting cases for inclusion in the surveys. The greater sensitivity of the antiglobulin technique will also yield figures that are not comparable with those derived from the standard test. The presence of antibodies in the general population nevertheless indicates a fairly widespread exposure to *Brucella* antigens. The higher rate of reactors among selected patients, particularly at a titre of 1:100, suggests that brucellosis accounts for a small but definite proportion of pyrexias of unknown origin in South Africa.

Bacteriological confirmation has occasionally been obtained in these surveys, usually by isolation of the causative organism from the blood stream. In recent years, strains of both *Br. melitensis* and *Br. abortus* have been isolated from human sources in several regions in South Africa.[9, 42, 47]

Animal Brucellosis

The veterinary aspects of the disease in South Africa have been fairly well documented. The extent of the infection among urban and rural stock has been outlined, with special reference to involvement of cattle, sheep and goats. Van Rensburg *et al.*[48] noted a high incidence in sheep in the Upington district and other parts of the Karoo and North West Cape, which is significant in view of the long history of human brucellosis in that region.

The predominant organism appeared to be a variant of *Br. melitensis*, for which the name *Br. ovis* was suggested. Several melitensis-type strains had previously been obtained from humans, goats, cattle, and sheep in South West Africa.[49] Van Drimmelen[50] reported the isolation of *Br. melitensis var. karakul* from aborting karakul sheep in the Gobabis area of South West Africa.

Pullinger[51] commented on the widespread incidence of brucellar infection in cattle in South Africa, and Christie[13] reported between 5 and 7% of cattle in Southern Rhodesia to be infected. Lewin *et al.*[44] found 70% of composite samples of cow's milk on the Witwatersrand to contain whey agglutinins at a titre of 1:10. This would suggest the inclusion of a number of actively infected cows in each pool from which the samples were drawn. That the proportion was small was borne out by the finding that only 3 positive biological tests were obtained from 92 samples. Meara[52] found positive biological tests for *Brucella* in 16·1% of 217 samples in the same region.

A number of cultures from different parts of the country have been identified, and it is evident that both *Br. melitensis* and *Br. abortus*, together with several intermediate types, occur in animals in South Africa.[52]

ANNUAL NOTIFICATIONS TO THE DEPARTMENT OF HEALTH

A review of the annual reports of the Union Health Department[54] reveals several interesting facts. The term 'brucellosis' was first used in 1951, the disease having been notified previously as 'Malta fever', in accordance with the Public Health Act of 1919. Since 1952, both these terms have been employed indiscriminately. In a strict sense, Malta fever refers to *Br. melitensis* infection, so that technically there was no national legislation for the notification of human *abortus* infections before 1951, although Bevan had first described this condition some 30 years earlier. Still earlier, in 1907, the disease had been made notifiable in the Cape Colony under the name of 'undulant fever', which would have included both aetiological agents.

Fig. 1 shows the number of cases notified annually between 1920 and 1959. The wide range of figures probably reflects the fluctuating popularity of brucellosis as a diagnosis, rather than a true variation in incidence.

It will be observed that the numbers of White notifications show a steady downward trend, except for a distinct rise in the 1939 - 1944 period. Notifications of non-White cases, on the other hand, have increased sharply during the last 5 years. The recent rise in total notifications is almost certainly due to improved medical services in the country districts, and

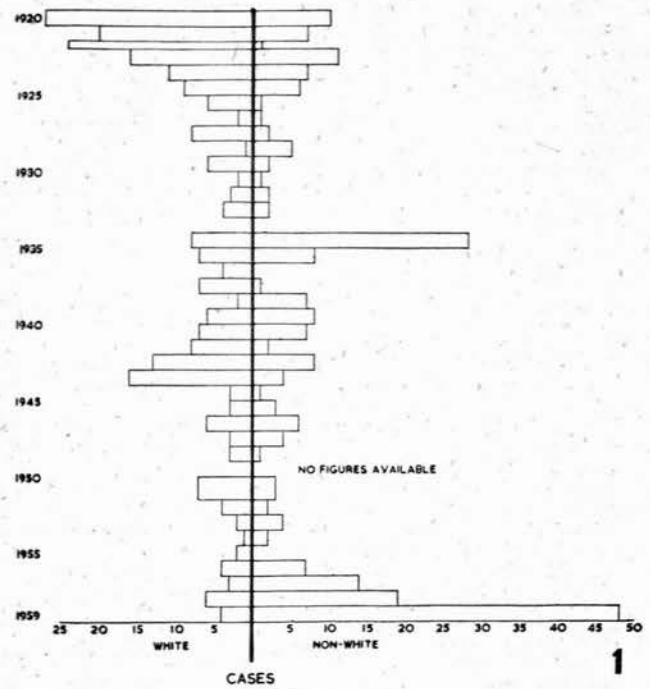

Fig. 1. Annual notifications of human brucellosis, 1920 - 1959. N.B. Notifications cover the following periods: (1) 1920 and 1921, January - December; (2) 1922, January - June; (3) 1922 - 1950, July - June; (4) July 1950 - December 1951; (5) 1952 - 1959, January - December.

the fact that the disease is now being considered and identified more frequently than in the past.

The racial and geographical distribution of the total of 513 notified cases is shown in Table II.

TABLE II. DISTRIBUTION OF 513 NOTIFIED CASES OF BRUCELLOSIS

	Cape Province	*Transvaal*	*Orange Free State*	*Natal*	*Total*
White	148	98	10	12	268
Non-White ..	63	165	5	12	245
Total	211	263	15	24	513

In the survey discussed below, new cases have been detected at the rate of about 35 a year, derived from limited areas of the Transvaal, the northern part of the Cape Province, South West Africa, and the Orange Free State. The actual number of cases occurring in the whole country must be considerably higher, taking into account the large number of specimens submitted to other regional laboratories. In addition, many cases in the rural districts, particularly among non-Whites, probably occur without medical advice being sought.

The records of the Department of Health must therefore be regarded as being incomplete, and the true number of cases must exceed the published figures by a considerable margin. This situation would be improved by a greater interest in the disease on the part of the medical profession as a whole, coupled with more conscientious notification of cases.

ANALYSIS OF CASES FROM PRESENT SURVEY

This survey was confined to specimens of blood or serum submitted to the Johannesburg laboratories of the South African Institute for Medical Research between 1956 and 1959, and excluded material sent to branch laboratories, private pathologists and laboratories in other parts of the country. The geographic areas from which the specimens were derived included parts of Johannesburg and the Reef, the East and West Transvaal, the northern part of the Orange Free State, the North West Cape, South West Africa, and Bechuanaland Protectorate.

Possible cases were detected in the first instance by a positive reaction to the tube agglutination test for brucellosis, at a titre of 1:50 or higher (confirmed by a repeat test). The agglutination tests were done in parallel, over a dilution range from 1:50 to 1:400, using smooth formalinized suspensions of *Br. abortus* and *Br. melitensis* respectively, with suitable saline controls. Sera showing positive reactions were re-tested to establish the final titre of antibodies. The antigenic suspensions were controlled by means of a standard antiserum obtained from the Veterinary Laboratory, Weybridge, England.

In 250 such cases, questionnaires were sent to the medical attendants, requesting information such as age, sex, race, laboratory findings, duration of illness, and predominant clinical features. Out of a total of 159 returned forms, 116 fulfilled one or other of the following criteria for a definite or probable diagnosis of brucellosis:

1. Isolation of *Brucella* organisms on culture (definite cases).

2. Agglutination titres of 1:100 or higher, together with significant clinical evidence of brucellosis (probable cases).

Patients with agglutination titres of less than 1:100, with or without clinical features of brucellosis, were regarded as doubtful, and were excluded from the survey.

The choice of 1:100 as the lowest significant agglutination titre was based on observations by Dalrymple-Champneys,[25c] who diagnosed the majority of his series of 1,500 cases on a clinical picture of undulant fever together with a titre of at least 1:100.

Significant clinical evidence, for the purpose of this classification, included one or more sign or symptom from at least 2 of the following groups of related features:

1. Intermittent pyrexia, night-sweats, or headaches, extending over not less than 10 days.

2. Joint pains, muscle pains, low backache, sciatica, or lumbago.

3. Lassitude, malaise, anorexia, loss of weight, insomnia, or neurasthenia.

4. Jaundice, and enlargement of spleen, liver, or regional lymph glands.

5. Anaemia or neutropenia.

6. Pathological lesions of skin, joints, or internal organs compatible with brucellosis.

A group of cases of this nature, selected initially on the basis of a positive agglutination test, and dependent for clinical assessment on the observations of over 70 different doctors, has obvious limitations with regard to statistical analysis. It is possible, however, to draw certain conclusions from the data, and to indicate where further study may yield information of value.

One can thus estimate the lower limit of the incidence of brucellosis in this country (assuming the total population to be 14 million) over the 3-year period of the survey, during which 83 South African cases were detected. This gives a figure of approximately 0·20 per 100,000 as the minimum annual incidence of new cases.

By comparison, 105 cases were notified to the Depart-

ment of Health in the years 1956 - 1959, inclusive, giving an annual incidence of 0·19 per 100,000 for the whole country, although some of these cases would undoubtedly fail to meet our criteria for a diagnosis. This figure clearly reflects a considerable degree of under-notification.

The distribution of cases (Table III) shows a high proportion from the Eastern Transvaal and South West Africa, thus confirming the findings of Barnetson[42] in a similar survey. This indicates the endemic nature of the disease in those areas, where cattle and goats are the probable reservoir animals. It is interesting that few cases are derived from the North West Cape, a region that had so much human brucellosis early in this century. In fact, only 33 cases have been notified between 1940 and 1958 in the whole Cape Province.[54]

TABLE III. GEOGRAPHIC DISTRIBUTION OF 116 BRUCELLOSIS CASES

Geographic area	*White*	*Non-White*	*Total*
Witwatersrand	18	7	25
North and East Transvaal, and Swaziland	22	30	52
North West Cape, OFS, Bechuanaland	9	0	9
South West Africa	21	9	30
Total	70	46	116

Of the patients living in Johannesburg, at least 3 had visited the Nelspruit-White River region a few weeks previously, and had drunk raw milk there.

The fact that brucellosis is a well-known occupational hazard among people working with infected animals or material, can be used as a basis for grouping the cases into 2 categories. Veterinary surgeons, stock inspectors, cattle farmers, butchers, and laboratory workers were placed in the occupational group, all others being regarded as chance infections. Table IV shows the results of this classification combined with age, sex, and racial distribution.

As might be expected, those exposed occupationally are mostly White adults (85%), while in the unrelated group almost half are under the age of 20 years, and only 43% are White. The overall sex incidence is predominantly male (77%). This is in close agreement with similar surveys in other countries.[19c]

The initial clinical diagnosis is of considerable interest, since, in retrospect, brucellosis should have been considered in many of these cases. Table V shows the various clinical diagnoses as supplied by the physician. Once again, the occupational group can be distinguished by the frequency with which brucellosis is diagnosed at the beginning of the illness (63%), as compared with the unrelated group (14%). In both groups, it is clear that many cases present as obscure pyrexias, and syndromes resembling typhoid fever or influenza, in which pains in the muscles and joints are prominent. Symptoms have usually been present for more than a week.

TABLE V. INITIAL CLINICAL DIAGNOSIS IN 116 BRUCELLOSIS CASES

Diagnosis	*Occupational group*	*Unrelated group*	*Total*
Brucellosis	29	12	41
PUO	9	17	26
Typhoid fever	1	12	13
Arthritis, sciatica	4	7	11
Influenza	2	4	6
Malaria	0	2	2
Rheumatic fever	0	2	2
Miscellaneous	1	14	15
Total	46	70	116

The initial diagnosis in relation to geography also brings out some interesting points, e.g. in South West Africa 22 out of 30 cases were correctly diagnosed as brucellosis, compared with only 17% of 75 cases occurring in the Transvaal. This is due mainly to the fact that the majority of patients from South West Africa were exposed by virtue of their occupations, but it nevertheless shows that general practitioners in that area are aware of the local prevalence of the disease.[55] In the Eastern Transvaal, where typhoid fever is not uncommon, no less than 28% of 42 cases were labelled typhoid, compared with only 2 of the 74 cases from other parts of the country.

With regard to the clinical features of these cases, the available information is listed in Table VI. The relative

TABLE VI. PROMINENT CLINICAL FEATURES OF 116 CASES OF BRUCELLOSIS

Clinical feature	*Number of cases*	*Percentage*
Persistent pyrexia	100	86
Joint pains	77	67
Backache	77	67
Night-sweats	70	60
Splenomegaly	52	45
Neurasthenia	46	40
Lassitude *	28	24
Bronchitis, cough	25	22
Headaches *	19	16
Weight loss *	18	16
Skin lesions	13	11
Hepatomegaly	9	8
Jaundice	5	4

* Information volunteered.

TABLE IV. AGE, RACE, AND SEX DISTRIBUTION OF OCCUPATIONAL AND UNRELATED CASES OF BRUCELLOSIS

Age (years)	*Occupational*				*Unrelated*				*Total*
	White		*Non-White*		*White*		*Non-White*		
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	
0–9	—	—	—	—	1	2	6	2	11
10–19	—	—	3	—	4	3	11	4	25
20–29	7	1	2	—	2	4	8	—	24
30–39	13	1	—	—	5	2	2	1	24
40–49	9	1	1	—	2	3	5	1	22
50 and over	6	1	1	—	1	1	—	—	10
Total	35	4	7	—	15	15	32	8	116

frequency of each sign and symptom cannot be accepted without reserve, since much of the information was given in reply to specific questions, while the doctor frequently volunteered other facts that were prominent in individual patients.

Since the majority of these patients lived in rural areas, laboratory investigations were usually confined to the serum agglutination test. All gave positive agglutination reactions, since it was on this basis that they were detected in the first place. The prozone phenomenon, owing to the presence of so-called blocking antibodies, was observed in 7 cases. The extent of blocking was 1:50 (4 patients), 1:100 (1), and 1:200 (2).

Out of 14 blood cultures that were attempted, 3 were successful, yielding growths of *Br. abortus* in 2 cases, and *Br. melitensis* in the third, the latter being from a proved laboratory infection.

SEKUKUNILAND SURVEY

During the course of the serological survey, it was noted that a relatively large number of cases (14) came from Sekukuniland in the Eastern Transvaal, *via* the Jane Furse Memorial Hospital. This region appeared to warrant further study, since it is a well-defined Native reserve with a stable population of approximately 250,000, living under fairly primitive tribal conditions.

In January 1959, an opportunity arose for the study of a group of Sekukuni Africans. Altogether, 142 individuals were examined for the presence of splenomegaly or hepatomegaly, and blood samples were collected for the *Brucella* agglutination test. The age and sex distribution of this group was as follows: under 10 years of age — 12 males and 39 females; 10 years and over — 27 males and 64 females.

All except 40 were apparently healthy persons, drawn from hospital staff, schoolchildren, and patients from antenatal and paediatric clinics. The remaining 40 were random patients attending the outpatient department for a variety of complaints, chiefly respiratory ailments, skin conditions, and infantile diarrhoeas. Hepatomegaly was observed in 16 cases, splenomegaly in 11, and in 3 cases there was simultaneous enlargement of both organs.

Agglutination tests were done on every individual, with serum dilutions ranging from 1 : 10 to 1 : 2,560. A total of 9 showed antibodies to *Brucella* species, including 1 at a significant level; this subject was presumed to have active brucellosis. He was a 12-year-old herd boy, with a temperature of 99·0°F., showing no enlargement of liver or spleen, who admitted to some loss of weight and joint pains. Together with several companions, he had been selected at random from a group of young boys playing in a field. The agglutination titres of the positive reactors were as follows: 1 : 10 (7 cases), 1 : 40 (1), 1 : 2,560 (1).

Although the figures are too small to have any real significance, the proportion of reactors (5·6% at 1:10 and 0·7% at 1:40, if we exclude the positive case) appears to be no higher than among random groups elsewhere in South Africa (Table I). An extensive serological survey of the indigenous African population and their domestic stock animals in the Eastern Transvaal would yield valuable information about the major reservoirs and vectors of the infection in this region.

CONCLUSION

The present-day situation with regard to human brucellosis in Southern Africa is that the disease appears to be endemic in parts of South West Africa and the Eastern Transvaal. Moderate numbers of new active cases occur in these areas each year, together with an unknown number of subclinical infections. Sporadic cases appear in all parts of the country outside the endemic areas, but some of these, particularly in the towns, can be traced to exposure in an endemic region.

The diagnosis is often difficult, but the disease should be suspected in all obscure cases of pyrexia lasting for more than a week, especially in the country districts. The standard agglutination test is sufficient to establish the diagnosis in most cases, but when it is negative, further evidence may be provided by blood culture, skin test, or modified Coombs' test.

With adequate antibiotic therapy, individual patients can expect a complete cure if the infection is identified in the first few weeks of its course. On the other hand, complete eradication of the disease in man must depend upon effective control of animal brucellosis, and elimination of the possible vectors of human infection by such means as compulsory pasteurization of milk, and stringent precautions on the part of all those exposed occupationally. Prophylactic immunization of animals with attenuated strains is effective and is widely practised, but there is little information on its efficacy in man.

SUMMARY

This paper reviews the history of human brucellosis in South Africa in relation to some of the neighbouring countries. After a brief consideration of the more important clinical and laboratory aspects of diagnosis, the incidence and distribution of the disease in South Africa are assessed from various published reports and from the records of the Department of Health. The results of a survey of 116 patients with brucellosis are analysed with regard to occupation, age, sex, geographical distribution, and prominent clinical features. Finally, there is a report on a small-scale serological survey of 142 Africans in Sekukuniland.

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