A STUDY OF THE LEUCOCYTIC PICTURE IN BRUCELLOSIS

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INTRODUCTION

The diagnostic tests so far employed without the use of corroborative laboratory findings frequently are of limited value in the detection of active brucellosis. Because of this fact it has been advisable to investigate certain abnormalities which accompany brucellosis as revealed by laboratory tests. It is hoped thereby to provide additional useful diagnostic criteria in the detection of this disease.

An opportunity presented itself recently to study certain aspects of the blood picture in seventy-six acute brucellosis cases from which Brucella melitensis was recovered. These patients were located on the island of Malta. The blood examinations were made from two to four weeks after the onset of the disease. All red blood cell measurements and leucocyte differentials were made from cover slip smears stained with Hastings' stain.

Studies have been made of the blood picture in brucellosis, but generally these studies were not made on a group of patients from whom Brucella organisms had been isolated.

Red Blood Cells

There have been many reports in the literature that brucellosis is accompanied by a secondary (1), (2), (3), (4) from a slight to moderate anemia (5). Brucellosis accompanied by an imperfect coagulation time and clot retraction time has been reported by Calder (6) and associates. Bracke and Garver (1a) find that jaundice may accompany brucellosis caused by enlarged lymph nodes which occlude the common duct.

Table I represents the findings from 32 cases. These cases revealed that there is a marked variation from the normal in the size of the red blood cells of the brucellosis patient. Calder (6) has reported frequent instances of macrocytic, hyperchromic type of anemia while Lisbonne and Janbon (7) consider a constant and extremely marked anemia an habitual symptom in certain classic descriptions of the disease. Decrease in hemoglobin and red cells are observed in malignant, prolonged and tenacious forms of undulant fever and in forms producing hemorrhage but in the usual cases the number of red cells remain at about 4,000,000 per cubic millimeter. Hardy (4) and associates report that a secondary anemia usually occurred with the hemoglobin and red blood cells both reduced, the amounts of decrease depending directly on the severity and duration of the disease. In the present investigation it was revealed in the first thirty-two cases studied, that 35 per cent of the patients had an increased number of red cells which were smaller than normal and in 19 per cent there was a tendency of the cells to be larger than normal. The average red blood cell measurement formula was of a 32: 36:25 ratio instead of the 33: 34:33 ratio (2). The red blood cells of some patients varied in size from three to ten microns, although the normal variation is from six to ten microns. This variation in size is probably effected by an accompanying splenic and liver pathology.

White Blood Cells

There are scattered reports in the literature to the effect that brucellosis is characterized by a leucopenia with a relative lymphocytosis (1), (2), or a monocytosis (3), (4). The determinations of

the total leucocyte counts are for the most part in accord with those of previous authors. The white blood cell count on the average is lower than normal with a relative and absolute monocytosis. (Tables I, II, III and Chart I). In a leucopenia the lymphocytosis at times is only relative which is made apparent by the reduction of granulocytes, (See Case No. 57, Table II). There is a quantitative increase in the non-filamented neutrophiles. Unfortunately many of the non-filamented as well as the filamented polymorphonuclear neutrophiles contain "toxic" granules, that is, there is a basophilic granulation of the neutrophiles. The theory of the leucocytic response in brucellosis is well demonstrated and explained by Haden (9). Our case No. 23 exemplifies his theory. The leucopenia is undoubtedly due to selective toxic effects of the Brucella melitensis organism which prevents normal cell maturation in the bone marrow of the neutrophiles. Such cells as released show evidence of damage by the presence of basophilic granulation in the cytoplasm. Haden (9) believes that these neutrophiles containing "toxic" granules are of little value in their normal function of defense. Evidence of bone marrow activity in brucellosis patients is demonstrated by a normal number of thrombocytes in these cases. The prompt polymorphonuclear response to Brucellin (the curative agent) seen in these patients also indicates that the bone marrow is active. For several hours after the injection of Brucellin there is an elevation of the leucocyte count due to the increase of the nonfilamented and filamented neutrophiles. During the course of treatment varying degrees of leucopenia may occur. The blood picture does not return to normal until recovery has taken place.

Table I. Red Blood Cell Size and Leukocytic Picture in 32 Cases of Brucellosis

Case No.	ERYTHROCYTE MEASUREMENT					W.B.C.	DIFFERENTIAL							L E	BG N	Remarks
	Min. size	<7.5u	7.5u	>7.5u	Max. size		E	B	MFP	FP	Lly	Sly	M			
1	3 at 6u	22	32	46	4 at 8.5u	6,000	0	0	9	14	49	12	16	3	3+	5 metalymphoblasts
2	1 at 6u	50	38	41	3 at 9u	5,000	1	2	12	16	41	18	10	2	4+	7 metalymphoblasts 20 large mature lymphocytes
3	1 at 5u	28	39	33	1 at 10u	6,200	0	0	15	15	53	11	6	3	3+	3 metalymphoblasts 12 lymphocytes with indented nuclei
4	2 at 5u	31	36	33	4 at 8u	6,100	0	1	15	17	42	13	10	4	4+	1 plasma cell
5	3 at 5u	50	38	12	2 at 8.5u	6,000	0	0	35	9	40	9	7	0	2+	
6	2 at 6u	28	36	36	4 at 8u	4,900	1	1	32	28	25	8	5	1	3+	
7	2 at 4.5u	51	34	15	1 at 8u	4,600	0	0	21	10	39	13	17	3	3+	1 monoblast pencil cells polychromatophilia
8	4 at 5.5u	45	35	19	3 at 9u	5,200	0	0	29	6	43	11	11	2	2+	10 lymphocytes with indented nuclei
9	1 at 4.5u	55	35	10	2 at 8.5u	6,500	0	0	32	15	31	13	9	0	3+	
10	4 at 6.0u	36	43	21	3 at 9u	5,400	2	0	37	30	21	0	10	1	2+	5 lymphocytes with indented nuclei
11	1 at 6u	38	40	22	2 at 9u	4,800	0	1	17	15	47	17	13	4	3+	2 plasma cells 12 large mature lymphocytes

Table I continued

Case No.	ERYTHROCYTE MEASUREMENT					W.B.C.	DIFFERENTIAL							L E	BG N	Remarks
	Min. size	<7.5u	7.5u	>7.5u	Max. size		E	B	NPP	FP	Lly	Sly	M			
12	3 at 6u	36	37	27	1 at 9u	4,600	0	0	27	17	41	9	6	2	3+	6 large mature lymphocytes
13	5 at 6.5u	33	32	35	4 at 9u	6,000	3	0	16	21	38	10	12	2	2+	5 lymphocytes with indented and clumped nuclei
14	3 at 4.5	55	29	25	1 at 8.5u	5,800	1	0	16	40	28	3	10	1	1+	
15	1 at 3.5u	32	29	9	1 at 8.5u	6,100	0	0	28	14	32	15	11	3	1+	Sl. poikilocytosis Occ. pencil cell
16	3 at 3.5u	75	26	5	4 at 7.8u	6,450	0	0	20	36	31	8	5	1	2+	Red cells spherical
17	3 at 3.5u	65	27	14	3 at 7.8u	5,025	0	0	30	27	28	7	8	1	2+	
18	4 at 3.5u	63	28	8	1 at 9u	6,000	0	1	23	15	43	11	7	3	3+	Sl. poikilocytosis 4 large mature lymphocytes
19	1 at 4.5u	27	52	21	1 at 9.5u	4,100	0	0	30	23	31	9	7	2	3+	3 normoblasts
20	3 at 4.5u	43	34	23	9 at 9u	7,000	1	2	24	12	43	11	7	3	3+	Red cell elongated 4 indented nuclei lymp 30 large mature lymphs
21	1 at 4.5u	19	34	47	5 at 10u	7,250	2	1	20	32	31	10	4	0	2+	3 metalymphoblasts
22	1 at 3.5u	29	36	33	3 at 9.5u	6,800	0	0	1	42	46	7	2	2	3+	4 lymphocytes with indented nuclei 1 monoblast

Table I continued

C	e	ERYTHROCYTE MEASUREMENT					W.B.C.	DIFFERENTIAL							L E	LG H	Remarks
	.	Min. size	< 7.5u	7.5u	> 7.5u	Max. size		E	B	MFP	FP	Lly	Mly	M			
		3 at 4.5u	34	40	26	4 at 9u	2,900	0	0	26	23	31	14	6	2	4+	5 lymphocytes with indented and clumped nuclei
	24	3 at 4.5u	34	34	32	1 at 9.5u	7,200	0	1	21	10	48	10	10	4	3+	2 juvenile neutrophiles Occ.shadow red cell
	25	5 at 4.5u	36	31	33	2 at 9.5u	4,450	0	0	21	20	38	6	14	2	3+	3 metaly phoblasts 11 large mature lymphocytes
		4 at 4.5u	34	39	27	1 at 9.5u	3,300	0	0	33	20	30	12	5	1	3+	7 lymphocytes with indented nuclei
		4 at 6.0u	33	34	33	1 at 9.5u	3,500	0	0	15	30	35	9	11	0	2+	1 monoblast Anisocytosis
	28	3 at 4.5u	34	32	14	1 at 9.5u	6,300	0	1	16	19	51	11	3	4	2+	24 large mature lymphocytes
	29	5 at 4.5u	43	39	18	4 at 9u	4,900	0	0	4	33	39	14	10	3	1+	
	30	7 at 4.5u	32	33	35	1 at 9.5u	4,600	0	0	31	21	31	8	9	1	3+	21 large mature lymphocytes
	31	8 at 6u	30	35	35	7 at 9u	5,020	0	0	11	49	22	5	13	1	3+	16 large mature lymphocytes
		1 at 4.5u	25	39	36	1 at 9.5u	7,750	0	2	4	24	45	13	8	3	3+	12 lymphocytes with indented nuclei
	ver.		39	36	25		5,485	.3	.4	21.3	23	38	10	8	2	3	
	orm.		33	34	33		8,000	.1	.5	6	60	8	20	4.5	0	0	

Table I continued

Key to symbols

W.B.C. = White Blood Count

E = Eosinophile

B = Basophile

NFP = Non-filamented polymorphonuclear neutrophile

FP = Filamented polymorphonuclear nuetrophile

Lly = Large lymphocyte

Sly = Small lymphocyte

M = Monocyte

LE = Liver Endothial cell

BGN = Basophilic granulation of the neutrophiles

+ = degree of basophilic granulation

Table II. A Study of the Leucocyte Picture in Forty Brucellosis Cases

Case No.	W.B.C.*	DIFFERENTIAL											
		Eos.	B	JFP	FP	Lly	Sly	Mo	M	LMly	LE	BGM	Remarks
33	5,250	1	0	13	13	22	28	13	3	1	1	1+	
34	8,555	1	0	36	32	13	12	6	2	0	1	1+	1 plasma cell
35	7,100	1	0	10	19	44	22	4	2	12	3	1+	lymphocytic fenestration
36	14,150	0	0	60	35	1	4	0	0	0	0	3+	5 juveniles
37	8,300	1	0	15	33	18	26	7	3	0	1	1+	1 plasma cell
38	2,050	0	0	20	13	24	40	3	2	4	0	2+	2 plasma cells
39	3,450	0	0	40	10	23	19	8	0	0	0	1+	lymphocytic fenestration
0	7,600	0	0	19	40	17	14	10	3	0	1	2+	
1	6,150	0	0	22	10	39	18	11	2	4	1	1+	

Table II continued

Case No.	W.B.C.*	DIFFERENTIAL							E*	L*ly	LE	FGI	Remarks
		Eos.	B	NFP	FP	Lly	Sly	Mo					
42	5,050	0	1	26	25	23	16	9	1	0	1	2+	2 monoblasts 1 mo. cont. red cell
43	6,250	0	0	7	8	61	18	6	2	11	2	1+	lymphocytic fenestration
44	6,500	0	0	11	11	44	24	10	2	9	0	1+	3 monoblasts
45	5,300	0	0	21	17	29	23	10	2	2	1	1+	
46	7,900	0	0	14	40	10	22	4	1	0	0	2+	
47	4,700	0	0	24	13	22	35	6	4	5	1	2+	+ platelets
48	3,250	0	0	21	18	37	17	7	3	3	1	2+	1 nucleated RBC
49	2,950	0	0	27	39	19	6	9	4	0	3	3+	
50	7,200	1	0	30	10	41	7	11	5	0	4	1+	1 plasma cell, poly. cytopl. vacuolated

Table II continued

Case No.	W.B.C.*	DIFFERENTIAL											Remarks
		Eos.	B	MP	FP	Lly	Sly	Mo	M	LMly	LE	BM	
51	3,050	0	0	29	27	23	10	11	4	0	3	2+	lymphocytic fenestration
52	5,600	0	0	37	15	33	12	3	5	1	0	3+	
53	4,600	0	0	17	11	33	28	11	4	7	3	2+	
54	7,800	2	0	15	20	35	22	6	4	6	3	3+	2 plasma cells
55	6,000	0	0	15	19	31	24	11	5	4	3	2+	
56	7,100	1	0	32	14	26	15	12	3	2	2	3+	
57	3,500	1	0	14	33	26	21	5	3	3	0	2+	
58	4,200	1	0	20	24	23	22	10	3	5	2	2+	
59	5,500	0	1	20	28	22	22	7	2	2	0	2+	

Table II continued

Case No.	W.B.C.*	DIFFERENTIAL											Remarks
		Eos.	B	APP	PP	Lly	Sly	Mo	M	L Mly	LE	B'H	
60	5,200	1	0	22	19	17	34	7	4	2	1	1+	
61	8,100	0	0	39	17	22	17	5	2	0	1	3+	
62	4,000	0	0	14	24	30	17	13	3	0	1	2+	
63	5,000	0	0	23	8	36	22	11	5	5	1	2+	
64	6,150	0	0	32	13	27	20	8	5	1	0	3+	
65	4,600	0	0	39	17	19	13	7	3	0	0	3+	
66	6,700	0	0	24	6	36	25	9	3	9	3	2+	2 plasma cells
67	7,600	0	0	30	9	44	12	5	4	8	1	3+	
68	7,200	0	0	39	9	34	13	6	5	2	0	1+	1 plasma cell

Table II continued

Case No.	W.B.C.*	DIFFERENTIAL											Remarks
		Eos.	B	MPP	FP	Lly	Sly	Mo	IM	LLly	LE	BGN	
69	6,000	0	0	15	22	47	9	6	2	5	1	2+	
70	3,650	1	0	22	31	26	13	7	2	0	0	3+	
71	4,000	1	0	12	23	38	16	5	3	3	1	1+	
72	7,950	2	0	22	19	37	13	7	5	0	1	1+	2 normoblasts
verages	5,703	.35	-	23.1	20.0	27.0	10.8	7.6	2.9	2.6	1.2	2.1	

* Key to symbols

W.B.C. = White Blood Count

Eos. = Eosinophile

B = Basophile

MPP = Non-filamented polymorphonuclear neutrophile

FP = Filamented polymorphonuclear neutrophile

Lly = Large lymphocyte

Sly = Small lymphocyte

Mo = Monocyte

IM = Infectious mononucleosis cell

LLly = Large mature lymphocytes

LE = Liver endothelial cell

BGN = Basophilic granulation of the neutrophile

+ = degree of granulation of the neutrophiles

Table III*

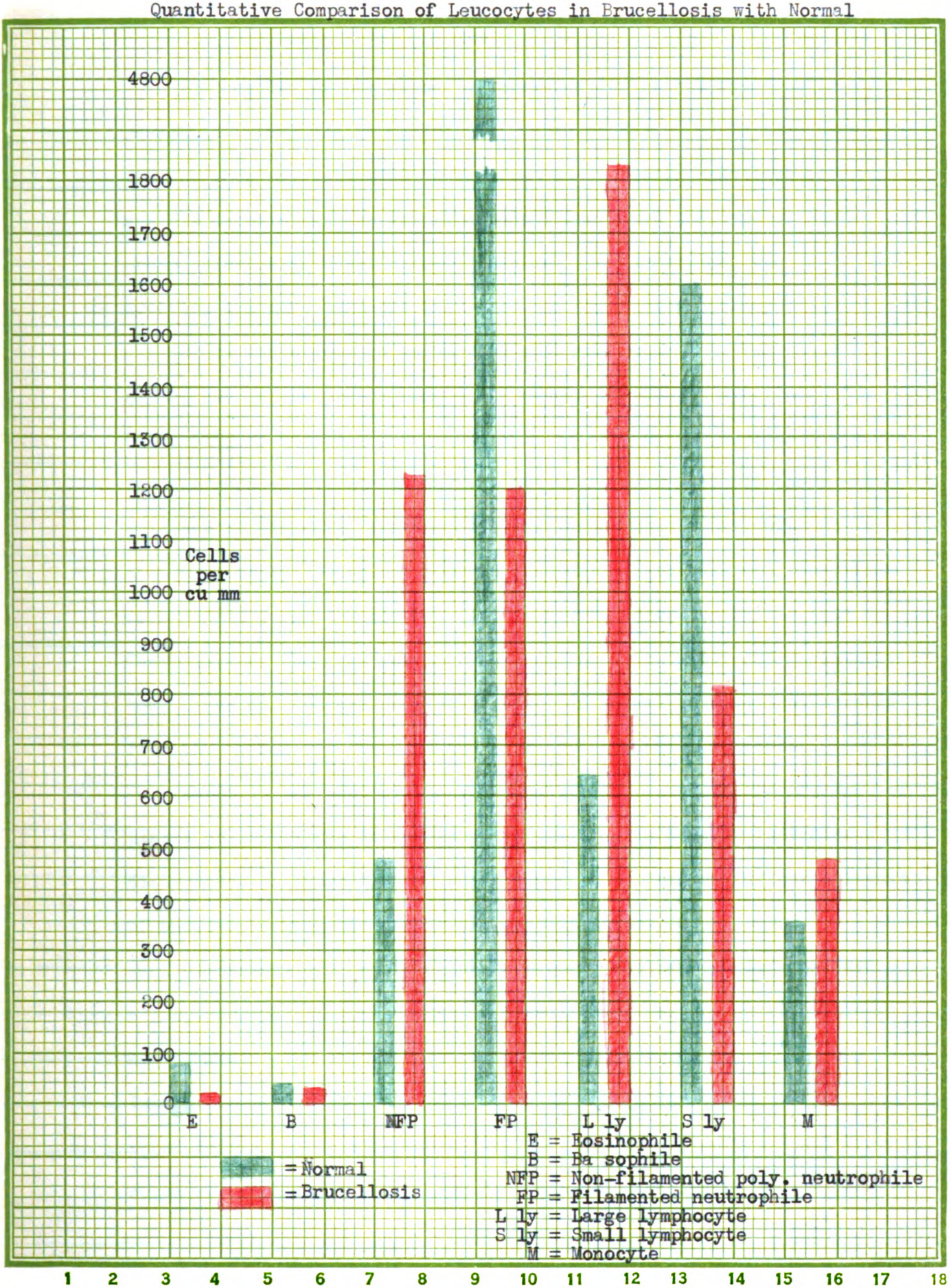
Quantitative Comparison of Leucocytes in Brucellosis with the Normal

	Normal		Brucellosis	
Cell	Number	Per cent	Number	Per cent
E	80	1.0	17	0.3
B	40	0.5	22	0.4
LFP	480	6.0	1230	22.2
FP	4800	60.0	1203	21.5
Lly	640	8.0	1810	32.5
Sly	1600	20.0	815	14.4
M	360	4.5	486	8.7
Total	8000	100.0	5594	100.0

* Accompanies Chart I.

CHART I

Quantitative Comparison of Leucocytes in Brucellosis with Normal



The results of the author's investigation of the eosinophile and basophile values are in accord with those of Hardy (4) in that they did not show any essential change from the normal. Baldridge (10) and his associates have described and illustrated the type of basophile observed in these cases. This cell is larger, and the granules are more numerous than those of the ordinary basophile.

Since there seem to be varying opinions regarding the staining affinities of the prolymphocyte and mature lymphocyte cytoplasm (6), (11), (12) it has been found advisable to rely on the nuclear structure for the purpose of determining the age of lymphocytes. If there was evidence of nucleoli, and the cell was larger than normal with an abundance of cytoplasm but not too basophilic, the cell was classified as a normal large lymphocyte. It was found, according to the data in Chart I, that the greatest increase both quantitatively and qualitatively took place in the case of these cells. An actual qualitative decrease from the normal was found in the case of the small lymphocytes.

About 10 per cent of the patients studied revealed the presence of plasma cells. Since the presence of these cells usually indicates a disturbance of lymph glands, their appearance provides further evidence of the lymphocytogenic effect of Brucella infection.

Clinicians and hematologists are quite well agreed in considering a preponderance of lymphocytes in brucellosis, many of which are forms not commonly seen in the blood of normal individuals (4), (6). One interesting point encountered in this investigation which has not been noted before in the literature, is that many of the mature small lymphocytes are much larger than normal. This cell is similar to a type of

infectious mononucleosis lymphocyte. By some authors these have been termed "atypical lymphocytes", and others have named them "large mature lymphocytes". These cells have all the appearance of small lymphocytes, the ratio of the nucleus to cytoplasm being similar to that of a normal small lymphocyte. Occasionally the nucleus appeared to be of a more homogenous structure than ordinarily seen in mature lymphocytes but there was no evidence of nucleoli. These large mature lymphocytes are about 12 to 14 microns in diameter. The normal small lymphocytes usually measure from 8 to 10 microns in diameter. As many as 5 to 10 per cent of the lymphocytes appeared as this type of cell in about 50 per cent of the brucellosis patients studied.

Other cytological similarities to the infectious mononucleosis cells were observed. A lymphocyte with an indented nucleus was classified as an infectious mononucleosis type of cell. The tabulated data in Table I show an average of 1.45 lymphocytes with indented nuclei which correspond to the infectious mononucleosis cells (I.M.) of Table II. Lymphocytes were observed showing condensation of chromation in the nucleus. This type of cell made up about 40 per cent of the circulating infectious mononucleosis cells. A good illustration of the latter cell has been demonstrated by Baldridge (10) and associates.

Osgood (13) characterizes infectious mononucleosis by the presence of lymphocytes with nuclear fenestration. According to Table II fenestration in otherwise normal lymphocytes were observed.

The significance of the nuclear fenestrated lymphocytes is yet to be determined.

Sabin (12) by supervital staining has found, in cases of brucellosis, an increase in the type of monocyte which is similar morphologically to the type of monocytes associated with various forms of hepatic involvement (11). These appear to be similar to the atypical monocytes found in catarrhal jaundice. (14). In disease associated with liver pathology, Isaacs (15) has described "a cell averaging 15 by 13 microns, with an oval nucleus, rather dense chromatin (lymphoid in character), foamy blue-staining cytoplasm (monocytoid), but with absence of the minute, red staining granules of the monocyte. There is no perinuclear clear zone, as in the lymphocyte. Occasional inclusion granules are found in the cytoplasm. The margin is wavy." The "liver damage cell" more recently named "liver endothial cell" of Isaacs was present consistently in nearly all of the cases of brucellosis examined.

Another interesting point that has been noted and previously discussed in this paper is that in Brucella melitensis infection there is a marked basophilia of the granules of the neutrophiles. In this country brucellosis patients having the melitensis type of infection have been encountered whose neutrophiles did not possess the basophilic granulation. These granules are similar in size to the Brucella bacteria and stain similarly. It is suggested that a control plain smear always be made without the bacteria when a phagocytosis test is performed. A toluidin blue staining technique has been perfected by Huddleson for the staining of phagocytosis smears

from Brucella melitensis infected patients. The basophilic granules do not take the toluidin blue stain.

DISCUSSION

There was great difficulty in classifying the abnormal cells because of the fact that all gradations from the small normal lymphocyte to the "liver endothial cell" and the various infectious mononucleosis cells were present.

The abnormal cells in the blood of brucellosis patients may have a definite function, however, it is believed that these cells are not produced to combat any specific condition found only in brucellosis. The writer does not agree with Turk (16) who believes that abnormal lymphocytes enter the blood stream to replace polymorphonuclear cells which are not available for the blood because of temporary exhaustion of the bone marrow. At present the specific cause for either the entrance of abnormal lymphocytes into the blood stream or the absolute decrease in the number of circulating neutrophiles in brucellosis is not known. It is definitely known (1b) that some of the abnormal lymphocytes originate in the hyperplastic lymph nodes in the brucellosis.

There was not observed an increase of monocytes in the cases of brucellosis studied. This is in accordance with the findings of Calder (6) and associates. The tabulated data in Table III indicate that the number of monocytes is not greatly increased over the normal. It is believed by Rosenthal (17) and associates and by Doch (18) that a prognosis is more favorable in a granulocytosis when accompanied by a monocytosis.

SUMMARY

It was found in the study of Brucella melitensis infected individuals that the blood picture reveals a leucopenia with a relative lymphocytosis and slight monocytosis.

The red blood cells tend to be slightly smaller than normal; however, some patients gave evidence of macrocytosis.

There was an increase of the non-filamented neutrophiles over the normal value.

The presence of "pathologic lymphocytes" in 40 per cent of the brucellosis cases is significant. "Liver endothial cells" were found consistently in these patients.

Finally varying degrees of "basophilic granulation of the neutrophiles" was found in all cases of brucellosis studied.

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