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Infectious mononucleosis

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(Glandular Fever)

Infectious mononucleosis may be described as an acute infectious disease characterized by fever, enlargement of the lymphatic glands, and changes in the blood, especially lymphocytosis.(1)

Since the introduction of the serologic diagnostic test of Paul and Bunnell in 1932, there has been an awakened interest in infectious mononucleosis. Cases which were formerly entirely overlooked or only suspected could be confirmed as examples of infectious mononucleosis by this test.(2) Between 1928 and 1932 such men as Chevallier of Paris, Glanzmann of Berne, Lehndorff and Swartz of Vienna, and Nyfeldt of Copenhagen published some excellent monograms on infectious mononucleosis.(3)

I. History

A. Earliest Descriptions. Emil Pfeiffer is given credit for the first description of this disease which he called "Drusenfieber" (glandular fever). This scientific paper which appeared in 1889 gave a comprehensive discussion of its clinical aspects. In addition to the more marked signs of infectious mononucleosis he noted that the glands did not suppurate, that abdominal pain may be a feature, and that the angina present in a great many cases is not sufficiently marked to serve as the primary cause of the illness. He failed to recognize that generalized glandular enlargement may occur as it does in a vast majority of cases.(2) Filatow, a Russian pediatrician, in 1885 described a disease which he called "idiopathic adenitis" occurring among children which is probably what we today know as infectious mononucleosis.(4) He considered the disease which he described to be different from that described by Pfeiffer from the fact that there was generalized glandular enlargement.

Since the clinical picture of infectious mononucleosis is associated with a variety of conditions, it is difficult to attribute with certainty the distinction of original description to any one man. An article written in 1897 by Cantlie refers to twenty-three cases of "glandular idiopathic enlargement" which he reported at the Medical Society in Hong Kong in 1891. He diagnosed these cases as a "peculiar form of mumps," as neither the parotid nor submaxillary gland was involved. Like Pfeiffer, he stressed the involvement of glands in the posterior triangle of the neck, noted the possible confusion with mumps when there was enlargement of glands in the area of the parotid and submaxillary glands, and recalled the term "peculiar form of mumps" was employed to designate Astrakan disease in 1877.(5) An article under the title "Lymphadenitis" was published by Gourichon in Paris in 1895, giving credit to previous publications of Filatow, Korsakow, and two other Russians, Kisel and Rauchfuss, who presented a case at a meeting in St. Petersburg in 1888. Williams in 1897 noted that there was involvement of the axillary lymph nodes. He gave the case history of two patients whom he had in 1896. One was a girl of five years who presented the characteristic physical findings of infectious mononucleosis. One of her chief complaints was that of abdominal pain for which no cause could be found. Five days after seeing this first patient he was called to attend the patient's brother, aged 3½ years, who also presented the same clinical picture. Following a course of three weeks she recovered completely with only an anemia for several weeks afterward. Subsequently it was learned that a week or more before the attack in the girl, an elder brother suffered from a mild attack of glandular swelling, thus bearing out the observation of Pfeiffer that the disease

was infectious. In the same year Chapman reported a case of glandular fever in which there was the complicating clinical finding of epistaxis.(7)

The thirty years following Pfeiffer's article saw a discussion concerning the clinical aspects of the disease. It was first noted by Desplots in 1894 that the axillary and inguinal nodes were usually enlarged. Horschelmann in the same year described a scarlatiniform eruption and also the occurrence of a severe membranous angina.

It was not until 1896 that any reference was found to infectious mononucleosis in American literature. The article was one written by West who described an epidemic of three years' duration, localized in eastern Ohio. In all he noted a series of 96 cases.(8)

B. Terminology. Infectious mononucleosis is a fitting term for the disease, since in all likelihood it is infectious and at some time in its course must be associated with an increase of mononuclear cells in the blood. Since neither fever nor glandular enlargement is an essential sign, glandular fever is a less fitting term, but for the sake of convenience both terms are used interchangably. In the recent literature the names glandular fever (Drüsenfieber of Pfeiffer) and infectious mononucleosis mentioned by Baetjer in 1915, but more properly introduced by Sprunt and Evans in 1920, are favored. Since the particular aspects of the disease have appealed to individual authors, such names as lymphoid-cell angina or monocytic angina, acute benign lymphoblastosis, and acute lymphadenitis appear in the literature.(1,9)

C. Developmental Phases.

1. Clinical. After the original description of infectious mononucleosis, articles were printed which were mere repetitions of the

clinical aspects of the disease. In 1897 the attacks upon glandular fever as an entity had already begun. Neumann in 1891 published a series of cases in which he tried to prove that glandular fever was only a local pyogenic cervical adenitis. Since in half of his cases there was suppuration of the glands it is clear that he described cases which had no relation to infectious mononucleosis, as suppuration never occurs in this disease. It was suggested that it was secondary to rhinopharyngitis by Labbe` in 1901. Some attributed it to a complication of influenza in Germany as late as 1924.

From the years 1906 to 1920 few articles appeared concerning the disease. Between 1915 and 1920 Tidy was unable to find a record of a single paper with the title of this disease.(1) Gourichon in 1895 noted a mild leukocytosis in the disease. The credit for noting the differential form of the leukocytes goes to Burns who reported an epidemic of infectious mononucleosis in a Baltimore hospital in 1909. He noted that there was an increase of the "small mononuclear" elements of the blood and, most important, reported a case in which the mononuclear cells composed 86% of the total leukocytes.(10)

2. Hematological. It was not until the years between 1918 and 1920 that the characteristic blood picture was recognized. For several years previous to the above dates, cures of leukemia by some method of treatment had been described. Curschmann in 1906 diagnosed a case of abnormal mumps with a white blood count of 50,000 per cu. mm., and with lymphocytes of 78%, which is apparently the first record of a blood count in a case which may be accepted

as infectious mononucleosis.(1) Türk in 1907 gave the diagnosis of hopeless prognosis to a patient only to find he soon recovered completely. He noted at the time the patient's blood contained 85% mononuclear cells. In 1913 Marchand reported several examples of adolescents with sore throat, fever, general glandular enlargement, splenomegaly and a lymphocytosis as high as 90%. He attributed the blood changes to sepsis, though this is now disbelieved. Cabot in the same year gave similar histories on two patients which he differentiated from leukemia by the benign course.(2)

Deussing (1918) described two cases in children of absolute lymphocytosis which he diagnosed as angina resembling diphtheria with a lymphatic reaction. His description of the clinical course and of the cells was characteristic of those written today on infectious mononucleosis. He believed the angina was of ordinary non-diphtheritic type and that the lymphocytosis was the result of a constitutional tendency to "lymphatic reaction" on the part of each individual patient and did not recognize that he was dealing with the results of a specific disease.

The existence of infectious mononucleosis was first stated in 1920 by Sprunt and Evans in this country. They made no reference to Pfeiffer's glandular fever, but did describe the typical symptoms and findings which he had noted. The six cases were in their opinion examples of a definite infectious disease and they used the term "infectious mononucleosis."(9) In 1921 Tidy and Morley recognized that earlier cases which were described as being examples of "acute leukemia with recovery" and infectious mononucleosis were the same disease as Pfeiffer's glandular fever.(11) Bloodorn

and Houghton in the same year reported four cases of "acute benign lymphoblastosis" occurring in young adults, with which Vincent's organisms were frequently associated, and admitted that the disease closely resembled infectious mononucleosis.(12) Longscope accepted the views of Tidy and Morley and reported ten cases with special emphasis on the hematologic abnormalities and microscopic appearance of excised lymph nodes.(13) In 1923 Downey and McKinlay made a complete and comprehensive study of the blood changes in infectious mononucleosis to which little has been added since. It was their opinion that the disease described in young adults with acute tonsillitis or pharyngitis, absence of anemia, enlargement of lymphatic glands and frequently of spleen, lymphocytosis, and comparatively rapid recovery of the patient, could be differentiated from leukemia and other closely resembling diseases.(14)

By 1925 the identity of the two conditions of infectious mononucleosis and glandular fever was accepted in Great Britain and America, but on the continent the existence of the entity was doubted for many years. German and Austrian authorities between the years 1920 and 1930 were actively engaged in discussing the occurrence of "monocytic angina" and the "lymphatic reaction" without realizing that these were accepted as a form of infectious mononucleosis in England and America.

Foreign authors did not recognize the disease as an entity but considered the angina as a provoking factor toward a constitutional lymphatic tendency. Glanzmann (1930), Nyfeldt (1932) and Lehndorff and Schwarz (1932) strongly upheld the contention that monocytic angina and glandular fever were identical and put

forth their argument on the continent. The evidence for the identity was as follows:

1. In epidemics of glandular fever cases occur with and without angina of all grades, and between the two groups no difference can be found in the blood changes, the glandular swelling, and the enlargement of the spleen.
2. The cases with membranous angina cannot be distinguished from monocytic angina.
3. Similar changes in the mononuclear cells are found only in glandular fever and monocytic angina (except rubella), so far is at present known.
4. Monocytic angina differs from other forms of angina in:
   (a) the prodromal period;
   (b) the long duration of the angina and fever;
   (c) the general glandular enlargement; and
   (d) the frequency of recrudescences.

(1)

3. Serological. An observation was made by Paul and Bunnell in 1932 that there was present in the blood serum of patients with infectious mononucleosis, antibodies against sheep red cells in concentrations far above a normal titer. This observation was made entirely accidentally in the course of a study of non-specific serological reactions in a variety of clinical conditions. At present it is so widely accepted that it has come to be as accepted as the Wasserman reaction. During an epidemic in Colorado and California in 1935 Nolan made the discovery that patients had positive serological reactions in a number of cases of glandular fever.(2)

II. Distribution

A. Age. The earliest reports have always stressed the fact that the disease is found largely in children and young adults. Epidemics however have been found in older age groups in the army.

Frequent reports of epidemics among young college students are also to be found. Tidy and Morley calculated that at least 80% of all cases reported up to 1921 were under 13 years of age. The extremes of cases are those occurring in an infant of 7 months, recorded by Price in 1930,(15) and ~~cases~~ in the very old of 70 years, reported by Moir in 1930. The epidemic occurred in an isolated community in the Falkland Islands in 1926. Of the patients with the disease there was a total of 87 cases, of which 52 occurred in males and 35 in females. In these cases 8% were under 5 years, 20% between the ages of 5 - 15 years, 38% between the ages of 15 - 25 years, 24 between the ages of 25 -45 years, and 9% between the ages of 45 - 65 years, with one case in a male aged 70 years. Old and young alike have little immunity to the so-called disease of children in such a virgin community and this was true also of the complications.(16) Bernstein states that in his general practice 81% of cases occur between the ages of 15 - 30 years, with the youngest 6 years of age and the oldest 36 years of age. Kracke states that the disease occurs most frequently between the age of puberty and the early twenties.(17) Sprunt states that there is a definite age incidence, sporadic cases afflicting older children and young adults, and in epidemics there are many younger children afflicted.(3)

B. Sex. Incidence in males and females as calculated by Glanzmann and Nyfeldt and many other authors is in a ratio of 3:2, being more often in males.

C. Occupation. All authors are in agreement with the statement that although many cases have been observed among those people associated

with a hospital staff, the incidence is no higher among this group. The reason for its being reported so frequently in this group is the fact that on the slightest complaint these individuals are under the immediate care of a doctor and diagnosis is made early and easily through the practice of routine blood counts. There seems to be no racial preference, although few cases have been reported among negroes.

D. Geographical. Infectious mononucleosis has a world wide distribution. In addition to America, Europe, and Australia cases have been recognized in Egypt, the Falkland Islands, Trinidad, the Philippines, Hong Kong, and Japan. It was not until 1937 when the Japanese began using the Baul-Bunnell test that they were able to recognize cases of suspected infectious mononucleosis and establish relationship to diseases known as tosa-netsu, tokuchima-netsu, and Kagami-netsu.

E. Seasonal. Most epidemics occur in the Spring and Fall, while cases in the Summer are rare. Sporadic cases occur the year around with no particular time of occurrence.(1, 2, 17)

III. Clinical Picture.

A. Introduction. The disease is peculiar in that it may be so mild as to be entirely overlooked while on the other hand be so severe with a high fever over a period of many weeks, possibly with relapses, so that the victim is incapacitated for a number of months. Like syphilis but on a moderate scale it can appear under the guise of many diseases, such as follicular tonsillitis, jaundice, appendicitis, Vincent's stomatitis, meningitis,

agranulocytic angina, or acute leukemia. In cases of epidemics the disease is easy to recognize but it has not been until recently that sporadic cases have been recognized. There is no doubt that infectious mononucleosis is a common affliction, otherwise it would be hard to account for the large number of sporadic cases reported in the past few years.(2)

B. Clinical types. Sprunt and Evan's term "infectious mononucleosis" has been commonly used in this country. The term "glandular fever" is a loose term and embraces such conditions as cervical adenitis.

From the survey of Lehndorff and Schwartz two main types are described: (1) the Pfeiffer or glandular type, and (2) the angiose type. In the Pfeiffer type enlarged glands are typical and in the angiose type involvement of the throat is outstanding. They consider cases described as monocytic angina to be of the angiose type (cited from McKinlay,(18)). Tidy recognizes three main types, (1) and (2) being the same as those recognized by Lehndorff and Schwartz and (3) a febrile type with a prolonged fever. He states that all intermediate forms of these types may occur, however. Blume favors this classification.(19) It might be added that Kracke, writing in 1940, describes cases whom he calls the "walking type" in which the symptoms are so mild that the disease may go unrecognized.(17) Bernstein does not believe that cases can be classified into types because the presenting symptoms of infectious mononucleosis are so variable. In his opinion, there is no essential difference between the sporadic and epidemic cases. He states that the reason sporadic cases have such high blood counts recorded

is that the disease is recognized late in its course so that by this time there is a good deal of stimulation of the lymphatic system.(2)

C. Epidemics. Epidemics occur in such places as colleges, schools, foundling homes, individual homes, children's hospital wards, military and naval bases, and in general communities where the victims live in close proximity to one another.(2)

Davis reported an epidemic which occurred in the Santa Chiara Nursery in Chicago in November, 1928, and for which the source could not be determined. All of the children in the nursery and one nursemaid contracted the disease.(20) An epidemic also occurred in various parts of London in 1930, according to Krestin. This epidemic was different in that it affected those in the second and third decades of life and presented a picture of prolonged pyrexia with glandular swelling appearing at an irregular time in the course of the disease.(21)

During the years 1928 to 1930 the disease reached epidemic proportions in several parts of Europe, as pointed out by Glanzmann, Lehndorff and Schwartz, Tidy and Nyfeldt.(3)

D. Period of incubation. Tidy and Davis have made very accurate observations and report an incubation period of eleven days; Tidy states 5 - 15 days. In spite of their observations there is a wide divergence of opinion among all authors.

E. Degree of infectivity. Susceptibility appears to be almost universal but the degree of infectivity is not high. It is probable that the disease is infectious only in the early stages.(1)

Sporadic cases show little tendency of contagion, but sweeping epidemics in boy's schools have resulted from a sporadic case among the teachers. During epidemics susceptibility to infection is quite general. The mode of spread is generally thought to be by way of droplet infection.(3)

In the epidemic which occurred in England in 1930, Cantor describes three stages: (1) Onset, (2) Stage of appearance of rash in successive crops from 7th to 10th day, and (3) Stage of glandular enlargement from 10th day on, with splenic enlargement following. Pyrexia persisted through all stages.

F. Onset. The onset of infectious mononucleosis in the majority of cases presents in the first four or five days the vague constitutional complaints that accompany so many infectious diseases and the individual is not brought to the attention of the doctor until after this period of time when the patient's condition becomes more acute. An attack may, however, start suddenly with chill and rapid rise of temperature. Cases on the other hand may be so mild as to go unrecognized. Sprunt describes pain in back as a frequent prodromal symptom. Patients often have chills and sweats, loss of appetite; they find themselves "lackadasical" and must drive themselves to accomplish the usual routine.(22)

G. Duration of attack. The acute febrile stage of the disease usually lasts from 7 to 21 days and, barring relapses which may prolong the course to as long as six months, the duration is rarely more than one month. For years or months, however, glandular enlargement, splenomegaly or hematological changes may persist.

Sprunt followed an individual who apparently remained well for 2½ years with generalized lymph node enlargement and changes in the blood suggestive of infectious mononucleosis, only to observe the subsequent development of lymphosarcoma with a fatal termination.(2) This is the only case on record of such an outcome.

H. Initial symptoms.

1. General. The initial symptoms of infectious mononucleosis are variable. Associated with the fever there may be chills and sweats, headache either of frontal or occipital type,(21) faintness, and malaise or an irritability at the onset and during the course of the disease which is often impressive.(2) Fatigue may be such that it seems out of proportion to the disease. Anorexia is common; nausea and vomiting less so. There may be the initial symptoms of an upper respiratory infection such as rhinitis, hoarseness, or cough.

Sprunt in 1933 summarizing the symptoms states that the symptomatology is highly variable. The outstanding symptoms are the febrile course, the enlargement of the superficial lymph nodes, and the occurrence at some time during the illness of the characteristic blood picture with an increase in the number of lymphocytic cells and the occurrence of many pathological lymphocytic forms. Other less outstanding symptoms include general toxemia with fever, pain, and tenderness incident to the rapid increase of the lymphatic swelling, secondary infection of the throat and mouth, pressure of the enlarged glands against the bile ducts, trachea and bronchi, functional disturbances of the gastro-intestinal tract, skin rashes, conjunctivitis, and, less commonly, jaundice and hematuria.

Characteristically, this disease has variability of predominate symptoms, clinical course, and duration more than any other infectious disease.

Typically the picture in an epidemic case is that of a child with a brief prodromal period of fatigability, and wishes to lie around instead of playing as usual. The child might show signs of irritability or restlessness, anorexia, and constipation. There is a rapid onset of high fever and the appearance of enlarged lymph glands on the first day or certainly they appear on the second or third day. In younger children there is usually no complaint of pain while in older children they complain of pain and tenderness that may cause stiffness of the neck and a turning of the head toward the direction opposite that of the chief swelling. One after another, the glands in such regions as the axilla, groin, and epitrochlea become enlarged. The spleen may be palpable in the beginning or only after several days or may never be palpable. Once the fever has gone down the patient feels quite well except for weakness. The lymph nodes decrease in size more slowly, and as slowly does the blood picture return to normal. The glands may remain enlarged for months or years, just as may the blood picture--as previously noted. There is the added marked tendency of recurrence.

In the typical sporadic case, the prodromal period is of varying length, although usually it is from a few days to a week. The symptoms become worse with increasing headache and malaise, with higher temperature and the patient goes to bed. At this stage in the illness the glands are usually enlarged and there is slight reddening of the throat with perhaps some discomfort on swallowing.

The spleen may be palpable on the first day but may not be felt for a week or two. The general state of the patient is quite variable from a feeling of not being very well to marked prostration to a state seen in typhoid fever. By the time the patient is seen by the doctor, blood changes are present. In the early stages there may be a leukopenia with a relative lymphocytosis or an initial polymorphonuclear leukocytosis, but this picture changes after several days so that there is a leukocytosis with an absolute lymphocytosis.

The throat symptoms in many sporadic cases are mild at first, later becoming very marked and dominating the clinical picture. In some cases the tonsils will become inflamed and may be filled with exudate or may have a pseudomembranous exudate covering them such that an erroneous diagnosis of diphtheria is made.(31)

2. Sore throat. Is frquently present but is not an essential feature of the disease; it is thus considered as a complication of the disease. The time at which the throat symptoms appear is variable. It may precede the disease, be associated with the onset or course of the illness, or make its appearance after recovery has taken place. (24, 2) Williams in 1897 noted cases in which the throat symptoms were minimal.(6) Of cases reported by McKinlay, 78% had signs of throat infection,(18) and in 77% of the cases observed by Bernstein it was present. The throat involvement was of four types: diffuse injection, follicular tonsillitis,(25) ulcerative pharyngitis,(26,4) and membranous pharyngitis. Sporadic cases have a greater tendency to have the above throat involvement. From the appearance of the throat there is nothing to differentiate from

the ordinary acute follicular tonsillitis or from pseudomembranous types of diphtheria. The tonsils may be intensely reddened and swollen and the membrane may spread from the tonsils to the pillars and to the palate and also to the posterior pharyngeal wall, but extension to the larynx never occurs. Nor will the membrane involve the upper pharynx or the nose. Glanzmann described the membrane as being very smooth, almost mirror-like surface of deposit. Secondary infection rarely occurs in these tremendously inflamed tonsils.(3)

3. Pain in neck. Symptoms of pain in the neck and stiffness are probably referable to enlargement of the posterior cervical lymph nodes.

4. Abdominal pain. In the cases reported by West, 75% of the patients complained of peri-umbilical pain, sometime during the course of the disease.(8) A case reported by Davidsohn was that of a young man who had symptoms of an appendicitis and narrowly escaped an operation when a blood smear revealed a mononucleosis of 84%. Two cases are cited by Kracke (1940) in which surgery was considered and prevented when a blood smear was taken and infectious mononucleosis was diagnosed. It is his contention that the pain is due to enlarged mesenteric lymph nodes.(4) The pain in the abdomen may appear at the onset or in the course of the disease. It is colicky in nature, lasting from one to two minutes, with much longer intervals between pains during which time the child may be quite comfortable. Tenderness may be localized over McBurney's point or in the region of the gall bladder.(3)

5. Gastro-intestinal tract. The observation of the frequency of constipation noted by Pfeiffer still is accepted by all men who have studied the disease.

I. Temperature. Fever is not a definite or characteristic symptom. It may be of a septic type with two marked peaks during the 24-hour period with chills and sweating.(3) There may be a remittent form of fever which usually reaches its peak in 4 - 8 days, and then disappears by lysis in contrast to fall by crisis in cases of tonsillitis.(18) Of the cases reported by Bernstein, 70% had a temperature between 100° and 104°. These observations are borne out by the majority of authors.(2) Mills and Sprunt have noted that there may be a characteristic secondary rise after an initial drop to normal, which may appear coincident with the late onset of glandular swelling or sore throat.(3) Tidy in his report of cases has frequently observed this secondary rise of temperature.(1) Pel-Ebstein fever of Hodgkin's disease with alternating febrile periods is reported by Sprunt (1930.(22)

J. Pulse. As a rule the pulse closely parallels the fever but it is not uncommon to find it particularly slow.(1,18) This was especially the rule in the cases reported by Gooding during an epidemic in London in 1930. "The pulse rate was, in uncomplicated cases, slower than would be expected in view of the temperature. A pulse of 92 with a temperature of 102° F. was the rule rather than the exception." Bernstein had one case in which the patient's pulse was sufficiently dicrotic in character to suggest a tentative diagnosis of typhoid fever.(2) It has been the observation of many authors in recent years that associated with the bradycardia

there is an associated increased intracranial pressure and many interpret the bradycardia in infectious mononucleosis as being due to the meningeal involvement.

K. Lymph glands. The hyperplasia of the lymphoid tissue is generalized, involving Waldeyer's ring, superficial lymph nodes, adenoid tissue, the intestinal mucosa, spleen, and perhaps also the lymphoid tissue in the salivary glands, in the liver, and in other regions.(3)

All authors are in agreement that the time, size, and appearance of the lymph glands are variable in their presence or absence. Bernstein cites a case in which the enlarged glands followed after both fever and changes in the blood. In the 50 cases studied by McKinlay, generalized enlargement of the lymphatic glands was the outstanding and constant clinical feature. Lymph nodes were discrete, somewhat soft and elastic, and rarely exquisitely tender; usually there was no appreciable pain.(18) Duration of enlargement is variable. They may be enlarged as long as a year or as transitory as a day or two. Of considerable importance are the cases in which there is no change in the peripheral glands, but changes in the blood, lymphadenopathy of the deep glands, and a positive Paul-Bunnell test. It is the opinion of authors that cases of infectious mononucleosis do not occur without enlargement of some of the cervical glands. Caution in examination and being able to determine the normal size of lymph nodes will serve as to the extent of lymph node involvement.

Size of the glands is usually 1-2 cm. in diameter.(2) They may vary in size from that of a pea to that of an orange.(20,1) The normal contour of the neck and axilla may be entirely lost

through the enlargement of the lymph nodes in these areas.(27)

There is usually no reaction in the surrounding tissue but there may be periglandular edema and possibly some redness of the skin. Swelling of the glands may be quite rapid as mentioned by Tidy, in which case there was no glandular enlargement in the forenoon, but by evening glands were enlarged to the size of a fist. Patients with marked tenderness of cervical glands hold the neck rigid, suggesting an erroneous diagnosis of meningitis.(3)

In the patients observed by McKinlay the posterior cervical lymphatic chains were constantly enlarged, those in the posterior triangle of the neck being less prominent. The extent of lymphadenopathy was out of proportion to the intensity of the lesion in the throat and was especially striking in the absence of angina. Suppuration did not occur and has been rarely reported. The posterior auricular nodes are not usually enlarged, in contrast to the adenopathy noted in cases of rubella.(18) The disease is recognized by the lymphoid changes in the throat and in the cervical region, particularly in the posterior triangles behind the sternocleidomastoid muscle.(1,3) There was cervical lymphadenopathy in 98% of the 100 consecutive cases reported by Lyght in 1938.(24) It was noted by the earliest authors that the glands on the left side were frequently involved first. This observation even led to the theory that the etiological agent may enter the body through the gastro-intestinal tract and thence by way of the thoracic duct to the cervical lymph nodes of the neck.

The axillary nodes are next to the cervical nodes in frequency of enlargement and may even enlarge to the size of a hen's egg.

Individual glands remain discrete as do those in the cervical region.

A "thoracic form" of the disease has been mentioned by a few authors, in which the peritracheal and peribronchial nodes show evidence of more marked hyperplasia than those in any other part of the body. Compression of the trachea with definite stridor has been reported in which there was X-ray evidense of enlargement of the peribronchial glands and compression of these glands on the bronchi with pulmonary signs of bronchial obstruction.(31,2) The lymphocytosis of whooping cough adds to the problem of differential diagnosis.

As long ago as 1897 enlargement of ~~this group of~~ the inguinal glands has been recognized.(5) At this point it is important to differentiate this disease from lymphogranuloma inguinale.

Mesenteric glands are infrequently enlarged. Glanzmann discusses this as an "abdominal form" of infectious mononucleosis which never runs an acute course, but may cause recurring pains, as previously mentioned (p. 16), indistinguishable from that of umbilical or gall bladder colic.

Suppuration when it does occur is undoubtedly an example of pyogenic cervical adenitis rather than infectious mononucleosis. The most frequent secondary invaders are streptococci, staphylococci and influenza bacilli. When the complication arises it is usually associated with retropharyngeal abscesses which may precede or follow them. Any of the sequelae of upper respiratory infections, such as otitis media, mastoiditis, or even sinusitis may appear.

L. Salivary glands are rarely involved and there have been no reports in the literature read for this paper.(2)

M. Eyes. Puffiness of the eyelids, sometimes referable to edema of the lids, appeared at the onset of one of the cases reported by Bernstein. Other than this, the only other ocular sign is conjunctivitis, and occurs rarely. It is usually of a dry granular type and may involve only one eye.(1) In the cases reported by Schulz (1933) there was an incidence of 12% during the first several days of a follicular conjunctivitis. Some authors consider the finding of a follicular conjunctivitis as a frequent sign at the beginning of an attack of infectious mononucleosis. According to Glanzmann (1930) there may be a yellowish exudate at first which soon disappears. Both the bulbar membrane and the palpebral conjunctivae may be a fiery red, outlining the punctate whitish follicles. Of interest is the fact that in laboratory animals injected with B. monocytogenes, there will appear a conjunctivitis like that seen in humans with infectious mononucleosis.

N. Herpes. Has been considered infrequent but Glanzmann noted its frequent occurrence in children and mentioned a scorbutic-like reddening and swelling of the gums. He states that due to lymphatic infiltration tiny papular lesions on the palate which become confluent, or a granular appearance to the mucous membrane of the lower lip may occur.(2)

O. Pulmonary signs. There is usually a dry rhinitis and nasopharyngitis, or perhaps a mild serous exudate but rarely a mucopurulent coryza, according to Baldridge and his associates.(29) Other pulmonary signs have been previously stated.

P. Cardiac involvement. There is a trend in recent years to attribute mitral rheumatic lesions to infectious mononucleosis.

A severe attack of infectious mononucleosis in an individual with an already damaged heart may bring on acute cardiac failure.(28)

Q. Spleen. The spleen may be said to be palpable in from 50% to 75% of the cases.(24,30) Usually the edge is near the costal margin and is firm and rounded. The time when the spleen is palpable during the course of the disease is variable, but usually it is palpable at the height of lymph node enlargement. There is no parallelism between the severity of the disease and the degree of splenic enlargement. There may be tenderness and spontaneous pain in the region of the spleen.(3,2,4)

R. Liver. In 16% of the cases recorded by Baldridge and his associates occurring among medical students, there was distinct enlargement of the liver.(29)It is usually attributed to hyperemia and parenchymatous swelling, though the possibility of lymphocytic infiltration is mentioned by some authors.(2,3)

S. Jaundice occurs infrequently.(1,3,30) It may appear in the absence of an enlarged liver; Bernstein reports two cases in which this was true. DeVries (1938, cited by Bernstein) has made a comprehensive study of the "icteric form" of infectious mononucleosis and classifies it into three types:

(1) a form in which jaundice is the first symptom, followed subsequently by glandular enlargement;
(2) a form, described first by Chevallier, in which jaundice occurs along with glandular enlargement; and
(3) a form in which jaundice with or without fever occurs as the only symptom.(2)

T. Nephritis. Among 270 cases reported up to 1921, nephritis appeared in 6%, a figure which parallels the report of Moir in his

87 cases.(32)

Abnormal constituents of the urine are red and white cells and albumin of a slight degree usually; less commonly hyaline and granular casts are observed. Renal function remains unimpaired, the course is benign, recovery rapid and invariable. No other symptoms of renal involvement occur. Glanzmann encountered four cases of hemorrhagic nephritis appearing between the fifth and eighth days. The possible cause is that of increased permeability of the renal capillaries; it could account for the urinary abnormalities and is merely a manifestation of the hemorrhagic diathesis that is not infrequently associated with infectious mononucleosis.

U. Hemorrhagic phenomena. As early as 1895 it was recognized that a severe epistaxis might usher in the disease.(7) Epistaxis varies widely with epidemics. The bleeding may be so profuse as to cause anemia,(1) but is usually mild and may appear at any time during the disease, but usually it appears at the onset. It may recur over a period of several days. Like the finding of blood in the urine, the epistaxis is attributed to a hemorrhagic diathesis.(2)

Absence of bleeding is not a differential diagnostic point from leukemia for it may appear in infectious mononucleosis, especially petechial and purpuric hemorrhages in the skin and mucous membranes. Israëls reported a case in 1937 in which the patient presented a picture of thrombocytopenic purpura and infectious mononucleosis, coexisting.(33)

V. Skin. In addition to the purpuric eruptions, other types of rashes have been observed, but they are not characteristic of the

of the disease, since a great variety are recorded.

Cantor and Shulman, describing in 1930 a series of 40 cases observed during an unusual epidemic, which Balme in June, 1930, confirmed as glandular fever, observed a maculo-papular rash. About the fourth to the seventh day, the rash appeared; most frequently on the abdomen and chest, and at times on the face, legs, and arms. The spots were about one-fourth inch in diameter, pink at first, becoming tinted with blue, then light brown, and finally yellow before fading. Spots came in successive crops and were in numbers between 8 and 50, being quite discrete and easy to see. The rash would last about a week.(34)

Other rashes which have been described are urticaria, morbilliform, scarlatiniform eruptions, typhoid-like, erythema multiforme, and vesicular eruptions. The eruptions appeared in 9% of cases seen by Bernstein.(1,2,3,30,29)

W. Central nervous system. Headache is especially frequent and cerebral manifestations of the fever and general toxemia occur as in other acute infections.(3) In 1931 Johansen, Epstein, and Dameshek were first to describe symptoms of serous meningitis occurring in cases of infectious mononucleosis. In many instances the picture of meningitis will precede the symptoms of infectious mononucleosis, therefore presenting the picture of benign lymphocytic meningitis, encephalitis, or abortive poliomyelitis. Headache, the usual sign of meningeal irritation, and blurring of vision are the commonest initial symptoms in this form, while occasionally there may be convulsions, stupor, or coma. Changes in the spinal fluid are moderate pleocytosis, with or without increased pressure

and usually with some alteration in the protein content. There may be clinical signs of meningitis with normal spinal fluid findings and vice versa. In an epidemic of 70 cases among children described by Tooney in 1936, pleocytosis was found in 16 of 18 patients whose spinal fluid was examined. Recovery occurs as in the ordinary course of the disease.(1,3,2,17) That the spinal fluid cellular reaction parallels the cell counts of the peripheral blood was pointed out by Epstein in 1935. He suggests that it indicates a close relationship between the two systems and between the disease infectious mononucleosis. Thus such diseases as infectious mononucleosis may produce cerebral changes, and conversely that so-called lymphatic meningitis is merely symptomatic of some as yet unknown systemic disease.(35)

Schmidt and Nyfeldt (1938) stressesthe importance of treatment of these cases to the extent of preventing possible sequelae in the form of chronic changes due to involvement of the central nervous system.(36).

X. Association with other diseases. Vincent's angina, follicular tonsillitis, and purpura hemorrhagica are sometimes so intimately associated with infectious mononucleosis as to be considered part of the disease. Syphilis has often been found in conjunction with the disease. In a child suffering from nephrosis, infectious mononucleosis supervened without affecting the course of the underlying condition according to a report in 1925 by Bass and Herman (cited by Bernstein). Infectious mononucleosis has been reported associated with typhoid fever, scarlet fever, chicken pox, diphtheria, and in the course of lymphogranuloma inguinale.

Associations of infectious mononucleosis with pulmonary diseases are of some importance since these have produced several rare fatalities.

Y. Relapse. Relapses not uncommonly occur. Three patients in the series reported by Bernstein had a return of fever within three to seven days. Usually the relapses are milder and shorter than the original attack of infectious mononucleosis. The same glands originally involved will become enlarged and there will be a return of the typical blood picture.

Z. Recurrence. Rarely there will be a recurrence of attacks. Two cases have been reported. One patient suffered four attacks five years apart and another four attacks in three years. In the cases with recurrences the presenting symptoms varied with each attack.(2)

AA. Contagiousness. During an epidemic multiple cases are frequently encountered in a single household, as noted by Pfeiffer, but on a whole the disease is of low contagiousness. Even among the medical profession with doctors in close contact with the patients, there is no spread of the infection.(20) During epidemics, however, it is highly contagious.(1) The occurrence of sudden widespread outbreaks suggests that there may be carriers.(2)

BB. Fatal cases. The benign outcome of infectious mononucleosis may be attributed either to the youth of its victims or else to antibodies which may appear in response to the infectious agent.

CC. Sequelae. Lehndorff has followed a number of patients for many years without any sequelae of note occurring.(2) This observation is generally accepted by all clinicians.

IV. Laboratory Findings

A. Blood.

1. Earliest changes. The fact that sporadic cases show an extreme mononucleosis is due to the fact that such cases when recognized are well advanced while during epidemics even a slight deviation from the normal blood count will be sufficient to cause a search for other manifestations of the disease. Bernstein refers to a case of his in which there was a polymorphonuclear leukocytosis of 87% and an absolute lymphopenia of 13% of a total white blood cell count of 6000. By the time blood counts are made, which is usually four to five days after symptoms have first appeared, there is a well-marked lymphocytosis.(2) York and Eckley (1937) stressed the importance of repeated leukocyte counts as it may be late in the disease process that the characteristic picture of leukocytosis and absolute lymphocytosis appears.(25) An epidemic (16 cases) of an atypical variety which broke out in a children's home was described by Reyersbach and Lenert in 1941 in which the only way a vast majority of the cases were diagnosed was by a routine blood count. This stresses the importance of the disease even in the absence of symptoms.(37)

2. Leukocyte count. The total white blood count is usually between 10,000 and 20,000 per cu. mm., with occasional counts of 30,000 and rarely as high as 60,000 or 80,000.(3,24) Up to 1934 only six cases were reported with leukocyte counts over 40,000 per cu. mm. All cases were found in very young children from ten months to four years of age. No cases have been reported in adults with a count of 40,000 per cu. mm. or above. In infants and young children a white blood cell count of 60,000 may be reached exceptionally, but only

85% of mononuclears will be present.(1) There may be a leukopenia at the onset, but this is rarely below 2000 per cu. mm.(3,2) It was noted that this initial reduction of granular leukocytes gives way to a subsequent increase later.(18) When high counts are encountered it is chiefly due to lymphatic increase with the polymorphonuclear cells taking little or no part in the process. At present all hematologists are in agreement that the lymphatic reaction to infectious mononucleosis is not on a constitutional basis, but is a response to a definite type of infection.(2,18,38)

3. Myeloid cells. In the presence of leukopenia, lymphocytosis, or a combination of these two factors, there may develop a neutropenia at times of a very low level, even to 1000 or 160 per cu. mm. There may occur as well, quantitative changes of the myeloid cells; notably an increase of young forms, according to Erf (1936). This shift to the left may persist even into convalescence.(2) Usually a non-filament count of over 50% indicates an unfavorable prognosis with the exception of infectious mononucleosis, where it carries a favorable prognosis.(24) It is not an exhausted or aplastic reaction, as it will still respond to an ordinary infection or a stimulus such as milk injection with a polymorphonuclear leukocytosis.(1,22)

4. Eosinophiles. During the acute phase, as in other infectious diseases, the eosinophiles are suppressed and rise to 5 or 6% during convalescence.

5. Mononuclear cells. Mononuclear cell increase is an essential sign appearing typically within the first four or five days of illness and rapidly reaching a peak within a week or ten days.(2) In the typical case lymphocytosis and the glandular enlargement develop at

develop at about the same time; however, lymphocytosis may precede the glandular enlargement by a day or two. After the maximum of the increased lymphocytes is reached, the lymphocytes then commence to diminish, at first rapidly for a few days and then more slowly, paralleling in a certain manner the size of the lymph glands.(22,3) They may disappear rapidly in six days or may persist fifteen days or in rare instances, 10 years.(39) The mononuclear cells most frequently are between 60 to 70%,(1) although commonly may be between 70 and 80%, while all percentages over 90% are rare. Extreme mononucleosis of 99%, such as occurs in lymphatic leukemia, never occurs in infectious mononucleosis.(1)

Characteristically, the abnormal lymphocytes (mononuclear cells) vary in size, structure, and staining properties, varying in size from that of a small lymphocyte to that of a monocyte.

Observers differ in their classification of these mononuclear cells, and also in their origin and as to whether certain cells are lymphocytes or "monocytic." By monocytes, they mean those cells which we commonly recognize as plasma cells, the origin of which is supposed to be from the reticulo-endothelial system. In a smear it is seen that the lymphocytes show gradations varying more and more from the normal and approaching more closely the characteristics of the plasma cells. Confusion thus arises as to the point when a cell can no longer be called an abnormal lymphocyte and when it can be called a plasma cell. There can be no sharp line of differentiation, and Tidy states that he has not found any criteria by which certain abnormal lymphocytes and monocytes can be differentiated.(1)

American authors from the beginning have recognized the abnormal cells as of lymphoid origin. Naegeli and a few others separate cases into two groups according to the predominance of cells suggesting lymphocytic or monocytic forms. Since the origin of these cells of infectious mononucleosis is unknown and they are so variable in their morphology, they have been called by Foord the "bastard cells of hematology."(4)

Sabin and Doan, Wilson and Cunningham, and Gall recently made extensive study of the abnormal cells in recent years. Gall observed that the circulating lymphocytes of normal individuals have refractile granules present in 25% of the cells. A series of 21 cases of infectious mononucleosis was reported in which the lymphocytes contained refractile granules not greater in any case than 15% with a minimum of 5% and an average of 11.6%. He noted a dearth of lymphocytes containing granules for several weeks to months, and that the motility of the cells of infectious mononucleosis was lymphocytic in character. The cytoplasm generally presented the characteristic hazy, faintly opaque appearance of normal lymphocytes, distinctive from the fine granular, ground-glass cytoplasm of the monocyte. Neutral red bodies generally increased in number. He stressed the difficulty encountered in studying the cells of infectious mononucleosis. That the cells of this disease are relatively mature but atypical, is substantiated by the character of the nucleus and the observations above.(40,48)

Abnormal mononuclears are larger than the normal lymphocytes with no standard chromatin of the nucleus and a cytoplasm which stains more basophilic than lymphocytes; vacuoles may be present, sometimes to a marked degree. The cytoplasm is usually sky-blue with a perinuclear clear zone. The presence of the vacuoles in the cytoplasm,

giving it a "foamy" appearance, stamps the cells almost without question as being the cells of infectious mononucleosis. The nucleus of the cells, which takes a darker stain than normal, may be round, oval, or bean-shaped, or may be markedly indented as in the Rieder cells or normal large mononuclear cells.(3,1,4,2,29,33) Bloedorn and Houghton (1921) state that the cells of infectious mononucleosis differ from cells of myelocytic origin, as an oxidase ferment is not present.(41)

There may in certain cases be a few extremely immature cells, and there have been described borderline cases in which the cells have been conspicuous and yet the patient recovered promptly after showing the usual features of infectious mononucleosis.(3)

6. Erythrocytes. Fragility of red blood cells is normal. There is no anemia unless there is a complicating feature of hemorrhage or dietary deficiency.

7. Platelets. In a few cases the platelets have been reduced to as low as 45,000 with or without hemorrhagic phenomena.

8. Bleeding and clotting time. Bleeding time may be prolonged as much as 25 minutes while the clotting time is not disturbed. Only three cases of a positive tourniquet test have been reported.

9. Blood chemistry. There is no change in the blood chemistry except when jaundice is present in which instance the icteric index may rise to 50 units.(2)

General conclusion on blood changes. Myeloid tissue is affected from the onset, acting initially with either a polynucleosis or a neutropenia, but in either case the total number quickly returns to about normal figures. The lymphoid tissue appears to respond to

the infection less rapidly, though finally to a greater degree. Evidence is such that the etiological agent of infectious mononucleosis transiently affects all blood-forming tissue, and no single blood picture is typical of the disease.(1)

B. Wasserman reaction. Numerous reports are found in the literature of the occurrence of falsely positive Wasserman reactions occurring during the time the patient is afflicted with infectious mononucleosis. The duration of a false-positive is brief, usually for a few days and rarely as long as three months. Bernstein in 1938 noted "an incidence of 18% false-positive reactions in a series of 44 cases.(2)

C. Other antibodies. False-positive Widal reactions have been reported, as well as agglutinins for organisms other than the enteric group, these being B. melitensis, B. aertrycke, B. suipestifer, and B. enteriditis.(2)

D. Urine. There is usually a trace of albumin, as may be found in the febrile stage of any febrile illness.(29) There does occur rarely albuminuria in proportion to a hematuria, and even cylinduria, but no renal impairment.

E. Cerebrospinal fluid. Irrespective of whether or not there are clinical signs of meningitis, changes in the cerebrospinal fluid may be found, as previously stated. These are a moderately elevated pressure, pleocytosis usually below 200 in which almost all the cells are mononuclears, normal sugar, and at times an increased protein.

F. Bacteriological. As a whole no organism has been found to be the cause of infectious mononucleosis, although Vincent's spirochetes have been revealed to be present in the throats of a large number of patients with the disease; however, these same organisms were also present in normal individuals.(2)

V. Diagnosis

A. General Remarks.

When a patient presents symptoms of fever and glandular enlargement out of proportion to any local inflammation, a blood examination is indicated. If a large number of abnormal lymphocytes are encountered, a tentative diagnosis of infectious mononucleosis is justified. This diagnosis will be confirmed when the benign course of the disease is completed with eventual complete recovery. This is the manner in which a diagnosis was made up to 1920. It was a slow process and when the patient's clinical picture took an unfamiliar turn, diagnosis was often not made until after recovery. With the advent of the Paul-Bunnell test early diagnosis was made possible, and clinicians became acquainted with the variable picture which infectious mononucleosis can present.(2)

The greatest pitfall in diagnosis lies in the failure to continue study after the initial examination has shown fever, mild catarrhal condition in the upper respiratory tract, and nothing else of particular interest. Under these circumstances a diagnosis of acute respiratory infection is made.(22)

Less typical cases in which the blood changes have not appeared will make the diagnosis difficult. This is especially true when an

initial polymorphonuclear leukocytosis is present, thus leading the diagnostician astray. It is therefore imparative that repeated blood studies from a qualitative and quantitative standpoint should be done to establish the diagnosis.(3) All necessary studies of the case history and blood picture may be made, yet no diagnosis can be reached and patients may be afflicted with the disease, in which cases the only diagnostic means is the Paul-Bunnell test.

B. Heterophile Antibodies: Historical.

"Heterophile antigens are substances which, when injected into certain animals, will elicit not only specific antibodies but also non-specific antibodies, the presence of these latter being demonstrable by their reaction with antigens other than those involved in their production." The Frossman antigen is an antigen of this type and is a substance which when injected into rabbits or a group of animals serologically similar, will call forth hemolysis and agglutinins against sheep erythrocytes. The importance of this antigen is in the Wasserman reaction. It was found that the sera of normal individuals might contain fairly large amounts of sheep-cell hemolysin and that this substance constituted a source of fallacy in the Wasserman reaction when alcoholic extracts of heterogenetic antigens such as guinea-pig or horse heart were employed.

Hanganutziu in 1924 noted in the reading of routine Wasserman reactions an instance of strong agglutination of sheep red-cells. Subsequently he found that the patient had been injected therapeutically ten days before with horse serum and that his serum contained a high titer of sheep-cell antibodies. Further studies of patients receiving horse serum revealed agglutinins against red-cells of

horse, guinea-pig, and several other animals. In each instance the titer of these antibodies was much higher than the hemagglutinins in the sera of normal individuals and that these antibodies appeared about the 10th to 11th day after injection, remaining for a number of weeks. Diecker in 1926 confirmed these observations.(2) Paul and Bunnell in 1932 accidentally ran across a patient with a high titer of sheep-cell agglutinins in his serum when experimenting with tests which might be used in the diagnosis of rheumatic fever. This patient was subsequently found to be the victim of infectious mononucleosis.(42)

C. Paul-Bunnell Test.

1. Materials and normal values. In order to determine the titer of sheep-cell agglutinins in the patient's serum the following materials are needed: a suspension of sheep red-cells, patient's serum, and physiological saline solution. The serum is inactivated for 15 minutes at 56° C., by keeping it in an ice-box. Its potency remains constant over a period of years. Dilutions are then made of the serum, starting with a 1:4 dilution and made as high as necessary. To each tube containing 0.5 c.c. of the diluted serum, 1.5 c.c. of the suspension of sheep-cells is added. After the suspension of sheep-cells is added to the patient's serum, the tubes are shaken and placed in a water bath at 37° C. for one hour and then placed in an ice-box overnight. The next morning the tubes are inverted three times, and if there is macroscopic agglutination of the sheep-cells the test is considered positive.(42)

In Davidsohn's studies including 850 normal individuals, both adults and children, he found 9% to possess agglutinins for

sheep-cells in dilutions of 1:4, while only a few had agglutinins in a dilution of 1:8 and none in higher dilutions.(43) Paul and Bunnell found the titer not to exceed on an average 1:8.(42) For practical purposes the diagnosis of infectious mononucleosis should not be made in the absence of a titer lower than 1:32, although occasionally the disease may occur without such a high titer.(17) Butt and Foord (1935) in a series of 50 cases found the titer of sheep-cell agglutinins to vary from 1:64 to 1:4096. (44)

Like any laboratory test, this test must be evaluated in view of the clinical findings. Since in both sporadic and epidemic cases of infectious mononucleosis a positive Paul-Bunnell test is encountered, the evidence has become established that the two are different forms of the same disease.

The titer of sheep-cell agglutinins bears no relation to the severity of the disease or the degree of lymphocytosis. The usual titer ranges between 1:320 and 1:10,240. In a series of 65 cases reported by Bernstein the test was positive in 92% of the cases. Most authors report a similar high percentage of positive tests.(2) Thus it is seen how highly important and accepted this test has become in the diagnosis of infectious mononucleosis.

2. Time of appearance. When the test is performed within the 4 to 5 days after the onset of the disease, the test will be positive if it is going to be at all. An exception to this statement is found in the report of Himsworth in 1940. He stated that during the early stages of the disease the Paul-Bunnell test may be negative. In the case reported it was negative for 14 weeks in which there were three successive waves of pyrexia. It was not until the

appearance of a positive test that the patient felt well and subsequently recovered. He concluded that since recovery of the patient followed the appearance of a positive test, this reaction may indicate the development of immunity to the unknown agent responsible for the disease.(45) The peak is usually reached by the end of the first week and invariably by the fourth week. In line with the other findings of infectious mononucleosis, as previously stated, the Paul-Bunnell test may be positive before there are any changes in the blood or may not appear for months after the disease has subsided.

3. Factors influencing titer. Factors such as age of cells, concentration of cells, the temperature at which the tubes are incubated, and the length of incubation will influence the outcome of the test. Therefore, it is highly important that the test be made as closely as possible under standardized conditions.

4. Duration of antibodies. The duration varies between wide limits. In the cases studied by Bernstein the earliest return to a normal level occurred in one within 7 weeks of the onset of the illness, but usually the interval was 4 or 5 months. Thus it is possible to diagnose a case of infectious mononucleosis many months after recovery from some unknown malady.(2) Davidsohn states that the heterophile antibodies remain on an average of 56 days, and he observed them for as long as over 100 days.(43)

5. Modifications. There have been several modifications of the original method in order that an early diagnosis can be made. Such a rapid has been devised by Butt and Foord in which one loopfull of blood serum to be tested and four loopfulls of a 2% suspension

of sheep cells in normal saline are mixed together and examined on a hanging drop slide.(44)

D. Nature of Sheep-Cell Antibodies in Infectious Mononucleosis.

Paul and Bunnell assumed that the antibodies occurring in infectious mononucleosis were of the Frossman variety, but soon there appeared evidence that this was not true. Frossman antigen is contained in human group "A" cells and it was noted that patients with infectious mononucleosis, irrespective of the blood group, contained these sheep-cell agglutinins. It was further found by Burgess that sheep-cell agglutinins in normal serum are absorbed by guinea-pig kidney, but not by beef cells; those in the serum of persons with infectious mononucleosis, by beef cells but not by guinea-pig kidney; and those in the serum of persons with serum sickness, by both buinea-pig kidney and beef cells. These sheep-cell agglutinins in the serum of persons with infectious mononucleosis appear to be different from those in normal serum and in serum of persons with serum sickness.(46) Bailey and Raffel also concluded that infectious mononucleosis antibodies are not of the Frossman type since the hemolysins are absorbed by non-heterophile ox-cells.

E. Origin of Antibodies of Infectious Mononucleosis. It can be concluded from the above that the antibodies of infectious mononucleosis are of a unique type and cannot be considered to arise from a non-specific stimulation. The origin may either be extrinsic or intrinsic. If of an extrinsic source, it must be found in the organism or virus which causes the disease (42) while if of intrinsic source it must be associated with the tissues of the patient, some

breakdown product of these tissues, or of the abnormal leukocytes. (2,42) Van Ravenswasy (cited by Marshall) believes they are built by virus antigen action or that they represent increased normally present agglutinins.(47) Kracke (1940) believes they develop as a result of extreme and quick reticuloendothelial proliferation.(17)

F. Relation of Paul-Bennell Test to the Wasserman Reaction. That there is no relation between the Wasserman reaction and the sheep-cell antibodies of infectious mononucleosis is borne out by these facts:

1. The partial removal of sheep-cell agglutinins makes the complement-fixation test more positive, rather than decreasing its strength;(17)
2. A positive Wasserman reaction may occur in the presence of low titers of sheep-cell antibodies, while a negative Wasserman may accompany extremely high titers; and
3. Sheep-cell antibodies may persist for many months after the Wasserman test has become negative and may even increase in titer coincident with reversion of the Wasserman to negative.(2)

G. Serum Therapy and Infectious Mononucleosis. If horse serum is injected into patients with infectious mononucleosis there will be no increase of the antibody titer already present. Thus there is no greater danger in using horse serum in infectious mononucleosis patients than in the normal individual.

H. Paul-Bunnell Test in Other Conditions. The Paul-Bunnell test has been tried in thousands of infectious diseases and has only rarely been positive; some of these include yaws, rat-bite fever, and other infectious diseases. Only occasionally has an increased titer been reported in scarlet fever, rubeola, tuberculosis, and filiariasis, but this is very uncommon.(2)

VI. Pathology

A. Biopsy. The earliest findings of lymph nodal changes taken in the 1900's were in general lymphoid hyperplasia with, in some cases, description of reticular cells and the endothelial cells of the sinuses. Capsules of the enlarged nodes were stretched but rarely invaded by cellular tissue, while the peripheral sinuses were full of cells. There was no inflammatory foci, no evidence of granulomata, and no areas of necrosis.(3)

Pratt in 1931, suffering from the disease himself, removed a node during the acute stage. He observed marked active hyperemia and much serous exudate within the glandular tissue. There was marked hyperplasia of the reticulo-endothelial cells and numerous areas of hemorrhage and intravascular clotting in smaller vessels. A node removed one year later showed considerable fibrosis and a good deal of congestion, serous exudate, and old hemorrhages were still present. The germinal centers were particularly involved in a picture of degeneration. These latter observations have been contradicted by recent authors. He concluded that the histological picture was due to a toxemia produced by a virus where the main response is called forth from the reticulo-endothelial system, and where the damage is particularly shown in the walls of small blood vessels.(49) An observation similar to that of Pratt's was made in 1926, in a gland removed six months after the disease by Baldridge, Rohner, and Hansmann.(29)

The pathological picture of lymph nodes is not a uniform one and the microscopic appearance of the lymph nodes varies with the stage at which the biopsy was performed. Longscope emphasizes

the importance of both the lymphoid and reticulo-endothelial elements. In one case he found a picture indistinguishable from Hodgkin's disease, which has been the observation of many authors.(2) Downey and Stasney (1935) reported that the hyperplasia of lymphocytes is not as extreme or as uniform as in cases of lymphatic leukemia. In infectious mononucleosis the regeneration of lymphocytes follows a normal scheme, except that the development from the reticulum is accentuated and many of the cells become atypical. The hyperplasia of the reticulum is due to swelling and proliferation of reticular cells, giving sections a spotty and nodular appearance identical with that described by Nishii after staphylococcic reinfections. Changes in the node together with the atypical structure of the lymphocytes and the increase in their number, indicate that the disease is due to infection with some organism or virus which has a very specific stimulating effect on the lymphocytic system. Sinuses were obliterated in some of the cases, but were present in other instances and showed hypertrophied reticular cells. Many observers describe germinal center hyperplasia associated with many mitotic figures occurring early in the disease or as a late process. (1,2,38,50) Fox, writing in 1927, noted the small number of large mononuclear cells in the lymph nodes. He found small mononuclear cells comprised as much as 95% of the cells in the lymph nodes. Phagocytosis of fragments, but not of whole cells, was seen.(48)

Bone marrow reveals an infiltration of the marrow with the lymphocytes as found in the peripheral blood stream.(51) Study of the tonsils shows a marked proliferation of small mononuclear cells.(2)

B. Autopsy. Autopsy is of little value since those that die usually are fatalities from a secondary infection. DuBois in 1930 (cited by Bernstein) had a case in which the patient died of an empyema and findings, which may be of note, were an atrophy of the Malpighian corpuscles in the spleen, together with endothelial proliferation of the sinuses and distention of the lymph spaces by mononuclear cells, many with mitotic figures also in the spleen. In the liver the portal spaces were infiltrated by large mononuclear cells. He drew no conclusions in the lymphoid elements as he regarded these changes as secondary to edema of the primarily involved reticulo-endothelial tissue.(2)

VII. Differential Diagnosis

Infectious mononucleosis is important because of the difficulty in differentiating it from other diseases, particularly those of a more serious nature. It has features which are similar to a variety of diseases, but on more careful examination it is found that these similarities are only superficial in nature. However, it simulates certain other diseases so closely that a long period of study is needed to arrive at a diagnosis, only to find that the Paul-Bunnell test must be relied upon as the sheet-anchor of diagnosis.(2,22)

A. Hematological Disorders.

1. Acute lymphatic leukemia. The patient with acute leukemia is severely ill; there is a marked anemia, pallor, and a high proportion of leukocytes are recognized as being immature. On the other hand, a patient with infectious mononucleosis has an illness of rapid onset which is clinically mild, and there is a mononucleosis

in which only a small proportion of the cells can be interpreted as being immature. The total white count is of no value as the majority of cases with leukemia have a white blood cell count below 40,000 per cu. mm., and many have a count under 10,000 per cu. mm. The morphology of the mononuclear cells is very important and this, along with the clinical picture of the disease, helps in the differentiation. Of great value in diagnosis is the Paul-Bunnell test which is negative in all cases with leukemia.(33)

2. Chronic lymphatic leukemia. It is a disease commoner in old people. There is a slow, insidious onset with anemia, and the lymph nodes are firmer and less tender. The great predominance of nearly normal small lymphocytes is in direct contrast to the bizarre group of abnormal cells seen in infectious mononucleosis.(29)

3. Leukopenic infective monocytosis. Typically, this disease affects older individuals more than does infectious mononucleosis. It is characterized by necrotizing lesions of the oral cavity, marked leukopenia, and the absence of lymphadenopathy or splenomegaly.

4. Agranulocytosis. It is more common in elderly females with a history of drug ingestion. The atypical lymphocytes aid in the diagnosis of infectious mononucleosis in cases where there is a leukopenia. At times, however, abnormal cells do arise in agranulocytosis.

5. Thrombocytopenic purpura. As noted previously, infectious mononucleosis in rare instances may mimic this disease by having a hemorrhagic phenomenon, prolonged bleeding time, reduced platelet count, and a positive tourniquet test. In these respects only

does infectious mononucleosis resemble thrombocytopenic purpura.

B. Diseases Associated with a Sore Throat.

1. Vincent's angina may have lymphocytosis as high as 60 - 70% with the presenting features of infectious mononucleosis, in which case the Paul-Bunnell test is the only differential means. As has been stated before, Vincent's angina and infectious mononucleosis may occur simultaneously.(2)

2. Diphtheria. Cervical adenitis is quite common in diphtheria although it is usually not especially marked at the onset.(29) Infectious mononucleosis differs clinically from diphtheria in the long prodromal period, the long febrile course which may occur, in the general glandular and splenic enlargement, the mild constitutional effects, and the tendency of recurrence. In diphtheria there is an absolute polynucleosis increasing with the severity of the infection, which never changes to a lymphocytosis.(1)

3. Follicular tonsillitis. Infectious mononucleosis may be ushered in by a β-hemolytic streptococcic follicular tonsillitis. In general, the course of follicular tonsillitis is of shorter duration than that of infectious mononucleosis.

4. Aphthous stomatitis produces no changes in the blood. It may be one of the prominent signs of infectious mononucleosis.

C. Diseases Associated with Glandular Enlargement.

1. Syphilis. Secondary syphilis may closely simulate infectious mononucleosis, and infectious mononucleosis may occur in an individual with early or late syphilis. In either event, history, a blood smear, and the Paul-Bunnell test will differentiate the two.(2)

2. Hodgkin's disease. Age, sex, and occupation will differentiate the two. Anemia is characteristic of Hodgkin's disease and the glands are more apt to be firm and less tender than in infectious mononucleosis. Hodgkin's disease has a slow, insidious onset; a fact which usually is the diagnostic tip-off.

3. Tuberculosis. History and the profound nature of a miliary tuberculosis infection are helpful. Clinical course and laboratory findings will differentiate the two readily.(29) Tendency of glands to break down in tuberculosis and the character of their distribution are very helpful.

4. Tularemia. There are no examples of mononucleosis occurring in tularemia. A characteristic local lesion at the site of inoculation in tularemia is a strong differential point.

5. Pertussis may be mistaken in the thoracic form of infectious mononucleosis.

6. Granuloma inguinale is easily differentiated by the clinical course of infectious mononucleosis, blood picture, the character of the lymph glands, and especially their location and distribution.

7. Mossman River fever is a supposedly insect borne disease which occurs in Australia. The disease affects adults. It is characterized by glandular enlargement, especially of the axillary and inguinal groups, a macular eruption, a benign course, and a tendency of recurring at yearly intervals. Leukocytosis is as high as 13,000 per cu. mm., with a lymphocytosis of 45%.

8. Haberfeld's disease is a disease found in Brazil and is insect borne. The disease occurs in the Spring and Fall, and has a generalized lymph node involvement. Once a person is afflicted

a permanent immunity is conferred.

9. Dengue. In dengue there is a typical skin rash, glandular enlargement chiefly of the inguinal lymph nodes, and a leukopenia with a relative lymphocytosis up to 60%. Rarely, there is splenomegaly. The characteristic "break-bone" pains and the etiology of dengue will serve in the differential diagnosis.(29)

10. Mumps. A point of similarity is the onset of unilateral swelling with later contralateral swelling. A previous history of mumps is of assistance. Character and distribution of the glands involved will differentiate the two diseases.

D. Diseases Associated with Cutaneous Eruptions.

1. Chicken pox. Lymphocytosis in varicella may attain the high degree seen in infectious mononucleosis, but rarely does.

2. Scarlet fever. One may be led to an erroneous diagnosis of scarlet fever when there is a scarlatiniform rash with desquamation in cases of infectious mononucleosis.(1,2)

3. German measles. Rubeola has less extensive glandular swellings, confined as a rule to the occipital or posterior group of glands with rare enlargement of the cervical glands, and still more rarely those of the axilla and inguinal regions. The spleen is rarely palpable. In rubeola the lymphocytosis is not as great and there is a higher percentage of plasma cells. There is not the variability of the lymphocytes as seen in infectious mononucleosis. (3,4)

4. Erythema nodosum and multiforme. There may be eruptions of both types with infectious mononucleosis.

5. Influenza. It is similar to infectious mononucleosis only in fever, symptoms, and epidemic nature.(29)

E. Miscellaneous Infections.

1. Typhoid. The two may be identical with the following symptoms of headache, epistaxis, bradycardia with a dicrotic pulse, splenomegaly, rose-spots, leukopenia, and lymphocytosis. In view of this and the fact that infectious mononucleosis may give a positive Widal test, the diagnosis between the two may be difficult.

When there is a negative culture for typhoid, one should strongly suspect infectious mononucleosis.

2. Undulant fever. The onset of the two is similar and infectious mononucleosis may even give a false positive agglutination for B. melitensis.

3. Malaria. Differential diagnosis may be very difficult, as the two may occur simultaneously.

4. Acute rheumatic fever. The two may be exceedingly alike, even to the extent of cardiac involvement.

5. Pneumonia. If one notes too closely the pulmonary signs, delay or complete failure to discern the other manifestations essential in the diagnosis of infectious mononucleosis may result.

6. Acute infections of the central nervous system. Similarity of cells in the cerebrospinal fluid to those in the blood stream is characteristic of the findings in central nervous system involvement by infectious mononucleosis. As previously noted, symptoms and signs of meningeal irritation as well as abnormalities in the cerebrospinal fluid occur in infectious mononucleosis, thus making

it pertinent to differentiate from pyogenic or benign lymphocytic meningitis, encephalitis, or poliomyelitis.(2)

7. Gastro-enteritis and appendicitis. These may be differentiated from infectious mononucleosis by the absence of signs of peritoneal irritation and by presence of concomitant lymphadenopathy and blood picture in infectious mononucleosis.(18)

8. Catarrhal jaundice. The differentiation from infectious mononucleosis may rest entirely on the Paul-Bunnell test.

9. Paranasal sinus disease. In acute cases the symptoms, X-ray, and microscopic findings are usually sufficient to establish the diagnosis. In chronic sinusitis the lymph glands are firm, not tender, and are found in the region drained by the sinuses.(29)

F. Other Diseases.

1. Nephritis. Infectious mononucleosis must be eliminated on the basis of renal manifestations in instances of atypical acute nephritis, particulary where hematuria is out of proportion to other signs.

2. Serum sickness. The only means of differential diagnosis in view of the similar clinical signs is a differential absorption test.

3. Drugs. Quinine and adrenalin may cause a transitory lymphocytosis.(2)

VIII. Etiology

The evidence is overwhelmingly in favor of the lymphoid reaction being due to a specific agent or virus peculiar to the disease, but as yet this etiological agent is unknown.(3)

A. Pathogenesis. Infectious mononucleosis has been considered by the earliest authors as an infectious process. It is apparent that the disease is a generalized infection with secondary disorders of sore throat, meningitis, and involvement of other parts of the body. (2) Park West concluded "all symptoms of the disease were manifestations of a protective reaction, excepting those that were due to direct action of the invader and its toxic products." (8)

B. Possible Relations with Other Diseases:

1. Leukemia. Only one case of leukemia has been offered (by Glanzmann in 1930) in defense of the view that infectious mononucleosis is the initial stage of a disease which may terminate in leukemia (cited by Bernstein). (2)

2. Vincent's angina. The frequent occurrence of fusospirochetal organisms in the inflamed throats of patients with infectious mononucleosis has led such observers as Schmerel, Zikowsky, Friedeman, and Eckeles to attribute to these organisms an etiological role in the general disease. Graham, Smith, and Hunt have been the only men to furnish any experimental observations in support of this hypothesis (cited by Bernstein).

3. Rubeola. Glanzmann, impressed by the clinical similarities between rubeola and infectious mononucleosis, concluded that the diseases must be closely related to a lymphotropic virus.

4. Influenza. As late as 1935 many believed infectious monomucleosis represented the lymphatic form of influenza. During the influenza pandemic of 1918-1919 no associated infectious mononucleosis was noted and there is no reason to believe the two conditions have the same etiological agent.

C. Animal Inoculation Experiments:

1. Monkeys. With rare exceptions animal inoculation has been hopeless, which is also true of blood and lymph node extract injections.

2. Toxoplasma. The experimental disease which Bland (1930) produced in rabbits by injection of blood from a human case of infectious mononucleosis was transmissible serially to other rabbits and to monkeys. He was unable to culture the organism. The etiological agent he believed was a protozoan of the genus Toxoplasma and called "GFI" strain. Toxoplasmiosis is natural to many animals, including rabbits, and the question whether this is a specific toxoplasma remains undecided.(1,2,3,4)

3. B. Monocytogenes hominis. Nyfeldt in 1934 (cited by Bernstein) isolated an organism known as Bacillus monocytogenes from cases of infectious mononucleosis. By special cultural media this small, non-motile, slowly growing bacillus was cultured from the blood of patients with infectious mononucleosis. By injecting the cultured bacteria into rabbits he produced the same blood picture as in humans with infectious mononucleosis. According to him the organism is agglutinated by the serum of the convalescent patient. Recently Schmidt and Nyfeldt were able to grow these organisms from the cerebrospinal fluid of 4 out of 5 patients with infectious mononucleosis, in only one of whom there was clinical evidence of meningitis.(36)

Julianelle, working in 1940, points to the confusion of this bacterium with a diphtheroid. He found that while laboratory animals are easily infected, the monkey is more or less resistant.

The impression gained is that while infected animals manifest the blood changes of infectious mononucleosis, the picture suggests rather than duplicates that seen in humans. He could find no instance in which Listerella monocytogenes stimulated the formation of heterophile antibodies. It is known that the bacterium causes a meningo-encephalitis in man. At present the laboratory work is insufficient to make definite conclusions concerning the etiological role of B. monocytogenes hominis in infectious mononucleosis.(27)

D. Miscellaneous organisms:

Baldridge and his associates in 1927 found a diphtheroid bacillus in the lymph nodes, as well as in the throats of patients with infectious mononucleosis, but they were inclined not to stress their importance in the etiology of the disease, but considered them rather as secondary invaders.(29)

Wising in 1939 (cited by Kracke) pointed to the disease as caused by a virus. Lymph nodes were removed from an infected patient and macerated. In the course of study a laboratory worker accidentally pricked his finger and contracted a proven case of infectious mononucleosis. Wising was unable to prove by the heterophile antibody test that he produced the disease by injection of the material into monkeys.(4)

E. Concluding Remarks:

The etiological agent is still unknown. Best lines of investigation suggest that the causative agent is either a virus or the B. monocytogenes hominis. It is believed that the etiological agent gains entrance into the body through droplet infection, by kissing,

or barely possibly by means of food, and that the portal of entry is the upper respiratory tract in most cases, and perhaps the gastro-intestinal mucosa in a few cases. The lymphoid tissue all over the body becomes invaded. Besides the fever and other toxic manifestations there is a marked hyperplasia of the lymphatic tissue and the entrance into the blood stream of atypical lymphoid cells.(2,3) As a general rule, blood cultures and cultures from the enlarged nodes are uniformly negative.

IX. Therapy

A. Drugs. Treatment is symptomatic and the patient should remain in bed during the febrile period; he should have a bland diet and an abundance of fluids as is true in any acute infectious disease. (1,3,24)

Other measures of treatment should be directed toward the individual symptoms. For the painful lymph nodes, cold packs or the use of mild analgesics will give relief, and if pain is marked codeine is indicated.(1,2)

The throat symptoms are greatly relieved by irrigations with warm cleansing solutions of sodium perborate, potassium permanganate, or gentian violet.(39) It is very often true that Vincent's organisms are present in the throat, in which case local application of neoarsphenamine, gm. 0.15, in glycerine, gm. 10.0, is of value.(22) Should the disease be complicated by a β-hemolytic streptococcal tonsillitis or sore throat, sulfanilamide should be employed as always. When sulfanilamide is used in the absence of a streptococcal infection it does not seem to shorten the course of the disease.

The use of arsenic by mouth or intravenously is without effect.(2) The tendency to constipation will require attention.

Should a patient have numerous relapses, a blood transfusion from a convalescent patient may be useful and may serve to cut short the illness.(22,1)

The doctor should realize that the disease will run its course within one to three weeks, that the patient usually will have an uneventful convalescence, and finally will be quite well with no ill effects of a permanent nature.(17)

B. Isolation. All authors are of the common opinion that strict isolation measures should be carried out during epidemics, even to the extent of an isolation period of from three to five weeks. Whether or not sporadic cases should be treated in such a manner is debatable. Sprunt states that the same measures must logically be taken in sporadic cases as with epidemic cases, since it is probably from sporadic cases that epidemics take their origin.(3) Others do not believe in any isolation measures of these sporadic cases, even going to the extent of treating them on the ward.(22,1,2)

C. Convalescence. How long bed rest should be enforced is best answered by saying that the dictates of common sense should be followed. During convalescence iron and tonics should be given to combat any anemia which may be present and generally to build up the weakened body.(2,17)

X. Conclusions

The doctor in his practice of medicine is faced with no infectious disease having greater variability than infectious mononucleosis. Of all the infectious diseases it is the most difficult to diagnose. Variability is definitely characteristic of the clinical picture, especially true of the onset and subsequent symptoms in the course of the disease. The blood picture too, shows this same confusing variability. A physician should constantly be on guard to keep from mistaking infectious mononucleosis with the more serious diseases manifesting changes in the blood. Even the "sheet-anchor" of diagnosis, the heterophile antibody, strikes home to us the variability of this infectious disease. Time of appearance, titer, and duration of these antibodies concern the ultimate diagnosis. Probably the greatest aid in the diagnosis of this disease having unknown etiology and negligible mortality, is the Paul-Bunnell test. The test is so simple a laboratory procedure that even the most modestly equipped laboratory would be able to give accurate results of the antibody titer in sera of patients afflicted with the disease. Acceptance of the value of this diagnostic test by all will bring to the realization of medical practitioners the unrecognized common occurrence of this disease. It behooves the doctor to be acutely aware of infectious mononucleosis, that he may more skillfully practice his art of healing.

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