that in our cases severe myoidema was a sign of malnutrition and was probably related to thiamin metabolism.

An explanation is attempted of the growing disrepute of myoidema as a physical sign.

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LYMPHADENOPATHY IN BRUCELLOSIS

BY

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Lymphadenopathy is not a prominent feature of brucellosis. Most of the textbook articles on the subject make no mention of the lymph nodes. Bloomfield (1942) made an extensive survey of published case reports in an attempt to discover if specific lymphadenopathy ever occurs in Brucella infections. He found that most authors omitted all reference to the nodes, and detailed information was difficult to obtain. He concluded, however, that noteworthy enlargement of the superficial glands was not uncommon, although its significance was seldom clear because the available data on the clinical course of the adenitis in relation to the progress and outcome of the disease were usually inadequate.

In view of the confusion, it was decided to make a careful clinical examination of the lymph nodes in patients suffering from melitensis fever in a military hospital in Malta. The series consisted of 42 cases, all the patients being under observation in hospital throughout the course of their illness. In 30 the diagnosis was proved by blood culture; in 11 repeated blood cultures were negative, but melitensis agglutinins were present in the sera in titres varying from 1 in 1,280 to 1 in 20,480; in the remaining case blood cultures and agglutination tests were negative and the diagnosis was made on purely clinical grounds. Generalized superficial lymphadenopathy was an outstanding initial feature in two patients, and in both instances caused difficulty in diagnosis. The other 40 cases were entirely free from lymph-node involvement during their stay in hospital.

Case 1

A Maltese man aged 21 was admitted to hospital on December 3, 1945, with a provisional diagnosis of glandular fever. His complaint was of headache, anorexia, and shivering attacks for five days. He looked very ill and his temperature was 102.4° F. (39.1° C.). There was bilateral and symmetrical enlargement of the cervical (anterior and posterior), axillary, epitrochlear, and inguinal lymphatic glands. The glands were mobile, discrete, firm, and non-tender, and varied in size from 1 to 2 cm. in diameter. The throat was clean. There was no enlargement of the liver or spleen. The leucocyte count was 6,850 per c.mm. (polymorphs 20%, lymphocytes 51%, monocytes 29%—a fair proportion of the latter resembled "glandular-fever cells"). The Paul-Bunnell test was positive in a titre of 1 in 32.

In the first few days the temperature intermitted between 104° F. (40° C.) and normal; the patient had several rigors and severe epistaxis occurred on three occasions. He complained bitterly of neuralgic pains in his arms and legs. The cerebrospinal fluid was normal. An initial diagnosis of glandular fever was made, but six days after admission his serum agglutinated *Br. melitensis* in a titre of 1 in 10,240. Blood culture was performed on the same day, and after 14 days' incubation a profuse growth of *Br. melitensis* was obtained. A radiograph of the chest showed no enlargement of the mediastinal glands. The acute symptoms subsided slowly and the temperature fell by lysis after remaining high for 10 days.

The subsequent course was typical of that pursued by a severe case of undulant fever—recurring bouts of fever, progressive anaemia, and flitting arthritis. The glands decreased in size very slowly, and by the end of the sixth week none were palpable. The Paul-Bunnell test was repeated twice and remained positive in the same titre (1 in 32). In the sixth week the leucocyte count was 6,700 per c.mm. (polymorphs 45%, lymphocytes 43%, monocytes 12%). The patient was discharged at the end of the third month, when he had been afebrile for three weeks.

Comment.—The enlargement of the glands, the blood picture, and the epistaxis were considered sufficient evidence, in the beginning, to allow a diagnosis of glandular fever. The titre of the Paul-Bunnell test was, however, not of diagnostic value. The melitensis infection was discovered subsequently only because local experience had taught the value of performing the appropriate bacteriological tests in all febrile patients in whom there was the slightest doubt about the diagnosis.

Case 2

A Maltese man aged 25 was admitted to hospital on June 3, 1946, with a provisional diagnosis of leukaemia. He had been ill for several weeks, and complained of vague febrile symptoms, weakness, and swellings of the neck. He was not severely ill and his temperature was 100° F. (37.8° C.). He looked pale but well nourished. The cervical, supraclavicular, epitrochlear, axillary, and inguinal glands were enlarged on both sides. They were firm, discrete, mobile, and non-tender, and were largest in the neck and axillae, where they measured up to 2 cm. in diameter. The tip of the spleen was palpable on deep inspiration but the liver was not enlarged. The blood picture was as follows: Hb, 70%; red cells, 3,650,000 per c.mm.; white cells 5,200 per c.mm. (polymorphs 45%, lymphocytes 45%, monocytes 10%—no abnormal cells present). The Paul-Bunnell test was negative. Low-grade fever continued and a tentative diagnosis of Hodgkin's disease was made.

A gland biopsy was arranged, but on the fifth day, before it was carried out, he had a rigor with high fever. At this time blood was taken for culture and the melitensis agglutination test. The latter was positive in a titre of 1 in 20,480, and after 17 days' incubation a profuse growth of *Br. melitensis* was obtained in the culture medium. During the next six weeks

there were three waves of fever before the temperature settled. The glands did not alter for two weeks; they then slowly decreased in size, and on discharge at the end of the ninth week only a few small nodes were palpable in the left posterior cervical triangle. At this time the spleen was not enlarged. Mild arthritis of the left knee developed but was not troublesome. Treatment was symptomatic.

Comment.—The anaemia, fever, lymphadenopathy, and splenomegaly suggested Hodgkin's disease. At first a diagnosis of brucellosis was not considered, and the melitensis infection was discovered, as in the previous case, by the application of routine tests.

Discussion

Conflicting statements appear in the literature about lymph-node involvement in brucellosis. McArthur (1939), in an important survey of the subject, made no reference to lymph glands. Musser (1938, quoted by Bloomfield, 1942) stated that general lymph-node swelling did not occur. On the other hand, Menefee and Poston (1938) found that lymphadenitis was often present. Avery (1942) noted that the glands were occasionally enlarged—either the cervical group alone or generalized.

Bloomfield (1942) consulted 191 unselected case reports and found specific mention of the lymph nodes in only 50—29 with enlargement and 21 without. In the 29 positive cases the distribution was as follows: cervical only, 13; generalized (superficial), 9; axillary only, 3; cervical and inguinal, 3; axillary and inguinal, 1.

As Bloomfield pointed out, the enlargement in many cases may have been merely incidental and not a specific manifestation of brucellosis. He was particularly doubtful about the cases with only localized involvement. In seeking evidence for the existence of a specific lymphadenopathy the important patients for scrutiny would seem to be those with generalized adenitis. This group consisted of nine cases, and further information about the glands during the course of the disease was given in only three. In one the swellings subsided about the fifth week and in another they persisted until the tenth month, when observation ended. The symptoms regressed rapidly in the third case and the glands decreased in size within three days of admission; biopsy showed chronic lymphadenitis with necrotic foci, and *Br. suis* was isolated from the excised node. This patient died after multiple relapses, and the necropsy revealed generalized lymphadenitis of no specific histological type. *Br. suis* was recovered from many sites, including the lymph nodes. Gland biopsies were performed in two other patients; the lesion in one was "inflammatory," and the other served to exclude Hodgkin's disease and leukaemia.

Bloomfield concluded from his analysis of the nine patients with generalized adenitis that the lesion was probably specific for brucellosis in five, possibly in two, and of doubtful significance in two. No special aetiological importance could be attached to any single variety of Brucella—all three (*melitensis, abortus, suis*) were incriminated. Bloomfield added a case of his own which had enlargement of axillary, inguinal, and epitrochlear glands. Biopsy resulted in a histological diagnosis of lymphatic leukaemia, but the patient improved rapidly without therapy and the glands disappeared in the course of a year.

The generalized lymphadenopathy in both cases described above was without doubt a specific manifestation of brucellosis, the proof being the disappearance of the swellings as the general condition of the patients improved. Its occurrence in only two out of 42 cases suggests that it is not common.

The importance of the occasional occurrence of lymphadenitis in brucellosis is the confusion that it may cause in diagnosis. This point is well demonstrated by both of my cases. In Case 1 the clinical diagnosis of glandular fever seemed to be confirmed by the haematological examination. Wise (1943) drew attention to the fact that the study of the leucocytes in brucellosis frequently reveals abnormal cells suggestive of the early stage of glandular fever. Leys (1943) had two cases of abortus fever in which the monocyte count was so high that mononucleosis was considered as a possible diagnosis.

Rubenstein and Shaw (1944) stressed the clinical similarity which often exists between brucellosis and glandular fever. They pointed out that glandular enlargement was strongly in favour of the latter. Case 2 shows a superficial resemblance to Hodgkin's disease. Anaemia, splenomegaly, and lymphadenopathy may be common to both brucellosis and lymphadenoma, and the resemblance may be even closer in those cases of the latter which are characterized by the Pel–Ebstein type of fever. Parsons and Poston (1939) were of the opinion that in some cases of brucellosis even the histology of the lymph nodes may suggest Hodgkin's disease.

It is apparent that great advances are being made towards the goal of specific therapy for brucellosis (Spink, Hall, Schaffer, and Braude, 1949; Herrell and Barber, 1949). With the discovery of effective chemotherapeutic and antibiotic agents early diagnosis, previously of little moment, takes on a new importance. In such a protean disease diagnosis is notoriously difficult and clinical suspicion requires bacteriological confirmation. Mistakes arise when the physician, faced with a case of obscure pyrexia, does not suspect brucellosis. In areas where the disease is not common the error may be one of simple omission; but occasionally, as in the cases described above, the presence of an unusual clinical feature may cause such close resemblance to other conditions that the true diagnosis is obscured unless the specific bacteriological tests are employed. An awareness of the specific lymphadenopathy of brucellosis may prevent cases being wrongly diagnosed as glandular fever, lymphadenoma, or even leukaemia. A serious prognostic error may therefore be avoided and adequate therapy will not be withheld.

Summary

Two cases of melitensis fever in which generalized lymphadenopathy was a prominent feature are described. One case closely resembled glandular fever and the other simulated Hodgkin's disease.

The occurrence of specific lymphadenopathy in brucellosis is discussed and the difficulty in diagnosis which it may cause is stressed.

Lack of knowledge of this cause of lymphadenopathy may result in a serious prognostic error, and by delaying diagnosis may prevent the use of therapeutic measures at their most effective stage.

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