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INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER), WITH
A REPORT OF TEN CASES.

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UNDER the term "akute sublymphoemische lymphomatosis," "glandular fever," "infectious mononucleosis" and "acute benign lymphoblastosis" there has been described a symptom-complex which, though not very common, is of sufficiently frequent occurrence to be of importance both from the practical and from the theoretical standpoint. The matters which are of practical importance have to deal with the diagnosis, the etiology and, should the disease prove to be an entity, with the mode of transmission and epidemiology; the matters of theoretical importance have to do with the classification of this symptom-complex and its relationship to other diseases of the lymphatic apparatus and most particularly to leukemia.

During the last few years it has happened that several acute infectious diseases which formerly were of comparatively rare occurrence and very imperfectly studied have assumed great importance by reason of the fact that they became epidemic. It is only necessary to call to mind in this connection poliomyelitis, encephalitis, influenza of course, and more recently a form of jaundice which has appeared in various parts of this country. The epidemics of these diseases serve to emphasize the fact that any acute infection is worthy of serious study and that every attempt should be made to add information about those which at the present time are imperfectly understood. It is for this reason that the following ten examples are presented of a disease or

symptom-complex which presents many perplexing features of interest.

In 1889, E. Pfeiffer¹ described a condition in children which he called "Drusenfieber," and which was characterized by a short febrile course accompanied by enlargement and tenderness of cervical lymph nodes. The disease occurred often in house epidemics. During the next fifteen to twenty years there were numerous references in literature to this condition of glandular fever, notably by Korsakoff,² Lublinski,³ Schlissner,⁴ Terflinger⁵ and Jones.⁶ In 1896, J. Park West⁷ reported an epidemic of 96 cases from eastern Ohio. The clinical descriptions in these older papers picture with considerable detail a febrile disease lasting nine to twenty-seven days, accompanied by an enlargement of the lymph nodes, especially those of the neck, but at times of all the superficial groups as well. In some instances there was abdominal tenderness and frequently the spleen and the liver were enlarged. Mention is sometimes made of the synchronous occurrence of infections of the upper respiratory tract, but frequently it is stated specifically that there was no accompanying tonsillitis. Recovery was the rule.

Unfortunately, in none of these reports is there any mention of the leukocyte count or of the condition of the blood, and though Tidy and Morley,⁸ who have recently reviewed the clinical aspect of this whole subject, regard the instances of glandular fever occurring in such epidemics as identical with the condition called today infectious mononucleosis, there is no proof that this identity exists.

The very unusual occurrence of a marked mononucleosis accompanying an acute infection has attracted from time to time the attention of several observers. Türk,⁹ in 1907, recorded 3 such cases that have frequently been alluded to in literature. One case with angina and glandular enlargement resembled an acute leukemia with recovery. Marchand¹⁰ recorded a similar case in 1913, and in the same year Cabot¹¹ reported 4 cases of acute local infections associated with lymphadenitis in which blood counts showed that the leukocytes varied from 9000 to 30,000 with a percentage of lymphocytes varying from 67 per cent to 82 per cent. A year later, in 1914, Hall¹² recorded an instance of what he believed to be acute leukemia with recovery. The disease occurred in a man, aged twenty-three years, and was characterized by fever, tonsillitis, enlargement of the lymph nodes and spleen, a leukocytosis reaching 35,000 with 89.6 per cent of mononuclear cells. There was complete and uneventful recovery. Deussing¹³ later reported 3 cases of diphtheria-like sore throat in boys associated with a lymphocytic reaction. In these cases also there was fever associated with enlargement of the lymph nodes and spleen and a leukocytosis varying from 11,000 to 19,400 with 52 to 87 per cent of mononuclear cells. Recovery occurred in all 3 instances. During the last year, Sprunt and Evans¹⁴ have reported under the term of infectious

mononucleosis 6 similar cases, all of which presented much the same clinical picture. Within the same year, Blaedorn and Houghton¹⁵ have described 4 cases which they term benign lymphoblastosis. Tidy and Morley 3 cases and Morse,¹⁶ under the term "glandular fever," 2 more cases. There are thus on record about 24 cases in which blood examinations have been made, though in only a few of these has any attempt been made to analyze accurately the blood picture or to investigate other important features of the disease.

It is, therefore, with an intent to add some information on these points that the following 10 cases are reported:

CASE I.—J. O. M., white, male, unmarried, aged twenty-two years. Medical student. First seen October 3, 1909. Febrile disease accompanied by enlargement of all lymph nodes, enlargement of the spleen and moderate mononucleosis. Recovery.

Complaint. Enlargement of lymph nodes.

Family History. Unimportant.

Personal History. Measles, scarlet fever, mumps, chickenpox as a child. Lived in North Carolina and had malaria every summer from the age of twelve to seventeen, for a period of a week or ten days with definite chills. Five years ago had pain in head with pus draining from nose and fever for one month. Last winter had "grippe" accompanied by headache and fever for four or five days. At this time leukocytes 16,000. Tonsillitis once or twice several years ago. Except for these illnesses physically strong athlete. Average weight 175 to 180 pounds.

Present Illness. About the middle of August, 1909, after getting water in ear from diving, noticed frontal headache, which later extended to top of head. He was slightly underweight. At this time fever every afternoon of 101° to 102° , at 3 or 4 o'clock. Three weeks after onset of fever, about September 4, all lymph nodes in body were enlarged to size of thumb nail. There was no sore throat, no digestive disturbances, diarrhea or cough. The fever persisted until September 16 and temperature has been normal since. After the middle of September, glands receded; he lost about 15 pounds in weight.

Physical Examination. Tall, well-built, muscular man. Throat was normal. No tenderness over frontal sinuses. All superficial lymph nodes were enlarged. Posterior cervical nodes visible and the size of beans; supraclavicular, the size of beans; axillary, the size of hazelnuts, firm, movable; epitrochlears were just palpable; the inguinal were the size of large beans. The lungs were clear. The heart was normal. The abdomen was flat; the spleen was readily palpable; the liver was not felt.

Course of Disease. By October 27 the patient had improved. The lymph nodes were smaller; the spleen could not be felt. On January 25, 1910, no abnormalities appeared in the physical exami-

nation. Seen again October, 1918, and found perfectly well; never had any further enlargement of lymph nodes, but two or three years ago had suffered with tuberculous pleurisy, from which he had completely recovered.

BLOOD COUNTS.

No.	Name.	Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono *	Lg. mono.	Bas.	Myelo. n.
I	J. O. M.	Oct. 3, '09	5,800,000	85	7500						
		Oct. 3, '09	4,846,000	75	6900	46.0	6.4	39.8	10.0	0.1	
		Oct. 27, '09	7200	52.4	1.2	35.2	10.0	0.4	...

* Owing to the difficulty of distinguishing many of the abnormal mononuclear cells from the small lymphocytes all of the cells have been classed together as small mononuclear cells.

Laboratory Examinations. During febrile period blood culture negative. Three injections of tuberculin negative. Wassermann reaction was negative.

CASE II.—P. F., male, white, unmarried, aged seventeen years. Student. Seen February 16, 1915. Subacute febrile disease with enlargement of lymph nodes and spleen, accompanied by nausea and giddiness, moderate mononucleosis. Recovery.

Complaint. Enlargement of lymph nodes.

Family History. Unimportant.

Personal History. Chickenpox, measles, mumps, whooping cough as a child. Jaundice at ten years of age. Mild scarlet fever at fourteen years.

Present Illness. On November 23, 1914, was feeling slightly under par, easily tired, had had occasional headaches with some giddiness. About December 9 he was occasionally nauseated. The temperature was 99.6°, the blood-pressure was 110/65. On December 10 he awoke with headache and chilly sensation and with a temperature of 101°. That afternoon the temperature rose to 102° and an irregular fever continued for three days, reaching normal on December 13. On December 16 the skin was clear, the lungs and heart were normal, the abdomen was soft, the spleen was felt just at the costal margin, the liver was not palpable. The cervical, axillary and inguinal lymph nodes were all palpable, the largest being the posterior auricular on the right side, which was about 1 cm. in length. These were quite soft and freely movable. The giddiness and enlargement of the lymph nodes continued.

Physical Examination. February 16, 1915 (summary): The patient was a nervous, overgrown, thin boy. The throat was normal. The lungs and heart were normal. The abdomen was soft. The spleen could be felt at the costal margin. The superficial lymph nodes were in the same condition as noted above. One lymph node in the left axilla was removed for microscopic examination.

Course of the Disease. The patient was placed on roentgen-ray treatment. From February 16 to 24 there was slight fever reaching 100° to 101° in the evening and 99° in the morning. After February 24 it became normal. The lymph nodes diminished in size. The eye-grounds were normal. On April 23, 1915, the patient was greatly improved, the lymph nodes having all disappeared. The spleen could not be felt. The patient gradually progressed to complete recovery.

BLOOD COUNTS.

Date.	H.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sma. mono.	L.g. mono.	Bas.	Myelo.	Uncl.
Oct. 16, '15	6300
Jan. 17, '16	4,000,000	85	...	51.0	3.0	37.0	9.0
Feb. 12, '16	5000	53.0	...	38.0	9.0
Apr. 23, '16	5200	65.0	11.0	17.3	5.7	1.0

Laboratory Examinations. On December 15 urine examination showed nothing abnormal. Sputum was negative for tubercle bacilli. No malarial parasites were found in the blood. Diazo reaction was negative. Later repeated examinations of the urine and sputum showed nothing abnormal. Roentgen ray on December 10 showed lungs clear, some increase in oval root shadow suggesting lymph node. The Widal reaction was negative. Microscopic examination of the lymph node excised was as follows: "This on section shows almost complete loss of the normal structure. There is marked lymphoid hyperplasia, while the germinal centers show karyorrhexis and karyokinetic nuclei. In the lymph spaces between the cords there is active proliferation of the epithelioid cells of the reticulum with formation occasionally of large uninuclear cells almost of giant size. A few of these large epithelioid cells are also mixed in with the cells in the lymph cords. Occasionally an eosinophilic leukocyte is seen. Picture suggests very strongly Hodgkin's disease, though one would scarcely dare to make a definite positive diagnosis. It seems advisable, however, to treat the case as such."

CASE III. G. E. (No. 15721), white woman, widow, aged thirty years, housewife. Admitted to the Presbyterian Hospital, July 29, 1915; discharged November 1, 1915. Acute febrile disease of forty-four days' duration, chills, sore throat, enlarged lymph nodes and spleen, moderate mononucleosis. Recovery.

Complaint. Headaches and fever of five days' duration.

Family History. Unimportant.

Personal History. Works as typist. Husband died two years ago. She was married at nineteen and had one child living and

well; there were no miscarriages. She had had measles and pertussis in early childhood; scarlet fever at twelve years. Two years ago she had had an operation on the nose for deafness in the right ear. There was no history of rheumatic fever, pneumonia or typhoid fever.

Present Illness. Five days ago she developed sore throat with cough and pain on swallowing. That evening she had a sudden chill followed by high fever. The fever continued. Headaches and stiffness in the back developed; she had eruptions and vomited on the morning of admission. She had continued at work until the day of admission.

Physical Examination. Well-nourished, acutely ill young woman. There was no dyspnea. Over the chest and abdomen were scattered pink papules and a few macules resembling rose spots. The patient was very deaf. The tongue was dry. There were several decayed teeth and moderate pyorrhea. The pharynx was very red; the thyroid gland was palpable. The lungs were clear. The heart was normal except for an occasional premature contraction. The pulse was 100. The blood-pressure was 126/72. The abdomen was full; the liver was not palpable. The spleen was just palpable. The extremities were normal. The temperature was 105.3°. Typhoid fever was suspected as a provisional diagnosis.

Course of the Disease. For two weeks after admission the temperature remained constantly between 101° and 103°. The lungs remained clear. The spleen increased slightly in size. No further eruption suggestive of rose spots appeared. There was only moderate prostration. On August 14, 1915, a small lymph node was noticed behind and anteriorly to each ear and a swollen tender node was found on the right side of the neck. On August 15 there was general enlargement of the lymph nodes of both posterior and anterior triangles, the largest being the size of a hickory nut beneath the angle of the right jaw. They were all discrete, firm, movable, somewhat tender. The epitrochlears were not felt. On August 18 the fundi were normal. The left ear drum was normal. The right ear drum was sclerosed and retracted. On August 23 a lymph node was removed for microscopic examination. By August 27 the nodes had somewhat diminished in size. The temperature was lower and did not rise above 100°. By September 4 the spleen was slightly enlarged and hard. The lymph nodes had practically disappeared except one in the right cervical region, which remained enlarged and firm. The patient rapidly improved and went on to complete recovery. The pulse varied during the course of the disease between 70 and 100.

An examination of the mononuclear cells in the blood on September 10 showed that they did not give an oxidase reaction. No malaria organisms were found (Fig. 1).

BLOOD COUNTS.

Date.	R. h.c.	Hb.	W. h.c.	Poly. n.	Poly. eos.	Ser. mono.	Lt. mono.	Bas.	Myelo.	Uncl.
July 30, '15	...	8.5	3,400	56.0	1.0	41.0	2.0			
July 31, '15	3,400	60.0	...	38.0	2.0			
Aug. 3, '15	5,400	54.0	...	43.0	3.0			
Aug. 9, '15	9,800	44.0	...	56.0				
Aug. 15, '15	5,616,000	81	8,800	28.0	1.0	71.0				
Aug. 26, '15	7,800	28.0	4.0	68.0				
Sept. 10, '15	7,600	35.0	1.0	63.0	1.0			
Nov. 1, '15	11,100	37.0	...	61.0	2.0			

Laboratory Examinations. On July 31 blood culture gave no growth. The Wassermann reaction was negative and the Widal reaction was negative. On August 7 the Widal reaction was again negative. The blood culture showed contaminating growth of bacteria. On August 8 bacterial examination of stool showed no

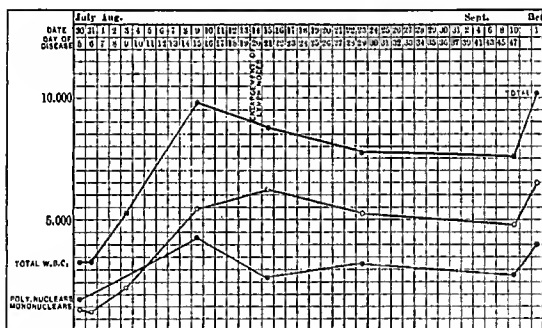


FIG. 1.—Case III. Chart showing changes in total number of white blood cells (upper line). Absolute number of mononuclear cells ("—") and absolute number of granular cells ("—").

typhoid bacilli. On August 9 cultures of urine were sterile. On August 20 blood culture was sterile, Widal reaction negative. On August 27 cultures from urine showed no typhoid bacilli. On August 29 cultures from stool showed no typhoid bacilli. On September 10 von Pirquet reaction was negative. The urine was usually acid, varied from 1014 to 1024, contained constantly a faint trace of albumin; the sediment showed epithelial cells and leukocytes.

CASE IV.—E. S., white, male, unmarried, aged twenty-one years, medical student. Admitted to the Presbyterian Hospital, April 14, 1916; discharged April 24, 1916. Acute febrile disease, ushered

in by acute tonsillitis, followed by chilly sensations, fever, profuse perspiration, marked enlargement of lymph nodes and spleen and marked mononucleosis. Recovery.

Complaint. Sore throat, one week's duration.

Family History. Unimportant.

Personal History. Measles as child; no scarlet fever nor diphtheria. Had been subject to sore throat (once a year) and had had one bad attack of tonsillitis. Stated that tonsils had been removed at age of nine or ten. Denied venereal infection. Had had antityphoid inoculations two years previously. Had usually had excellent health. Best weight, 150 pounds.

Present Illness. Two weeks before admission he had a cold in his head but was not ill; he suffered no constitutional disturbances. Seven days before admission had had severe headache and sore throat with chilly sensations next day and fever varying from normal to 102°. Had been at work; felt very badly; had had profuse perspiration. Appetite was poor. There was no nausea, vomiting, diarrhea nor cough.

Physical Examination. Well-developed young man, acutely ill. Right tonsil was largely absent; left tonsil was regular, swollen, very large, red and showed exudates in the crypts. The entire pharynx was red and the lymphoid tissue was swollen. The lungs and heart were normal. The pulse was 100; the blood-pressure was 124/60. The abdomen was full, the spleen was readily palpable 2 cm. below the costal margin, and the liver edge was palpable at the costal margin. The lymph nodes were all much enlarged and tender. The submental and cervical lymph nodes were the largest and were firm and movable. The posterior cervical, axillary, supraclavicular and inguinal nodes were all moderately enlarged and firm.

Course of the Disease. On April 17 the spleen reached 4.5 cm. below the costal margin. The lymph nodes were somewhat smaller. The throat was still much swollen and red. The disk of the right fundus was normal. The disk in the left fundus showed a hazy margin. On April 20 the lymph nodes remained about the same; the spleen was somewhat smaller but it was palpable below the costal margin. On April 24 the throat was still swollen and the cervical lymph nodes were large. The spleen was still palpable. The temperature varied between 100° and 102.5°, falling to normal on April 21. The pulse ranged between 80 and 100. The patient rapidly improved and went on to complete recovery. On November 23, 1916, he was in splendid condition; the tonsils had been completely removed. The cervical lymph nodes were just palpable. The axillary, inguinal and femoral nodes were the size of dried beans. The epitrochlears were just palpable. Both the liver and the spleen could just be felt. On October 28, 1919, the patient had remained in perfect health and for months neither the spleen nor lymph nodes had been palpable.

BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
Apr. 14, '16	...	85	8,800	30.0	...	30.0				
Apr. 15, '16	3,800,000	81	11,200	18.0	...	82.0				
Apr. 16, '16	14,800	8.0	...	92.0				
Apr. 17, '16	18,000	6.0	...	94.0				
Apr. 18, '16	23,000	5.0	...	95.0				
Apr. 19, '16	25,200	6.0	...	94.0				
Apr. 20, '16	24,400	10.0	...	90.0				
Apr. 21, '16	5,200,000	...	20,200	8.0	...	92.0				
Apr. 22, '16	5,400,000	...	19,200	0.0	...	91.0				
Apr. 23, '16	18,000	12.0	...	88.0				
Apr. 24, '16	17,500				
Nov. 28, '18	5,000,000	...	7,500	70.0	...	26.0		4.0
Oct. 27, '19	70.0	1.0	28.0	1.0			

A large proportion of the mononuclear cells were somewhat larger than the small lymphocytes; they possessed round, oval or lobulated nuclei, surrounded by a varying rim of basophilic protoplasm which did not contain granules. There were also cells typical of the normal small lymphocyte and a few cells could not be differentiated from large mononuclear cells. Stains for oxidase granules on April 20 showed only 1 to 2 per cent of the cells which possessed these granules (Fig. 2).

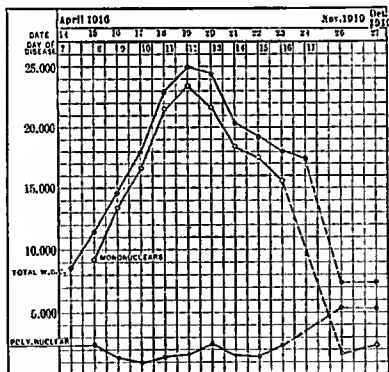


FIG. 2.—Case IV. Chart showing changes in total number of white blood cells (upper line) and in absolute number of mononuclear cells (—) and of granular cells (lower line —).

Laboratory Examinations. On April 15 blood culture showed no growth; throat culture showed no diphtheria bacilli; staphylococci predominated in culture. On April 16 the Widal reaction was

negative. April 17 the blood culture showed again no growth. On April 18 smears from the tonsils showed the predominating organisms to be lanceolate diplococci. There were also fusiform bacilli, spiral organisms and a few large Gram-positive diplococci. April 21, blood culture showed no growth. Throat culture showed *Staphylococcus aureus* and nonhemolytic streptococci.

CASE V.—T. P., white, male, unmarried, aged twenty-one years, student. Admitted to the Presbyterian Hospital, January 22, 1917; discharged, February 7, 1917. Acute febrile disease with enlargement of the lymph nodes and spleen; moderate mononucleosis. Recovery.

Complaint. Fever and malaise.

Family History. Unimportant.

Personal History. Measles, croup and scarlet fever as a child. Tonsillitis in summer and fall of 1910; tonsillectomy September, 1910. Occasional attacks of appendicitis with appendectomy in March, 1914. Colds in head during November, 1916. Denies venereal infection. Best weight, 145 pounds.

Present Illness. Gradual onset over a period of a week with continuous headaches, evening temperature reaching 101.8° at times; there was pain in the eyes, occasional slight cough without expectoration and general malaise, anorexia, and constipation. With the onset of fever the patient noticed enlargement of lymph nodes in the cervical and inguinal regions which had never occurred before.

Physical Examination. Well-built young man not very ill. The tonsils were absent. There was enlargement of the lymphoid tissue on the posterior pharyngeal wall. The lungs and heart were normal. The abdomen was soft, not tender; the edge of the spleen was easily felt; the liver was not palpable. The superficial lymph nodes were practically all enlarged. The posterior cervical nodes on both sides were quite large; the anterior cervical nodes were not so large except for one solitary submental node on the right side about the size of a lima bean. The supraclavicular nodes on the right side were slightly enlarged. The axillary and inguinal nodes were enlarged. The epitrochlears were not felt. All the nodes varied from the size of a pea to that of a lima bean, were discrete, firm, movable and not tender.

Course of the Disease. From January 22 to the 31st there was slight fever varying from 99.2° to 100.3° with one rise to 102.3° . On January 26 the fundi were normal, the posterior cervical lymph nodes were somewhat larger and tender on pressure, firm, isolated, freely movable; the submental and axillary nodes were unchanged; the inguinal and femoral nodes had increased slightly in size; the tip of the spleen was just palpable. By February 7 all the lymph nodes had diminished in size and the spleen was no longer palpable.

There was uncomplicated convalescence and recovery. On October 26, 1919, the patient was well. He had been in France on active service, had been gassed and had had influenza. At this time there was no enlargement of the lymph nodes; the spleen was not palpable. The heart and lungs were normal.

BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
Jan. 22, '17	10,700	25.0	1.0	67.0	6.0	1.0		
Jan. 23, '17	20.0	...	72.0	1.5	3.5	1.5	
Jan. 24, '17	0,700	27.5	0.5	56.5	5.0	1.0	1.0	8.5
Jan. 26, '17	4,530,000	90
Jan. 29, '17	8,250	43.0	...	52.0	5.0
Feb. 7, '17	8,750	42.0	3.0	47.5	5.0	...	1.0	...

A large proportion of the mononuclear cells were abnormal in appearance, being larger than the small mononuclear lymphocytes, showing a round, oval or lobulated nucleus; a few cells contained nucleoli. The protoplasm varied in width; usually took a basophilic stain and showed no granules. There were also cells indistinguishable from the normal small lymphocyte and from the large mononuclear cells. On January 24, 56 per cent of these mononuclears did not contain oxidase granules; 36 per cent of the polymorphonuclear cells did contain oxidase granules.

Laboratory Examinations. January 23, blood culture gave no growth of bacteria. The Wassermann reaction was negative in both antigens. The Widal reaction was negative. The urine culture showed no growth. Complement-fixation test for tubercle bacilli was negative. January 24, roentgen-rays of the lungs showed nothing abnormal. January 26 and 27, sputum showed no tubercle bacilli. January 30, von Pirquet reaction was questionably positive in seventy-two hours. Urine showed specific gravity 1020, acid, amber, no albumin nor glucose, no casts.

CASE VI.—A. B., colored boy. Admitted to the Presbyterian Hospital, February 6, 1917; discharged, February 23, 1917. Acute febrile disease with enlargement of lymph nodes, spleen and liver, and marked mononucleosis. Recovery.

Complaint. Cough, enlarged glands and night sweats of one month's duration.

Family History. Mother is said to have tumor of abdomen; otherwise unimportant.

Personal History. At the age of three years measles complicated with pneumonia. Had had attacks of tonsillitis and frequent colds. Tonsils and adenoids removed three months ago.

Present Illness. Cough for one month with enlargement of lymph nodes, night sweats and loss of weight amounting to 11 pounds in the last month.

Physical Examination. Well-developed colored boy. The tonsils were absent. The mucous membrane of the mouth and throat was very red. There were several decayed teeth. The lungs were normal. The heart was normal in size and position. There was a systolic murmur at the apex not transmitted. The abdomen was soft, not tender. Both the liver and spleen were palpable.

Courses of the Disease. Until February 16 the pulse, respiration and temperature were normal. On February 16 the temperature rose to 101° and the lymph nodes increased in size and became tender. The pharynx was red and swollen. The patient progressed to convalescence. On February 23 he developed chickenpox and was removed to another hospital. Later the carious teeth were removed and the remaining lymphoid tissue resected from the pharynx. On October 18, 1919, he was again admitted to the hospital, where he suffered an attack of typhoid fever, at which time typhoid bacilli were grown from blood culture. There was no pathologic enlargement of the lymph nodes at this time.

BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Nas.	Myelo.	Uncl.
Feb. 7, '17	20,600	60.0	...	30.0	30.0	1.0		
Feb. 8, '17	26,300	41.0	4.0	50.0	4.0			
Feb. 12, '17	14,100							

October 21, 1919, the coagulation time of the blood was twelve and a half minutes; the control was three minutes. The bleeding time was two minutes ten seconds; the control was one minute and five seconds.

Laboratory Examinations. On February 7, 1917, von Pirquet was negative. Roentgenogram of the lungs showed nothing abnormal. Cultures from the throat showed no diphtheria bacilli. On February 15 the Wassermann reaction was negative in both antigens. The urine showed a specific gravity of 1020, acid, no albumin nor glucose, no casts.

CASE VII.—S. M., white youth, aged thirteen years, choir boy. Admitted to the Presbyterian Hospital, June 13, 1917; discharged, June 18, 1917. Acute febrile disease, enlargement of lymph nodes and spleen, well-marked lymphocytosis. Recovery.

Complaint. Enlarged glands in neck of two weeks' duration.

Family History. Unimportant, except that his mother three years ago had had angioneurotic edema lasting one year.

Previous History. Measles and mumps on the right side, pertussis, chickenpox. He had been subject to colds and described two abscesses in the ears. A few years ago adenoids and tonsils were removed on account of occasional sore throat. No scarlet fever nor diphtheria. Best weight, 105 pounds. No previous glandular enlargement noted. On November 14, 1913, he had been examined at school and found normal.

Present Illness. Two weeks before admission he had accidentally noticed some glands in the neck. At the same time he had a slight fever reaching 101° at night and 99° in the morning, lasting from June 1 to June 11. On June 7 the temperature was 101.8°. On June 10 and 11 his physician had made leukocyte counts which are recorded below.

Physical Examination. On admission (summary): Temperature normal; pulse 60. The patient was a well-developed boy. The color was good. There were no eruptions. The throat showed nothing except some lymphoid tissue which remained in the right tonsillar fossa. The lymph nodes beneath the upper part of the sternomastoid on both sides of the neck were enlarged and readily palpable. There were also many shotty lymph nodes in the anterior and posterior triangles of the neck on both sides. The axillary, epitrochlear and inguinal lymph nodes were palpable but not definitely enlarged. The lungs were normal. The heart was of normal size; there was a loud systolic murmur at the apex with a marked sinus arrhythmia. The abdomen was soft; the spleen was easily felt 2 cm. below the costal margin. The reflexes were normal.

Course of the Disease. The temperature remained normal. By June 16 the patient was up and about the ward. The lymph nodes were definitely diminished in size but were still large, though not tender. By June 18 the spleen was smaller and the patient felt perfectly well. The enlargement of the cervical lymph nodes had decreased somewhat. Two oblong glands at the angle of the jaw were the largest. They were about 2 cm. long and 1 cm. wide, firm, movable but not tender. He left the hospital on June 18. On July 20 he was seen by Dr. Neergaard, who noted that all the lymph nodes in the neck were still palpable. On October 3, 1919, the patient had grown considerably and looked and seemed very well. All the superficial lymph nodes were still palpable. The spleen could not be felt.

BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
June 10, '17	...	85	16,000							
June 11, '17	...	85	15,266	10.0	1.0	76.0	13.0			
June 14, '17	5,200,000	85	9,200	3.0	...	90.0	6.0	...	1.0	
June 16, '17	8,600	13.5	...	73.0	13.5			
Oct. 3, '19	5,304,000	99	9,000	40.0	...	37.0	14.0			

June 14, 1917, blood group I, mononuclear cells (Hastings's stain) appeared from one-fourth to one-half as large again as the red blood cells, with large deeply staining nuclei; most of the cells have a narrow rim of basophilic cytoplasm without granules. Examination of the smear made on June 15 showed the following appearance: Mononuclear cells were of two or possibly three varieties:

I. Cells which could not be differentiated from the normal small lymphocytes of the blood.

II. Cells larger in size than the small lymphocyte with oval, kidney-shaped or slightly lobulated nucleus staining fairly deeply in Wright's stain, without definite nucleoli, usually eccentrically placed and surrounded by a fair amount of basophilic protoplasm of a general ground-glass appearance. The protoplasm of these cells did not contain definite granules.

III. Cells larger than type II and indistinguishable from the normal large mononuclear cells. Cells of type II predominated.

June 14, cells of type II were still predominating.

June 16, cells of type II were much less numerous, cells of type I predominating. None of the mononuclear cells contained oxidase granules.

Röntgen-ray of the lungs showed nothing abnormal. Urine varied in specific gravity from 1025 to 1030, acid, amber, and on one occasion showed a faint trace of albumin; no glucose; occasional leukocytes were found. The tuberculin reaction was negative.

CASE VIII.—F. de A. (No. 34874), Italian girl, unmarried, aged twelve years, school. Admitted to the Presbyterian Hospital, December 13, 1920; discharged, January 6, 1921. Febrile disease with moderate fever, accompanied by slight enlargement of the lymph nodes, moderate lymphocytosis, cardiac arrhythmia with premature contractions, abdominal pain, vomiting and constipation. Recovery.

Complaint. Pain in right side of abdomen of five days' duration.

Family History. Unimportant.

Previous History. She had had pneumonia, measles and an attack of diarrhea in infancy and had had frequent attacks of tonsillitis accompanied by fever and often by nausea, vomiting and constipation. During the summer of 1920 she had pain in the right shoulder for about one month without fever. No other evidence of rheumatic fever. No scarlet fever or diphtheria. Menses began at eleven years and six months, regular and profuse.

Present Illness. November 24, 1920; tonsillectomy was performed. Since then she had had intermittent fever with considerable malaise, constipation and vomiting at times. Five days ago she began to have abdominal pains, at times confined to the right side. Usually the pain was dull but during the last few days it had

been cramplike, coming on about every three hours accompanied by vomiting. Five days ago small pink spots appeared over entire body and extremities gradually increasing to large swollen areas, which disappeared.

Physical Examination. (Summary.) The patient was a well-nourished white girl, rather overdeveloped for her age. There was considerable pigmentation about the eyes. The lips and mucous membranes were slightly pale; there was no icterus. Over the abdomen there was a macular eruption of irregular, small, dull red spots. This did not itch. The tonsillar pillars and fossae were slightly hyperemic. The submaxillary lymph nodes were definitely enlarged, firm but not tender. The posterior cervical lymph nodes were small but tender. The axillary and inguinal lymph nodes were moderately enlarged but not tender. The lungs were clear. The heart was not enlarged. The pulse was 78. There was a soft blowing systolic murmur heard best at the apex; some accentuation of the second pulmonic sound; occasional premature contractions. The abdomen was soft. There was tenderness in the right lower quadrant. There was some voluntary spasm of the muscles. The liver and spleen were not palpable.

Course of the Disease. From the day of admission to December 31 the patient had an irregular fever varying from 97.8° to 101° and 102°. The pulse varied from 78 to 110. On December 17 the premature contractions persisted. On December 21, though she had been running a constant low fever, she felt perfectly well. There was no cough. The abdominal pain had disappeared and there were no night sweats. The lymph nodes remained persistently large and tender. By January 13 she had been well enough to go to school for several days. The posterior cervical lymph nodes were the size of beans, the submaxillary, anterior cervical and supraclavicular were the size of peas to beans; the axillary and epitrochlears were not definitely palpable. The inguinal and femoral nodes were just palpable. There was a loud systolic murmur at the pulmonic area. The spleen and liver were not palpable. On February 3 the lymph nodes were smaller but all were still palpable. By April 17 all the superficial lymph nodes could be felt but with difficulty.

BLOOD EXAMINATIONS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	L.g. mono.	Bns.	Myelo.	Und.
Dec. 16, '20	7,140,000	80	12,800	38.0	1.0	15.0	45.0			
Dec. 20, '20	3,800,000	68	12,800	21.0	4.0	60.0	15.0			
Jan. 13, '21	13,300	45.4	2.0	44.4	5.0	...	0.4	2.8
Jan. 21, '21	4,884,000	79	11,760	60.0	2.0	37.0	1.0			
Apr. 7, '21	0,200	65.7	2.0	23.0	7.7	1.6

The mononuclear cells were somewhat larger than the small lymphocytes and contained a round, oval or lobulated nucleus surrounded by a rather narrow zone of protoplasm which was basophilic. This type of cell predominated among the mononuclears.

Laboratory Examinations. December 13, 1920: An electrocardiogram showed rate of 125. A-V interval, 0.14 to 0.16. Ventricular premature contractions. T inverted. Blood culture gave no growth. Wassermann reaction was negative with both alcoholic and cholesterol antigens. The Widal reaction was negative. December 16, stool was soft, brown, guaiac reaction was negative for occult blood. December 22, blood culture again showed no growth of bacteria. December 31, roentgen-ray of the lungs showed slight accentuation of the linear markings of the right lung.

CASE IX.—E. C. (No. 50373), white, male, unmarried, aged twenty-eight years, physician. Admitted to the Presbyterian Hospital, May 27, 1919; discharged June 17, 1919. Acute febrile disease associated with chills, sweating, severe pharyngitis, enlargement of lymph nodes and spleen, marked lymphocytosis.

Complaint. General malaise for seven days, intermittent chills and fever.

Family History. Unimportant.

Previous History. The patient had always been healthy. He had had an appendectomy and two years ago tonsillectomy performed. In January, 1920, he had a suppurating abscess of the left tonsillar fossa from which creamy pus was evacuated.

Present Illness. The patient was perfectly well until a week ago, when he felt so chilly that he wore his overcoat. His temperature ranged between 99° and 100°. The next day there were vague aching sensations; the throat was red and sore. That evening the temperature was 101°. During the night he had a drenching sweat. He continued to feel badly. He had frequent chills lasting about one and a half minutes followed by fever of 102°, severe headache and drenching night sweats. He had had anorexia and irregular severe frontal and occipital headache. Since May 27 there had been no further chills. The eyeballs had been tender. The throat had been increasingly sore and he had had a little cough, with no sputum, epistaxis, no hemoptysis, no pain in the chest.

Physical Examination. The patient was a well-nourished well-developed man, with a flushed and feverish appearance, looking acutely ill, sweating slightly. The temperature was 100.4°; the pulse was 100. The conjunctivæ were deeply injected. Ear drums showed some redness. Buccal mucous membrane showed fine petechiæ along the line of closure of the teeth. The tonsils were not seen. The pharynx and soft palate were bright red and showed patches of dirty yellow exudate scattered over them. There was a

sharply raised red edge on the soft palate. A surgical scar on the left side of the neck was visible. The lungs were normal. The heart was normal in size and there were no murmurs. The pulse was regular, the rate was 96. The blood-pressure was 115/74. The abdomen was not tender. The liver dullness came to the costal margin. The liver was not palpable. The spleen was easily palpable, soft, slightly tender, descending 6 cm. below the costal margin. The reflexes were normal. The lymph nodes were definitely and generally enlarged. The left submaxillary nodes were large and tender. The posterior and anterior cervical group, particularly on the left, were definitely enlarged and tender. There was less enlargement on the right. The epitrochlears were enlarged and the left was $\frac{1}{2}$ cm. in diameter. One left axillary lymph node was 1 cm. in diameter. The inguinal nodes were not enlarged.

Course of the Disease. The condition remained about the same until June 2, with persistence of marked swelling, reddening and enlargement of the lymphoid tissue of the pharynx over which the exudate remained, and of the enlargement of the lymph nodes, irregular fever and drenching sweats. The voice became quite nasal. On June 2 he was better, fauces were less swollen, redness was disappearing, the lymph nodes showed decrease in size, tenderness of the spleen disappeared with diminution of size so that it was just palpable at the costal margin. By June 5 the temperature was normal. The throat had improved greatly. The lymph nodes were still palpable. The spleen could be felt 4 cm. below the costal margin. On discharge he looked and seemed well except for slight redness of the throat. The lymph nodes had diminished greatly in size, a few the size of peas were felt in the posterior cervical region. The left axillary and epitrochlears were just palpable. None were tender. The spleen could be felt only with difficulty. By July 26, 1921, the lymph nodes were no longer palpable except for a few in the axilla. The spleen could not be felt. Recovery was complete.

BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
May 23, '21	7,500	56.0
May 27, '21	0,044,000	130	10,700	25.0	...	68.0	6.0	1.0
May 28, '21	10,200	33.0	...	66.0	1.0
May 29, '21	13,000	24.0	...	75.0
May 30, '21	15,400	24.0	...	76.0
May 31, '21	13,320	21.0	...	70.0
June 2, '21	15,400	20.0	...	80.0
June 3, '21	16,800	10.0	...	81.0
June 4, '21	12,600	20.0	...	70.0	4.0
June 6, '21	14,700	35.0	...	63.0	...	2.0
June 7, '21	15,300	21.0	1.0	76.0	2.0
June 8, '21	14,600	20.0	...	71.0
June 13, '21	11,900	30.0	...	66.0	4.0
June 18, '21	10,600	32.0	...	68.0
July 26, '21	0,848,000	120	5,920	54.0	...	42.0	4.0

On May 27 the leukocytes were moderately increased. The predominating cell was a moderate size mononuclear cell with a clear robin blue cytoplasm containing in many cases a few azurophil granules. The nuclei were round or oval. In addition there were considerable numbers of abnormal mononuclear cells somewhat larger than the normal lymphocyte and showing a more deeply staining basophilic cytoplasm, occasionally containing vacuoles. The nuclei of these cells were of the Rieder type. On May 28 there were considerable numbers of broken cells and "basket cells" in the smears. On May 29 an oxidase stain showed that the mononuclear elements of the blood did not contain oxidase granules. The abnormal mononuclears, which varied considerably in size, were more numerous than on the previous examinations.

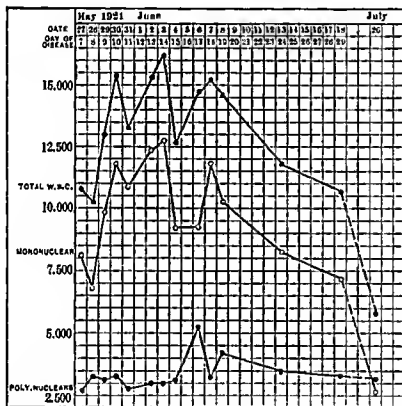


FIG. 3.—Case IX. Chart showing changes in total number of white blood cells (upper line). Absolute number of mononuclear cells (—○—) and of granular cells (lower line —○—).

Laboratory Examinations. On May 27 the blood culture gave no growth of bacteria. The Wassermann reaction was negative to both antigens. The Widal reaction was positive up to 1 to 40 and 1 to 80. On May 28, roentgen-rays of the lungs showed nothing abnormal. On May 30 smears from exudate and throat showed a few Gram-negative spirilla and many varieties of cocci and bacilli, none of which seemed to predominate. Blood agar plates were streaked and culture gave *Streptococcus viridans* and *Micrococcus catarrhalis*. On June 3 smears from the throat showed numerous cocci and bacilli, fusiform bacilli and spirilla of Vincent. Aerobic cultures showed no growth for pathogenic organisms. The urine

examinations showed specific gravity varying from 1018 to 1030, acid in reaction, amber. On May 24 a very faint trace of albumin, none afterward, no glucose. Microscopically there were no casts.

CASE X.—P. A., white youth, aged fifteen years, school-boy. Admitted to the Bellevue Hospital, March 6, 1922; discharged, March 23, 1922. Acute febrile disease, associated with tonsillitis, general enlargement of lymph nodes, marked mononucleosis. Recovery.

Complaint. Sore throat and swelling of right side of neck.

Family History. One sister has rheumatism and heart trouble, otherwise unimportant.

Personal History. Measles and whooping cough at two years, chickenpox at five years. Five or six years ago noticed swelling of glands in the neck and beneath the jaw during colds. Had had occasional sore throats which were not severe. Last year he had trouble with his ears and the right drum was incised.

Present Illness. Ten days to two weeks ago he had a cold in his head, earache on the right side and a spontaneous discharge from the right ear which he thought had been present for a week before admission. Four days before admission the right side of the neck began to swell, fever increased. There was no pain except when he touched the swellings. The left side of neck also became slightly swollen, but he paid no attention to it because this occurred every winter when he had colds.

Physical Examination. Adolescent boy, did not appear very ill, rather thin, somewhat pale, temperature on admission, 102.8°. There was no discharge from the right ear. The pharynx was deeply congested, the tonsils enlarged and red; there was no exudate. The lungs and heart were normal. The pulse was 110. The abdomen was soft; the liver and spleen were not palpable. Practically all the superficial lymph nodes were enlarged. Those in the posterior cervical triangle were largest, the one on the right side being visible, the size of an egg; the posterior cervical nodes and those in the anterior triangle were smaller. The right axillary nodes were much enlarged; the inguinal and femoral were the size of almonds. The right epitrochlear was the size of a bean.

Course of the Disease. On March 7 the tonsils increased in size and pus could be expressed from them. The temperature varied between 101° and 104° until March 17; the pulse between 120 and 128; the respirations between 24 and 26. The boy seemed acutely ill and rather severely prostrated. On March 16 the tonsils were still much enlarged, red and edematous. The lymph nodes, many of which were visible in the neck, averaged from 2 to 3 cm. in length to the size of a pea. The spleen and liver could not be felt. On March 17 the temperature ranged between 99.6° and 101°, and on March 18 the temperature was normal and from that time there

was uncomplicated convalescence. On March 22 the tonsils had diminished in size, they were still large and irregular, were only slightly red and the edema had disappeared. The lymph nodes in the posterior triangle of the neck were still visible, 1 to 2 cm. in length; the inguinal and femorals were 1 to 2 cm. The spleen and liver were not palpable.

BLOOD COUNTS.

No.	Name.	Date.	R.b.c.	Hb.	W.b.c.	Poly. n., per cent.	Poly. eos.	Sm. mono., per cent.	Lg. mono., per cent.
X	P. A.	Mar. 8, '22	15,400	16	...	84.0	
X	"	Mar. 10, '22	20	...	76.0	
X	"	Mar. 16, '22	16,500	27	...	71.4	1.6
X	"	Mar. 22, '22	8,000	33	...	53.0	14.0

Smears stained with Hastings's stain showed predominating mononuclear cells, which were somewhat larger than the normal lymphocyte, round or oval, had a rather deeply staining round, oval or lobulated nucleus without nuclei. Protoplasm varied slightly in amount, took a moderately deep basophilic stain and had a ground-glass appearance, but showed no granules. There were moderate numbers of cells which were indistinguishable from the small lymphocyte and a very few mononuclear cells that were identical with the large mononuclear cells in normal blood.

Laboratory Examinations. Blood culture showed no growth. March 10 and 22 throat culture showed no diphtheria bacilli, but *Staphylococcus albus*, and in the smears Vincent's spirilla were observed. On March 15 smears from the throat showed spirilla and fusiform bacilli. Cultures gave streptococcus in long chains.

An analysis of these 10 cases shows that the disease occurred twice in females and eight times in males. All of the patients were under thirty years of age. Two of them were medical students and one was a doctor. The onset was, as a rule, somewhat gradual. Headache occurred in 3 cases, fever in 9, sore throat and chills in 5, cough in 3, malaise in 3, sweating in 3 and abdominal pain and vomiting in 2. During the onset enlarged nodes were observed only four times by the patients; in 1 case enlargement of the cervical lymph nodes was the first symptom noted. The disease had usually existed for at least a week before the patient was first examined. Most of the patients appeared to be very uncomfortable when they were first seen and complained particularly of the moderate fever and sweats and soreness of the pharynx or tonsillitis. In 1 case the onset was preceded by an acute otitis media. In 3 cases the tonsils were swollen, red and acutely inflamed. In 2 other cases in which the tonsils had been previously removed the lymphoid tissue

of the pharynx was swollen and the pharynx was red. In 1 case the pharynx alone was red and in one instance the disease came on after tonsillectomy. In the 2 women a faint red macular rash was observed over the abdomen on the first examination.

In all but 1 case a striking feature of the first examination was the noticeable enlargement of the superficial lymph nodes. In this 1 case the cervical lymph-node enlargement did not appear until the second week of fever. In all instances eventually the cervical lymph nodes were enlarged, felt rather firm and were tender to touch. They varied from the size of beans to a hickory nut and in most cases averaged about 1 cm. in diameter. The submental nodes were usually the largest, but both anterior and posterior cervical chains were involved. In 3 cases the enlargement extended to all the superficial nodes except the epitrochlears, and in 5 cases all the nodes, including the epitrochlears, were involved. In a few instances the enlargement was very marked and in 1 case the epitrochlears measured 1.5 cm. in length.

During the increment of the lymph nodes the fever continued and in most cases it reached for a few days 101° to 103° , being irregular and of intermittent type with diurnal rise and fall. The fever lasted from three days to about three weeks, but continued approximately for from two to three weeks in 7 of the cases.

During the course of the disease in 8 of the 10 cases the spleen became palpable and sometimes tender. The liver was palpable in one instance. Sweating was common and was in a few cases a disagreeable feature. The pulse varied from 80 to 100. In one girl of twelve years frequent premature ventricular contractions were observed during the illness. In one instance there were nausea and vomiting and in another abdominal pain and vomiting.

With the subsidence of the fever evidences of acute infection in the throat, if they had been previously present, subsided and the enlargement of lymph nodes and spleen gradually receded. The lymph nodes remained palpable, however, for a considerable time and could be felt in several instances from one to six months after recovery.

Recovery was complete and uneventful in all cases.

The unusual feature of these cases and the one which places them in a unique position among the common infections is the degree and type of mononuclear leukocytosis which accompanies the disease. During the first week of the disease and at the time, apparently, of the enlargement of the lymph nodes there occurs an absolute and relative increase in the mononuclear cells of the blood with a slight but distinct decrease in the total number of granular cells. In Cases I and II, which were not seen until convalescence had been established, the total leukocytes were normal in number or even somewhat diminished, but in the other patients they were increased

and the highest counts recorded ranged from 9800 to 26,200. The duration of this high leukocyte count was not great, for it usually lasted but a few days. The course of the mononucleosis is best seen in the accompanying histories (Figs. 1, 2, etc.). They present the variations in the actual numbers of all forms of leukocytes, of the mononuclear cells and of the granular cells. For the purpose of preparing these graphic charts all forms of mononuclear non-granular cells have been estimated in one group and all forms of granular cells in another.

It can readily be seen from these charts that the leukocytosis is dependent entirely upon an actual increase in the non-granular forms of mononuclear cells. This increase was definite by the seventh day of the disease and reached its height usually about the tenth to the fourteenth day of the disease. From this period on there was a decrease in the total leukocyte count with a corresponding reduction in the number of mononuclear cells. Finally the normal relations between the different types of cells were established, but in many instances this required several days or even weeks. With the increase in the mononuclear cells there was an absolute reduction in the number of granular cells, so that instead of the normal number of 4000 to 6000 per cm. there were only 2000 to 4000 cells. With recovery the granular cells increase and finally reach their normal number. These variations in the total number of cells are apparently very characteristic and have occurred in the reported cases as well as in this series.

The histologic appearance of the mononuclear cells of the blood in this disease has been well described and pictured by both Sprunt and Evans and Blaedorn and Houghton. There are three types of mononuclear cells which are found in the blood of all these cases:

1. A small mononuclear leukocyte identical with the small lymphocyte seen in normal blood.
2. Large mononuclear cells identical in appearance with the large mononuclear and transition cells of normal blood.
3. Mononuclear cells of a type not usually encountered in normal blood.

It is the third type of cell that predominates and to which particular interest is attached. In the present cases these cells were somewhat larger in size than the small lymphocytes and contained oval, kidney-shaped, slightly lobulated or Rieder-typed nuclei, staining deeply in Wright's and Hastings's stain. They were usually without definite nucleoli and were often eccentrically placed in the cell. Sometimes the nucleus almost filled the cell but at other times it was surrounded by a fair amount of basophilic protoplasm of ground-glass appearance, which did not contain any definite granules. These cells varied somewhat in size and shape and frequently it was difficult to differentiate them on the one hand from small lymphocytes and on the other from the large mononuclear cells. Occa-

sionally mononuclear cells were observed with eccentrically placed nuclei and deeply staining basophilic protoplasm. Such cells resembled very closely the so-called stimulation form of Türk. In 3 cases in which the oxidase reaction was made the protoplasm of the abnormal cells was found to be free of granules. Though a few of these mononuclear cells presented somewhat the appearance of myeloblasts the absence of the oxidase reaction served to differentiate them from this cell, and it seems highly unlikely that they are derived from the myeloid tissue and much more reasonable to suppose that they arise from true lymphoid tissue. Neither Sprunt and Evans nor Blaedorn and Houghton obtained oxidase reactions in the cells from their cases, and these authors come to the conclusion also that the abnormal mononuclear cell is a derivative of lymphoid tissue.

With convalescence and a decrease in the leukocytes these abnormal cells gradually disappear from the blood.

In no instance was there an anemia associated with the abnormal blood picture.

The clinical course in all the reported cases presents a fairly uniform picture.

The disease has occurred usually in young adults or in adolescents. Curiously enough many of the patients have been medical students or young physicians.

The onset is rather gradual, with malaise, headache and an irregular fever occasionally accompanied by chills. In many instances at the onset there is a pharyngitis, an actual tonsillitis, a tracheitis or a cough. Sometimes the lymphoid tissue of the pharynx becomes much swollen. Very frequently the patients complain of sweating. In a few instances there has been abdominal pain with nausea and vomiting. Rarely the first sign of the disease noticed by the patient has been an enlargement of the cervical lymph nodes. More frequently the cervical lymph nodes became enlarged and tender during the first week of the disease. They may reach 1 or 2 cm. in diameter and are quite firm. In some instances the enlargement is confined to the cervical nodes but frequently the axillary, inguinal, even the epitrochlear and possibly the bronchial, lymph nodes are involved and become swollen, firm and tender. In some cases during the first or second weeks the spleen is enlarged, becomes readily palpable and is tender. By the seventh day the mononucleosis is well marked and from this time until the tenth to the eighteenth day the leukocytes increase in numbers and the mononucleosis advances. The fever, which is often mild and rarely goes above 102° or 103° , continues irregularly until the tenth to the twentieth day and then gradually subsides. With the fall in temperature the symptoms subside, the lymph nodes recede, the spleen diminishes in size, the leukocytes fall and the mononucleosis gradually disappears (Figs. 4 and 5). Convalescence is rapid and uneventful,

though the lymph nodes may remain palpable for weeks and a slight increase in the mononuclear cells of the blood may persist for some time.

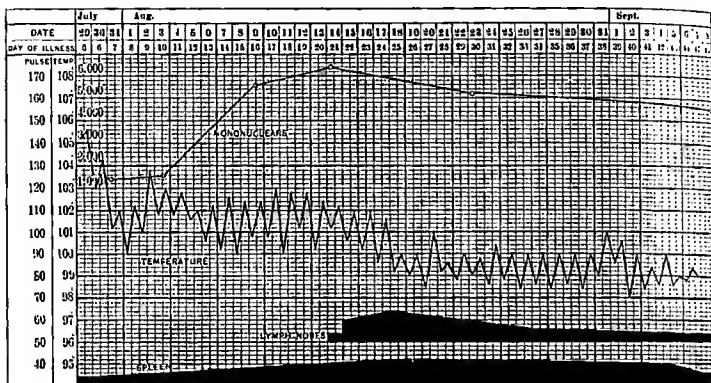


FIG. 4.—Case III. Chart showing temperature curve, changes in absolute numbers of mononuclear cells and variations in size of lymph nodes and spleen during disease.

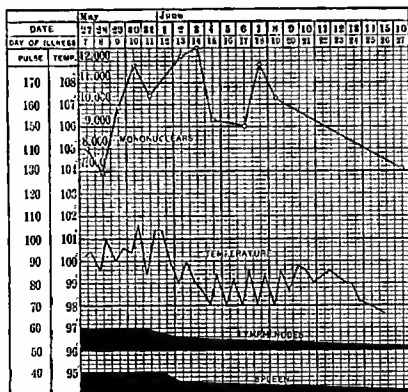


FIG. 5.—Case IX. Chart showing temperature curve, changes in absolute number of mononuclear cells and variations in size of lymph nodes and spleen during disease.

The accompanying charts show graphically the course of the fever and the way in which it precedes for several days the rise in mononuclear cells.

There is almost nothing known about the pathology of the disease. The lymph nodes from 3 of the cases reported by Sprunt and Evans were examined histologically. The sections are reported as being quite similar and as presenting a picture that could not be differentiated, save in the degree of hyperplasia, from lymphatic leukemia. The sections presented no indications of Hodgkin's disease, tuberculosis or lymphosarcoma.

In 2 of the cases reported here lymph nodes were excised and examined histologically. An axillary lymph node removed from P. F. (Case II), on February 16, 1915, presented the following appearance:

"From the left axilla the lymph node has been excised. This on section shows almost complete loss of normal structure. There is marked lymphoid hyperplasia of the germinal centers, the cells of which show karyorrhexis and karyokinetic nuclei. In the lymph spaces between the cords there is active proliferation of the epithelioid cells of the reticulum with the formation occasionally of large multinuclear cells almost of giant size. A few of these large epithelioid cells are also mixed with the cells in the lymph cords. Occasionally an eosinophilic leukocyte is seen. The picture suggests very strongly Hodgkin's disease, though one would scarcely dare to make a definite and positive diagnosis."

A cervical lymph node from Case III presented a picture which simulated in some respects Hodgkin's disease, but was not sufficiently characteristic to allow one to make that diagnosis.

Neither bacteriologic nor serologic examinations has thrown any light on the cause of the disease or served even to indicate whether it is merely an unusual form of reaction to an ordinary pyogenic infection or a disease *sui generis*. In the cases of Sprunt and Evans the stool examinations were negative in all. None showed a positive Wassermann test. In 4 cases blood cultures were made and were negative. Throat cultures were made in 2 cases, one of which showed a nonhemolytic streptococcus. Cultures of the cerebrospinal fluid in 1 case was negative. Animal inoculation of a gland from 1 case failed to disclose a definite etiological agent. Blackburn and Houghton state that spiral organisms were seen in smears from the throat of three of their four patients.

In the 10 cases presented here blood cultures taken in 7 and in several instances repeated more than once gave no growth of bacteria. The von Pirquet reaction was made in 4 cases and was found negative and the complement-fixation test for tuberculosis was done in one instance with negative result. The Wassermann reaction was negative in the 7 cases which were tested; the Widal reaction was performed in 5 cases and was negative in all. Urine

cultures were made in 2 cases without obtaining a growth of bacteria. Culture from the tonsils and the throat did not yield any constant results. In one instance in which there was tonsillitis *Staphylococcus aureus* was obtained; in another instance *Streptococcus viridans* and *Micrococcus catarrhalis*, in a third instance no bacteria of pathologic significance were obtained, and in a fourth streptococci and staphylococci. Smears from the inflamed tonsils and pharynx of 3 cases showed spirillæ and fusiform bacilli in small numbers.

No evidence of tuberculosis could be discovered in any of the patients. Radiographs of the lungs were made in 6 cases. In one instance (Case II) the bronchial nodes were rather large but not calcified. In one instance the linear markings were thought to be accentuated and in the other 4 cases the lungs were normal. One patient (Case I) several years after his attack developed tuberculous pleurisy, from which he recovered. The other patients have remained well for from one to seven years.

Discussion. From the results of this study of these ten patients and the reports in literature one is strongly impressed with the view that these cases represent instances of a definite disease entity. Certainly the clinical picture is sufficiently striking to differentiate these cases from other known forms of acute infections.

The disease has been mistaken for tuberculosis, typhoid fever, Hodgkin's disease and leukemia. In a few instances syphilis was suspected. There is no evidence to show that the condition is related in any way to any of these diseases. The resemblance to leukemia is perhaps most striking, but the early and marked enlargement of the lymph nodes, the absence of anemia and of purpura, and the histological and biological characteristics of the abnormal mononuclear elements of the blood practically exclude the possibility of considering these cases as instances of mild and transient acute leukemia.¹

There are only a few specific infections such as typhoid, pertussis, malaria, Malta fever and possibly tuberculosis, and intoxications such as those from arsphenamine and tetrachloride poisoning,^{17 18} which are known to produce in adults an absolute mononucleosis. Even in these instances the absolute increase in the mononuclear cells is not very great and is frequently insignificant when compared to the considerable mononucleosis encountered in many of the cases recorded here.

It has been suggested that the mononucleosis might be regarded as a peculiar reaction of the individual toward such common types of infection as those caused by streptococci or *Staphylococcus aureus*. Cabot considered that the infection in most of his cases was caused by streptococci. But it has been shown by Sprunt and Evans that an individual who has suffered an attack of "infections mononucleosis" may subsequently give a perfectly normal polymorphonuclear response to a simple pyrogenic infection. There does not seem to be, therefore, any direct evidence to uphold the

assumption that the mononucleosis is an individual characteristic. A much more rational view would seem to be that these cases represent instances of a specific infectious disease presenting very definite characteristics with such an unusual blood picture that this feature serves to differentiate the infection from most other acute infections of known etiology. If the disease is due to a specific agent it seems highly probable, both on account of the frequent and early implication of the upper respiratory tract and the uniform involvement of the cervical lymph nodes, that the virus gains entrance to the body usually through the tonsils or the upper respiratory tract itself, a conclusion that was also reached by Sprunt and Evans and Blaedorn and Houghton.

At the present time the etiologic agent is unknown. Blaedorn and Houghton, who found spiral organisms and fusiform bacilli in smears from the tonsils in three of their four cases, are inclined to regard the disease as a form of Vincent's angina. In none of the cases, however, does the appearance of the inflamed throat or tonsils resemble very closely the conditions seen in Vincent's angina; and though the occasional presence of spiral organisms and fusiform bacilli has been noted, the occurrence of these organisms in small numbers in many forms of throat infection is so common that it would be improper to attach too much importance to such findings. Only three of the patients who had tonsillitis in this series showed spiral organisms and fusiform bacilli in smears. Cultures from the tonsils and the inflamed throats showed such a diverse flora that no one organism seemed to occur with any regularity.

The clinical picture alone suggests very strongly that the "glandular fever" originally described by Pfeiffer is one and the same condition; but until epidemics of infectious mononucleosis are recorded, or until cases of characteristic glandular fever are described in which the blood picture differs essentially from that in "infectious mononucleosis," it will be impossible to settle this question. Pending the settlement of this point, however, the term "infectious mononucleosis" (Sprunt and Evans) is perhaps the best one to employ. It has the virtue of calling particular attention to the blood picture.

Conclusions. Ten cases of infectious mononucleosis are described. The relation of this disease to glandular fever is discussed.

The uniform character of this febrile disease and the association of an enlargement of the lymph nodes with a striking increase of mononuclear cells of abnormal type in the blood serve to differentiate the condition from other acute infectious diseases.

If the disease is an entity, as it appears to be, the specific cause is unknown.

It resembles most closely acute leukemia but may be differentiated by many characteristics.

The disease is of short duration and recovery is the rule.

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THE RELATIONS OF HYPERTENSION TO CARDIORENAL DISEASES.

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In the explanation of the vascular disorders associated with nephritis two opposing conceptions have been advocated. These two ideas are that these vascular changes are traceable to some metabolic disorder of which hypertension is a symptom, or second, that there is a primary change in the arterioles which in turn gives rise to hypertension and a consequent train of phenomena. Both ideas were suggested by Bright: "Either that the altered quality of the blood affords irregular and unwonted stimulus to the organ (heart) immediately, or that it so affects the minute and capillary circulation as to render greater action necessary to force the blood through distant subdivisions of the vascular system."¹

Changed in form of expression from time to time, these two conceptions have delimited, nevertheless, the pendulum of opinion even up to the present. Whether in its earliest form as advocated by Traube, or as more precisely stated by Weigert and Cohnheim, the essential idea of peripheral resistance remained the same. From this point of view vascular hypertension and cardiac hypertrophy are compensatory changes in an effort to meet increased peripheral resistance. Those of us to whom this general view made no appeal have from time to time studied the blood by methods either physical or chemical, searching for a clue to "altered quality."

¹ Guy's Hospital Reports, 1839, **1**, 338.