J. clin. Path. (1950), 3, 321.

THE COMMON CAUSES OF LYMPHOPENIA

BY

A. J. SHILLITOE

From the Kingston General Hospital and Western General Hospital, Hull

(RECEIVED FOR PUBLICATION MARCH 22, 1950)

Since differential blood counts are now reported in absolute numbers as well as in percentages, lymphopenia is frequently found and its significance questioned. Whitby and Britton (1946) say that the lymphocytes in the peripheral blood may be diminished in the acute stages of an infection, in conditions of exhaustion, after excessive *x*-ray irradiation, with vitamin deficiency, and in the terminal phase of uraemia. Wintrobe (1946) says:

> " Rarely, leucopaenia may be due to a reduction in the lymphocytes. This has been described in miliary tuberculosis and in instances of excessive exposure to irradiation. The action of certain chemical agents is much more pronounced on lymphocytes than granulocytes."

Wintrobe also regards a marked absolute reduction of lymphocytes as an unfavourable prognostic sign. These authors refer to the lymphopenia which is found in such haematological disorders as Banti's syndrome and agranulocytosis. To obtain a clearer picture of the common causes of lymphopenia differential leucocyte counts performed in one laboratory over a year were analysed. This laboratory serves a general hospital admitting all types of cases (babies and adults) except accidents, infectious fevers, and maternity cases. A few out-patients are also investigated at the laboratory. The children's department is small in relation to the rest of the hospital.

The blood counts were performed with the usual care and precautions taken in a hospital laboratory.

The lower limit of normal for a lymphocytic count is usually stated to be 1,500 per c.mm. (Wintrobe, 1939). However, it was decided to study only those cases in which the reduction was marked, so that, for the purpose of this paper, only lymphocyte counts of 1,000 per c.mm. or less have been classed as lymphopenic. The lowest count of all was one of 270 in a patient treated with *x* rays. Some patients with lymphopenia also had eosinopenia, but this finding was not constant.

A total of 647 patients had differential leucocyte counts performed on one or more occasions. Of this number 87 patients showed a lymphopenia at some time or other. The youngest was a boy of 8 years, an epileptic on tridione therapy, and the eldest a woman of 83 who was said to be suffering from pericolitis. The laboratory findings, diagnoses, and clinical notes of the 87 cases with a lymphopenia of 1,000 c.mm. or less at any point in the illness are set out in Tables I–VIII. The cases are grouped according to diagnosis.

TABLE I

GROUP I: TWENTY CASES OF CARDIAC DISEASE

Case	Age	Sex	Hb (g.%)	Total W.B.C (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.)	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
1	46	F	11.0	8,000	960	6,640	80	320	—	—	Hypertensive cardiac failure	Discharged ambulant; hypochromic anaemia
2	70	M	15.3	8,000	640	7,120	160	80	—	—	,, ,, ,,	Discharged ambulant
3	64	M	—	8,000	960	6,800	80	160	—	—	,, ,, ,,	,, ,,
4	75	F	14.5	14,000	980	13,020	—	—	—	—	,, ,, ,,	Died
5	68	F	8.6	8,000	560	7,280	—	160	—	—	,, ,, ,,	,,
6	73	F	8.0	4,000	760	2,960	160	120	—	—	,, ,, ,,	Bedridden; hypochromic anaemia
7	72	F	5.0	6,000	900	4,800	180	60	60	—	,, ,, ,,	,, ,, ,,
8	66	F	12.6	5,000	950	3,800	—	150	100	—	,, ,, ,,	Bedridden
9	57	M	—	12,000	840	10,920	—	240	—	—	Coronary thrombosis	Died
10	75	M	8.6	5,000	1,000	3,450	100	450	—	—	,, ,,	Died; hypochromic anaemia
11	67	M	12.9	11,000	770	9,680	—	550	—	—	,, ,,	Died
12	56	M	—	7,000	980	5,810	140	70	—	—	,, ,,	Discharged ambulant
13	79	M	14.5	10,000	1,000	8,600	100	200	100	—	Atherosclerotic non-hypertensive cardiac failure	Fibrillating; died
14	64	F	8.5	6,000	420	5,460	—	120	—	—	,, ,, ,,	Died; hypochromic anaemia
15	63	M	13.2	7,000	980	5,530	280	140	70	—	,, ,, ,,	Died; heart block; hypochromic anaemia
16	75	M	14.5	6,000	780	4,500	360	360	—	—	,, ,, ,,	Died; heart block
17	64	F	14.8	6,000	900	4,740	60	300	—	—	,, ,, ,,	Died
18	38	F	13.0	4,000	480	3,120	40	400	—	—	Mitral stenosis	Congestive failure; bedridden
19	56	F	—	10,000	1,000	8,800	—	200	—	—	,, ,,	Congestive failure; digitalis therapy; recovered
20	23	M	4.15	7,000	560	6,370	—	—	70	—	Coarctation of aorta	Bacterial endocarditis; responded to penicillin; discharged ambulant

TABLE II

GROUP II: TWELVE CASES OF GASTRIC OR INTESTINAL DISEASE

Case	Age	Sex	Hb (g.%)	Total W.B.C. (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.)	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
21	52	F	7.4	5,000	950	3,650	100	250	50	—	Anastomotic ulcer	Profuse vomiting; hypochromic anaemia; recovered
22	40	M	10.6	7,000	840	6,020	—	140	—	—	Carcinoma of stomach	Profuse vomiting; hypochromic anaemia; inoperable
23	57	F	13.0	7,000	770	5,950	—	280	—	—	Gastro-enteritis	Profuse vomiting and diarrhoea; recovered; cause not found
24	35	M	16.0	5,000	800	3,150	450	350	—	250	Malignant malaria	Presented as a case of profuse vomiting; recovered
25	61	M	6.5	6,000	960	4,980	—	120	—	—	Pyloric stenosis	Profuse vomiting; hypochromic anaemia; alkalosis; died
26	74	F	15.2	10,000	900	8,400	—	700	—	—	Gastric ulcer	Profuse vomiting; subsequently haematemesis; recovered
27	51	M	10.4	3,650	730	2,555	182	110	73	—	Duodenal ulcer	Severe melaena; recovered (count done after transfusion)
28	39	F	5.35	7,000	910	5,810	140	140	—	—	Peptic ulcer	Haematemesis and melaena; recovered
29	72	F	6.5	6,000	840	4,920	120	120	—	—	Carcinoma rectum	Severe diarrhoea; died
30	31	F	13.5	7,000	910	5,390	490	140	70	—	Ulcerative colitis	Condition not severe; recovered
31	?	F	8.0	5,000	750	4,000	—	250	—	—	Small intestine resected previously (? reason)	Hypochromic anaemia; out-patient; details untraceable
32	35	F	10.0	7,000	910	5,600	70	420	—	—	Tubal abortion	Post-operative tympanites of abdomen; recovered

TABLE III

GROUP III: TWELVE CASES OF RESPIRATORY DISEASE (EXCLUDING TUBERCULOSIS)

Case	Age	Sex	Hb (g.%)	Total W.B.C. (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.)	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
33	48	F	14.0	22,000	880	20,240	—	880	—	—	Lobar pneumonia	Subsequent empyema; recovered
34	73	F	—	10,000	800	8,600	—	600	—	—	,, ,,	Died
35	62	M	13.0	6,000	480	5,280	—	240	—	—	Bronchopneumonia	,,
36	28	F	15.2	7,000	700	5,950	70	280	—	—	Lobar pneumonia	Recovered; profuse growth of pneumococci in sputum
37	34	F	12.2	8,000	960	6,240	160	480	—	160	,, ,,	Not severely ill; recovered
38	78	M	15.6	10,000	900	8,900	—	200	—	—	,, ,,	Recovered
39	77	F	14.8	16,000	800	14,880	—	320	—	—	,, ,,	,,
40	56	M	—	9,000	990	7,470	—	540	—	—	Chronic bronchitis and emphysema	Admitted with exacerbation; recovered
41	46	M	14.2	6,000	960	4,800	—	120	120	—	,, ,, ,,	,, ,, ,,
42	62	M	10.6	10,000	600	8,900	—	400	100	—	,, ,, ,,	Exacerbation with small pleural effusion; recovered
43	17	F	13.0	5,000	900	3,450	—	650	—	—	Pleural effusion	Recovered. (May have been tuberculous, although included in this group)
44	60	M	8.6	11,000	880	9,020	110	990	—	—	Carcinoma bronchus	Pleural effusion; hypochromic anaemia

TABLE IV

GROUP IV: TEN CASES OF IATROGENIC AND OCCUPATIONAL DISEASE

Case	Age	Sex	Hb (g.%)	Total W.B.C. (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.)	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
45	65	F	7.7	7,000	980	5,600	—	420	—	—	Carcinoma bronchus	Nitrogen mustard therapy; pre-treatment lymphocytes normal; hypochromic anaemia
46	18	M	9.9	4,000	560	3,320	40	80	—	—	Lymphosarcoma	" " "
47	42	F	5.4	3,200	480	1,952	480	224	32	32	Carcinoma ovary	" " "
48	69	M	13.0	6,000	720	4,860	60	300	60	—	Carcinoma bronchus	Nitrogen mustard therapy; out-patient; pre-treatment lymphocytes not known
49	55	F	13.8	3,900	975	2,535	117	195	78	—	Carcinoma cervix	Treated with radium 9 years previously
50	?	F	12.9	3,350	938	2,278	—	67	—	67	*X*-ray worker	Routine check-up
51	70	F	4.15	27,000	270	13,500 (2,700 of these myelocytes)	—	—	—	—	Myeloid leukaemia	Following *x*-ray therapy (13,230 normoblasts included in total W.B.C.)
52	65	F	11.6	700	672	14	—	—	—	14	Agranulocytosis	Following "soneryl"; recovered
53	8	M	—	6,000	960	4,740	180	120	—	—	Epileptic	Tridione therapy; clinically satisfactory
54	15	M	11.2	47,000	470	42,535 (4,700 of these myelocytes)	1,410	940	1,410	—	Chronic myeloid leukaemia	Urethane therapy (235 myeloblasts included in total W.B.C.)

TABLE V

GROUP V: NINE CASES OF BLOOD DISEASE

Case	Age	Sex	Hb (g.%)	Total W.B.C. (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.)	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
55	69	M	6.4	14,000	700	4,960 (2,240 of these myelocytes)	—	280	—	—	Chronic myeloid leukaemia (untreated)	(3,720 myeloblasts and 4,340 normoblasts included in total W.B.C.)
56	46	M	9.8	1,500	900	495	—	105	—	—	Aleukaemic myeloid leukaemia (untreated)	Myeloblastic crisis and died after 8 months in aleukaemic phase
57	48	M	5.45	8,000	960	6,400	—	400	240	—	Pernicious anaemia (untreated)	Complicated by pneumonia and cardiac failure; responded to liver with complete recovery
58	46	M	9.2	5,000	950	3,450	500	100	—	—	,, ,, ,,	Responded uneventfully to liver
59	76	M	4.0	2,700	810	1,782	27	81	—	—	Hypochromic anaemia (untreated)	Cause of anaemia not found; responded to iron
60	32	F	8.6	6,000	960	4,740	120	120	60	—	,, ,, ,,	Out-patient; further details not available
61	66	F	10.8	1,000	800	140	20	40	—	—	Diabetes and leucopenia	Clinical condition good; leucopenia persisted after diabetes controlled; cause not found
62	19	M	7.6	3,700	999	2,479	37	185	—	—	Splenic anaemia (untreated)	Haematemesis; general condition remains good
63	28	F	14.2	5,000	850	3,550	300	300	—	—	Acholuric jaundice (post-splenectomy)	Lymphocytes normal before splenectomy

TABLE VI

GROUPS VI AND VII: FIVE CASES EACH OF TUBERCULOSIS AND LIVER DISEASE

Case	Age	Sex	Hb (g.%)	Total W.B.C. (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
64	59	M	13.3	6,000	300	5,640	—	60	—	—	Tuberculous broncho-pneumonia	Died 12 days later
65	52	M	4.75	5,000	800	4,100	—	100	—	—	Pulmonary tuberculosis	Numerous haemoptyses; died 20 days later
66	45	M	—	13,000	910	11,700	—	390	—	—	Severe sacro-iliac tuberculosis	Went home against advice and lost sight of
67	52	M	9.2	3,000	510	2,460	—	30	—	—	Pulmonary tuberculosis	Died 5 days later
68	25	M	—	6,000	600	5,220	60	60	—	—	Miliary tuberculosis	Died 2 months later
69	52	F	12.2	3,000	870	1,680	150	210	60	30	Infective hepatitis	Lymphopenia subsided as condition recovered
70	50	F	14.8	7,000	910	5,950	—	140	—	—	Obstructive jaundice; gall-stones	Recovered spontaneously; refused operation
71	69	F	14.5	9,000	630	8,100	90	180	—	—	Metastatic carcinoma of liver	Radical mastectomy 4 years previously, admitted with ascites: necropsy showed liver extensively invaded with metastases
72	68	M	4.75	3,000	660	2,100	60	180	—	—	Cirrhosis of liver	Haematemesis; recovered temporarily, but died 1 year later
73	14	M	11.8	2,850	740	2,024	—	86	—	—	,, ,, ,,	Ascites for some weeks. Died 1 month later

TABLE VII

GROUPS VIII, IX, AND X: THREE CASES OF RETENTION OF URINE; TWO PSYCHOGENIC CASES; TWO CASES OF LYMPHADENOPATHY

Case	Age	Sex	Hb (g.%)	Total W.B.C. (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.)	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
74	66	F	14.7	16,000	960	14,720	—	320	—	—	Cerebral thrombosis	Retention of urine; blood urea 68 mg.%: recovered
75	68	M	12.1	13,000	650	11,960	130	260	—	—	Prostatic hypertrophy	Retention of urine; blood urea 285 mg.%: discharged with a permanent suprapubic drainage
76	45	M	—	7,000	980	5,390	210	350	70	—	Disseminated sclerosis	Transient retention of urine with cystitis; subsided after treatment and discharged ambulant
77	23	F	14.8	4,000	1,000	2,840	—	80	—	80	Hysterical amnesia	No organic disease found
78	16	M	15.8	6,000	540	5,400	—	60	—	—	Anxiety state	Extensive investigation, but no organic disease found
79	52	F	8.9	11,000	660	9,900	110	330	—	—	Histiocytic medullary reticulosis (untreated)	Died within 7 days
80	43	M	12.2	2,800	560	2,072	—	168	—	—	Hodgkin's disease (untreated)	Died after a few months

TABLE VIII

SEVEN MISCELLANEOUS CASES

Case	Age	Sex	Hb (g.%)	Total W.B.C. (c.mm.)	Lymphocytes (c.mm.)	Neutrophils (c.mm.)	Eosinophils (c.mm.)	Monocytes (c.mm.)	Basophils (c.mm.)	Plasmocytes (c.mm.)	Diagnosis	Notes
81	17	F	5.0	500	455	10	—	—	—	15	Necrotic ileitis with *Bact. coli* septicaemia	Died on the day following admission. Cause of ileitis not found. 20 normoblasts included in total W.B.C.
82	23	M	—	20,000	1,000	18,000	—	1,000	—	—	Submaxillary abscess	Not severely ill; complete recovery with incision and sulphonamides
83	70	F	13.2	4,000	960	2,880	80	80	—	—	Cerebral thrombosis	Bedridden with hemiplegia for 3 weeks, slowly deteriorating
84	62	F	5.9	2,250	540	1,620	—	90	—	—	Sore tongue	Hypochromic anaemia, further clinical details not available (out-patient)
85	83	F	—	11,000	770	9,570	—	660	—	—	? Pericolitis	Further clinical details not available (out-patient)
86	53	F	14.2	2,900	841	1,972	29	58	—	—	Ulcerous stomatitis	,, ,, ,,
87	64	F	13.3	4,000	920	2,960	40	80	—	—	"Diarrhoea"	,, ,, ,,

Discussion

It appears that, although lymphopenia is sometimes associated with a poor prognosis, it is by no means invariably so. The commonest condition in which it occurred was cardiac failure, but this may be due partly to the high proportion of elderly patients with cardiac disease among the admissions to this hospital. Altana and Pulino (1947) have described the leucocyte picture in cases of heart disease, excluding as far as possible those cases complicated by chest or other infections. They express their counts as percentages only, but from their data the absolute values can be calculated, and it is then found that of 20 patients with well-compensated heart disease none showed lymphocyte counts of 1,000 or less; of 30 patients with a slight degree of congestion there were five with lymphopenia (17%); of 55 patients with severe congestion there were 17 with lymphopenia (31%); of 38 patients with left-sided cardiac failure and minimal venous congestion there were six with lymphopenia (16%); and of seven congenital malformations of the heart there were three with lymphopenia. In cases in the present series with pleural effusion repeated counts did seem to suggest that lymphopenia fluctuated with the presence of fluid in the chest, but in cases with cirrhosis of the liver it did not parallel the clinical condition. Case 72 had a normal lymphocyte count when almost moribund. In most of the cases in Groups II and III the prognosis was good, and in fact the only cases where lymphopenia gave a pointer to an ominous prognosis were those in Group VI. In other groups the prognosis depended on the primary disease.

The occurrence of lymphopenia in the lymphadenopathies has been noted by Robb-Smith (1947). The mechanism in these and in the blood diseases is presumably linked with the metabolic abnormalities of these disorders. The mechanism of its appearance in other conditions is more obscure and may be due to lymph stasis or the diminished production of lymphocytes. Wada (1940), having studied the lymphopenia of patients with uraemia and cholaemia, produced the condition experimentally in rabbits by inducing uraemia or cholaemia and related the blood findings to histological changes in the lymph nodes. He also found that removal of the rabbits' spleens exaggerated the lymphocyte depression. Another approach to some of the cases is provided by Selye's alarm reaction (1946) in which, during the phase of counter-shock, there is hypertrophy of the adrenal cortex and involution of lymphoid tissue. Reinhardt and Li (1945) have shown that administration of pituitary adrenotrophic hormone leads to a diminution of the lymphocytes entering the blood from the thoracic duct. Yoffey, Reiss, and Baxter (1946) have made further observations along the same lines.

Summary

Of 647 patients on whom routine blood counts were performed, 87 showed a lymphopenia of 1,000 per c.mm. or less at one time or another. The conditions with which this was associated have been analysed and the findings tabulated.

My thanks are due to my colleagues for making their case histories freely available to me, to Dr. C. Groves for valuable advice, and to Mrs. I. Gledhill for help in the collection of the records.

References

Altana, G., and Pulino, C. (1947). *Folia cardiol., Milano*, **6**, 193.
Reinhardt, W. O., and Li, C. H. (1945). *Science*, **101**, 360.
Robb-Smith, A. H. T. (1947). In *Recent Advances in Clinical Pathology*, ed. by Dyke, S. C., London.
Selye, H. (1946). *J. clin. Endocrinol.*, **6**, 117.
Wada, S. (1940). *Arb. med. Fak. Okayama*, **6**, 387.
Whitby, L. E. H., and Britton, C. J. C. (1946). *Disorders of the Blood*. London.
Wintrobe, M. M. (1939). *Bull. N. Y. Acad. Med.*, **15**, 223.
—— (1946). *Clinical Hematology*, 2nd ed. London.
Yoffey, J. M., Reiss, M., and Baxter, J. S. (1946). *Nature, Lond.*, **157**, 368.