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Infectious mononucleosis : analysis of recent cases at the University of Nebraska College of Medicine student health service

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INFECTIOUS MONONUCLEOSIS: ANALYSIS OF RECENT CASES AT THE UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE STUDENT HEALTH SERVICE

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INTRODUCTION

Within recent years on this campus, attention has been focused on the disease process, Infectious Mononucleosis. This has occurred mainly because of its rather frequent incidence among medical students and hospital personnel. In this paper a review of the charts and analysis of the resultant findings from the cases during the past six years, recognized at the University of Nebraska College of Medicine Student Health Service, will be presented. The majority of charts reviewed were primarily those of medical students and members of the School of Nursing. The only charts studied were those that have been listed in the Student Health Service or catalogued in the Medical Records Library of the University Hospital.

It should be noted here that at the time that these cases occurred, special studies were not undertaken with the view in mind that a specific analysis of the disease would be done at a future date. Therefore, the main purpose in presenting this paper is only to point out the incidence of the various clinical, physical, and laboratory findings that were present in definitely diagnosed cases of this disease; and to compare them with those cases that clinically resembled Infectious Mononucleosis, but could not fulfill the strict criteria for diagnosis that it is felt should be stressed.

The hepatic involvement that frequently occurs as a manifestation of the disease will be emphasized, and its relation to future liver disease mentioned.

SOURCE OF MATERIAL

The material for this paper is from the charts of 47 patients who were initially examined and followed by the Student Health Service of the Medical College. Of the total, 39 were medical students; 16 were student nurses; and one was a laboratory technologist. One faculty member was represented. All were in the 19 to 30 year age group; the majority being between 20 and 25 years old.

It is presumed that other students were examined and considered to have this disease, but the diagnosis was neither listed by the Health Service, nor recorded in the Medical Record Library; and therefore could not be included in this paper.

Initially a general survey of the charts was done to exactly determine the number of these cases that were considered to have mononucleosis. This survey revealed that a definite diagnosis was not returned in seventeen cases, although clinical suspicion was recorded by the attending physician.

Screening tests consisting of total white cell count, Schilling differential count, and heterophile agglutinations had been performed in the majority. In all cases inconclusive results were obtained and a diagnosis of Infectious Mononucleosis was not made. None of this group was hospitalized.

Four cases were discovered to have a completely unrelated diagnosis. Two patients were found to have acute pyelonephritis; one had acute sinusitis; and one patient was thought to possibly

have a hemolytic anemia. In this latter instance the presence of a hemolytic process was never proven; and, in addition, the clinical and laboratory evidence was not compatible with a diagnosis of Infectious Mononucleosis. Three of these cases were hospitalized.

Three cases were diagnosed to have infectious hepatitis. Infectious Mononucleosis was considered; but again the total clinical and laboratory picture, including heterophile agglutinations was not conclusive. All three cases were hospitalized.

Twenty-three cases were considered to have mononucleosis. Nineteen of these were hospitalized. It is from these cases that the main source material for this paper was derived; the remainder of the presentation will pertain only to this group.

CRITERIA OF DIAGNOSIS

In considering these cases, the initial problem met with was to determine which patients of this whole group were definitely proven to have had the disease. In come instances the evidence obtained from the analysis of the charts resembled that found clinically and hematologically with mononucleosis, but the serologic evidence as concerns heterophile agglutination was inconclusive or questionable.

This problem was well put forth by Hoagland (1) in 1952 when he postulated the concept that outbreaks of subclinical disorders with hematologic and clinical findings resembling Infectious Mononucleosis are in reality different disease entities. In addition, he further stated that the etiologic agents of these disorders may be micro-organisms closely related to the causal agent of mononucleosis or perhaps, a different strain of the same organism. These disorders, however, do differ serologically; and, he therefore places much emphasis upon the necessity of a positive heterophile reaction being present in addition to clinical and hematologic evidence.

To avoid confusion in the gathering of data for this paper, strict diagnostic criteria were adhered to. It is the belief of the writer that the views of Hoagland in 1955 (2) concerning the diagnostic requirements are most logical in accurately evaluating this disease. He states that the diagnosis can be definite only when the three criteria, mentioned above, are present. These are the clinical,

hematologic, and serologic criteria which together form a basic diagnostic triad. We will discuss each separately and how they relate to this paper.

In regard to the clinical criteria, reference is again made to Hoagland (1) who was one of the first to state that clinically, this disease is not protean in its manifestations; but that the majority of patients fit into a clinical syndrome resembling either a pharyngotonsillitis or typhoid fever. According to symptoms and physical signs, he makes a general classification as follows:

a. Pharyngeal group
b. Typhoidal group
c. Gastro-intestinal group

The pharyngeal and typhoidal groups are very similar in that the symptomatology consists of fever, chilliness, headache, and malaise. They differ only in the presence or absence of pharyngitis. The gastrointestinal group is manifested by symptoms of abdominal pain, nausea, vomiting, and diarrhea. Of his series of 56 patients, 78.6% fit the pharyngeal group; 19.6%, the typhoidal group; and 1.8%, the gastrointestinal group.

Bender (3), in 1954, on examining 410 cases of Infectious Mononucleosis, stated that 96% had a pattern characterized clinically by a pharyngitis of moderate severity with distress much less than the physical findings. He considered the basic syndrome to consist of physical findings of pharyngitis and posterior cervical lymphadenopathy. He stated that posterior cervical adenopathy was the most

constant sign found in mononucleosis and was present in 99% of his cases. Splenomegaly and hepatomegaly were considered helpful diagnostic signs, if present, but not essential to the diagnosis. In regard to clinical criteria in this paper, special note was made of the above stated signs and symptoms. The presence of these in the history and physical examination was considered to be very indicative and consistent with Infectious Mononucleosis.

In regard to the hematologic criteria, relative or absolute lymphocytosis and the presence of atypical lymphocytes are considered to be the characteristic, but non-specific, findings of mononucleosis (2). Early in the course of the disease, a polymorphonuclear leukocytosis and leukopenia may be present, and be followed by these characteristic findings. The presence of the characteristic findings has been noted before as findings that are also characteristic of many viral diseases. This was well explained by Liebowitz (4). Although non-specific, this hematologic picture is essential to the diagnosis. No attempt was made to differentiate the various morphological types of atypical lymphocytes, in this work. In analyzing the hematologic findings of the cases studied, the following changes were looked for, and definite standards adopted in determining our hematologic criteria.

a. Leukocytosis - white cell count greater than 10,000 per cubic mm.
b. Lymphocytosis - lymphocytes compose more than 40% of the differential cell count.
c. Atypical lymphocytes - compose more than 10% of the differential cell count.
d. Leukopenia - - white cell count less than 5000 per cubic mm.

In regarding the serologic criteria, emphasis has been placed by many upon the presence of a significant heterophile reaction as an absolute necessity for the diagnosis of mononucleosis. This has all occurred because of the work of Paul and Bunnel (5) in 1932, when they initially described the presence of heterophilic agglutinins in the serum of patients with Infectious Mononucleosis. It has been shown by Bender (6) and others (1), that mononucleosis with negative serologic evidence in the 17 to 32 year age group is rare or non-existent.

In cases with an equivocal titer, a definite aid has been the differential test of Davidsohn (7). Basically, this test differentiates the antibody of Infectious Mononucleosis from other heterophilic antibodies by the selective absorption of the patients serum with guinea pig kidney antigen and beef erythrocyte antigen. It is used to exclude disease processes that are hematologically and clinically indistinguishable from mononucleosis, but with a borderline titer serologically; in late cases of mononucleosis with a low titer of heterophilic antibodies; and in recognizing cases complicated by the recent injection of horse immune sera.

In the series of cases being considered in this paper only one differential test with guinea pig kidney was done. Therefore, the serologic requirements have been altered. Bender (3) states that a titer of 1:56 on unabsorbed serum with a proper differential absorption is a minimal requirement.

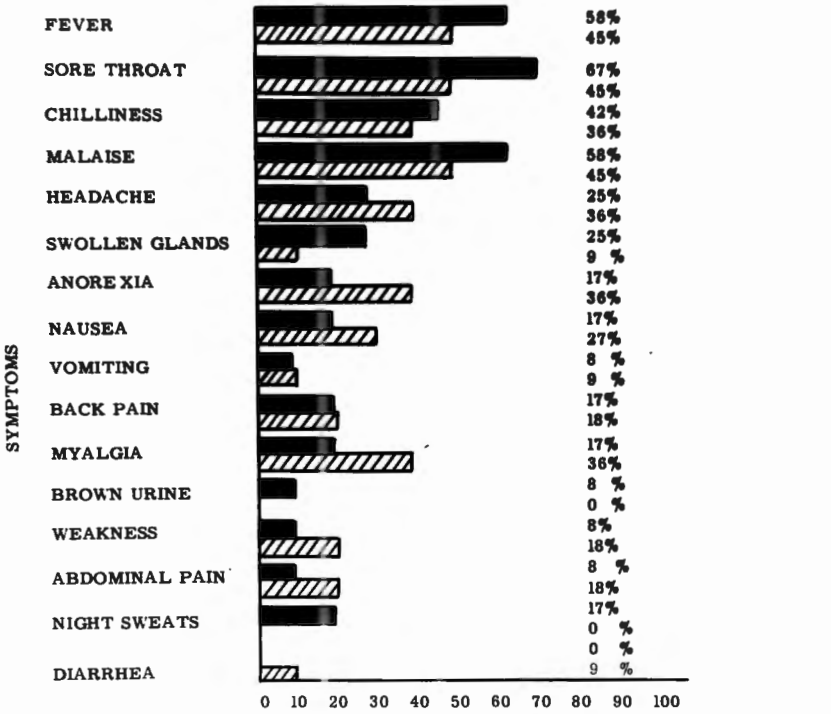
In this paper, the work of Menolascino (8) was adhered to. He states that with positive clinical and hematological findings, a heterophile reaction of 1:224 or greater is a strongly presumptive test. This is also the feeling of McFadden (9). He reserves the differential absorption test to: (a) cases in which the titer is 1:112 or less in suspected cases; (b) cases in which the titer is 1:56 or greater without clinical or hematologic findings; (c) cases with a history of horse serum injection with a titer of 1:56 or more. In this paper, a positive heterophile titer was considered to be 1:224 or greater unabsorbed.

ANALYSIS OF CASES STUDIED

Not all of the 23 cases considered superficially to have Infectious Mononucleosis could be given a definite diagnosis according to the diagnostic triad established. Twelve cases conformed to this triad, and eleven conformed partially. Of the latter cases, nine had two criteria, the clinical and hematologic; two had only one criterion. In each of the latter instances, only the clinical picture was suggestive. Therefore, a division into two groups was thought to be advisable in order that the clinical findings, laboratory and liver function test alterations of each group could be compared. To that end, a division into the definitely proven and probable groups has been made. An attempt will be made to determine whether these probable cases represent Infectious Mononucleosis, or the variants described previously.

The pertinent initial complaints will be considered first. In the definite group, the most common presenting complaints were sore throat in 67%, fever and malaise in 58 %, chilliness in 42%. Headache and swollen glands were each present in 25%, anorexia and nausea in 17%. Back pain and myalgia were also present in 17%. Night sweats were initially present in 17%. Brown urine was one of the initial complaints in 8%.

In the probable cases the complaints were basically the same. The three most common initial complaints were once again sore throat, fever, and malaise; each being present in 45% of the group. The main difference



INCIDENCE OF MOST FREQUENT INITIAL COMPLAINTS

= DEFINITELY PROVEN CASES

= PROBABLE CASES

in symptoms was the greater frequency of headache, anorexia, and myalgia. Each was present in 36% of the group compared to a lesser frequency in the definitely proven cases. Diarrhea was present in 9%, and absent as a presenting complaint in the proven cases. Night sweats and brown urine were not complaints in this group.

In regard to the common physical findings, posterior cervical lymphadenopathy was the most common finding among the definitely proven cases, being present in 92%. Axillary adenopathy was present in 50% of the cases. Fever was present during the course of the illness in 67%. The highest temperature noted was 102° F., and the average was 100.1° F. In most cases initially the temperature was about 99° F. The posterior pharynx was noted as being injected in 58% of these cases. Follicular tonsillitis was described as being present in 25%, and in each instance was in association with posterior pharyngitis. An orange-red palate, and injection of the soft palate were each described as occurring in 8% of this group. Splenomegaly was noted in 75% of cases; hepatomegaly was likewise noted in 58%.

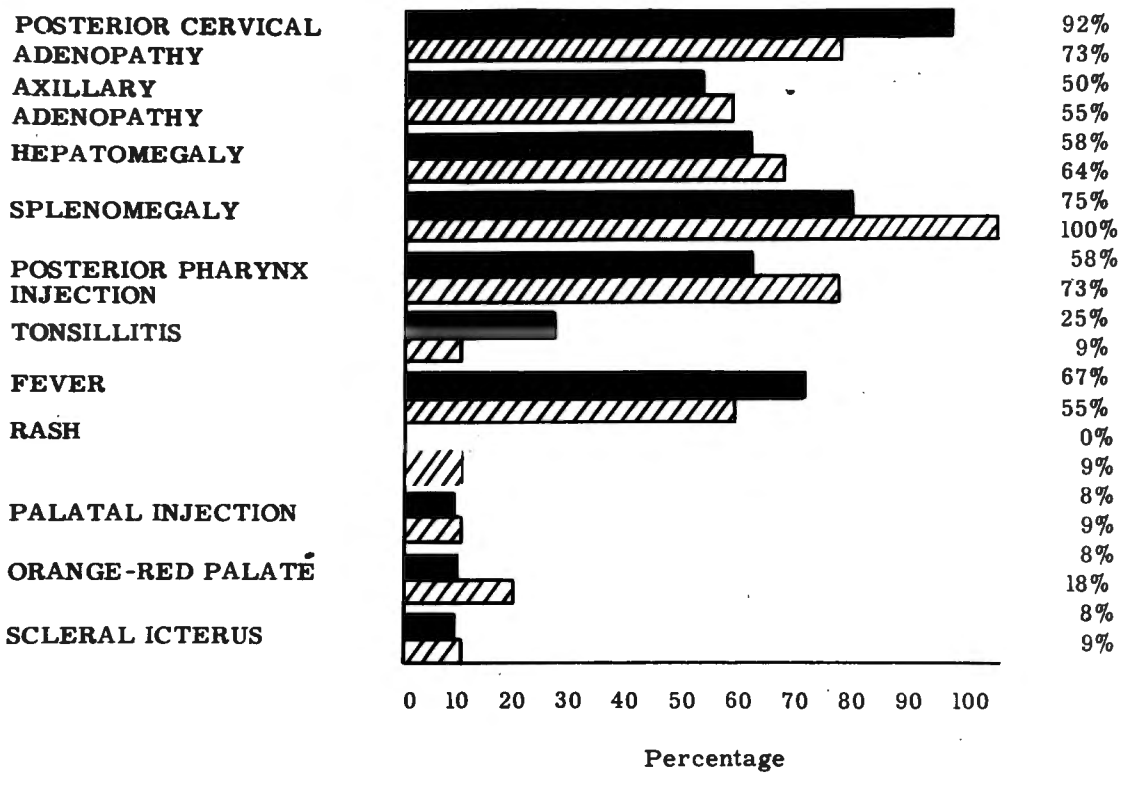
In comparing the physical findings to those found in the probable group of cases, the most striking difference noted was the higher incidence of splenomegaly among the probable cases. It was noted in each of the 11 patients. Posterior cervical adenopathy was present in only 73% of cases, whereas axillary adenopathy was noted in 55% of cases. Fever was present in 55%, but was not further studied. Posterior pharyngeal injection was present in a slightly greater percentage than in the definite cases, being noted in 73%,

but an associated tonsillitis was only present in 9% of these cases. An orange-red palate was present in 18%, and soft palatal injection was noted in only 9%. Hepatomegaly was noted in 64%, which is slightly more than with the definite cases. In contrast to the definite cases, a skin rash was noted during the clinical course in 9% of the patients. Scleral icterus in this group also was only noted in this case.

In analysis of the laboratory findings one factor stands out. By virtue of the diagnostic requirements previously stated, a positive heterophile agglutination titer was present in all of the definitely proven cases. Eleven of the cases had a titer of 1:224 or greater by the sixth day. In one case, the heterophile agglutination became positive between the 10th and 17th day of illness. Five of twelve cases were followed until the heterophile titer was not significant. In three cases the titer was normal by ten weeks; in one case by eight weeks; and in one case by four weeks.

Leukocytosis was present when the blood was initially examined in 33% of the cases definitely proven. In 33% of the cases the leukocytosis first appeared later in the course of the illness. The latest that it appeared was the 18th day, but this was only in one case. The highest count recorded was 19,800/cmm. The average leukocytosis was 14,000/cmm. The duration of the leukocytosis was variable and could not be accurately recorded.

Lymphocytosis was present in all, except one, of the proven cases (92%) at some time during the course of the illness. Initially it was present in 83% of the cases, and in the remainder of the cases, it was



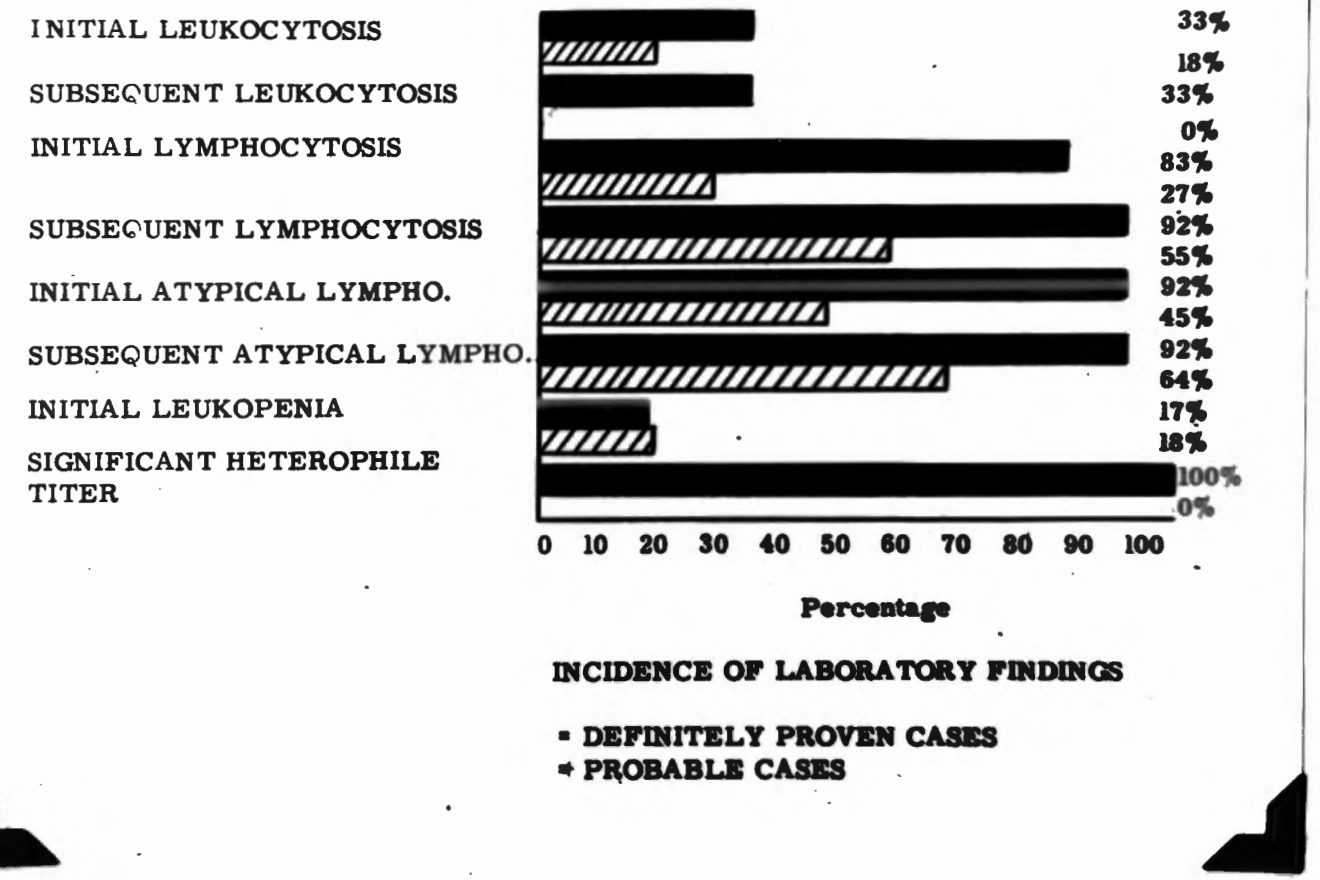
INCIDE NCE OF MOST COMMON FINDINGS

present by the second week. The highest lymphocyte count recorded was 89% of the differential count. The average count recorded was 70% of the differential. The lowest count was 41%. There was no relationship between the total leukocyte count and the percentage of lymphocytes present.

Upon initial examination of the blood, atypical lymphocytes were present in 92% of cases. They were present during the remainder of the clinical course in 92%. Here again by virtue of the diagnostic requirements, all twelve cases showed atypical lymphocytes at some time during the illness. Nine cases had atypical lymphocytes when the blood smear was examined between the second and seventh day after the onset of symptoms. Two cases showed this finding by the tenth day. In one case these cells first appeared on the 25th day after onset of symptoms. The highest percentage of atypical cells recorded was 62%, the lowest percentage recorded was 15%, and the average was 41%.

Initial leukopenia was noted in only 17%.

The group of probable cases showed a marked variation from the laboratory findings present with the definitely proven group. The heterophile titer in each member of this group was not significantly altered. An initial leukocytosis was present in only 18% of the cases, and was not present when the blood was subsequently re-examined. Leukocytosis never appeared at any time later in the clinical course. Lymphocytosis was present initially in 27% of the cases, and it subsequently appeared in 55%. Atypical lymphocytes were noted to be present initially in 45% of cases, and occurred later in only 64% of the cases.



INCIDENCE OF LABORATORY FINDINGS

▪ DEFINITELY PROVEN CASES
▪ PROBABLE CASES

Leukopenia initially did not differ significantly from the occurrence in the proven group, and was present in 18%. The atypical lymphocytes never rose to a value greater than 10% of the differential count.

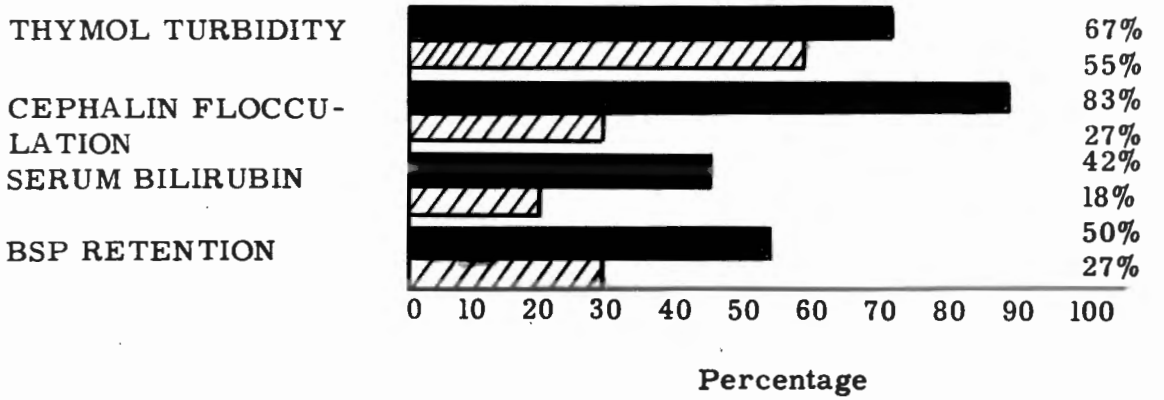
In addition to the above studies, alterations in liver function tests were looked into. In analysis no attempt was made to correlate the presence of significantly altered tests with the time at which such alterations occurred. Only the percentage of tests that were altered was recorded.

The following values were accepted as an indication of abnormality of the respective liver function test: (1) A cephalin-cholesterol flocculation of 3 plus in 24 hours, and 4 plus in 48 hours was considered unequivocal; (2) A thymol turbidity value of over five Bodansky units was considered altered; (3) A serum bilirubin of over 1.2 mg.% by the Van den Bergh method was considered abnormal; (4) A bromsulfalein retention of over 5% in 45 minutes with an administration dose of 5 mg./kg. was considered abnormal. Only these four tests were consistently used in an attempt to ascertain the state of hepatic function.

Among the definitely proven cases the cephalin-cholesterol flocculation was the most frequently altered test, being abnormal in 83%. The thymol turbidity was altered in 67% of the cases; the highest value noted was 19.5 units. Bromsulfalein retention was altered in 50% of the cases; the highest value recorded was 55% retention in one case. This value, however, was transient, lasting only two or three days. The serum bilirubin was altered in 42%; the highest value recorded was 9.6 mg.%. In three cases, the cephalin flocculation was not

used; in two cases, the serum bilirubin was not used. In three cases, the bromsulfalein retention was not used.

In the probable cases, the thymol turbidity was the most frequently altered, being abnormal in 55% of the cases. The cephalin flocculation and bromsulfalein retention were abnormal in 27%. The serum bilirubin showed only slight alterations in 18% of the cases.


THYMOL TURBIDITY
67%
55%
CEPHALIN FLOCCU-
LATION
83%
27%
SERUM BILIRUBIN
42%
18%
BSP RETENTION
50%
27%
0 10 20 30 40 50 60 70 80 90 100
Percentage
ABNORMALITIES OF LIVER FUNCTION TESTS
= DEFINITELY PROVEN CASES
= PROBABLE CASES

TYPICAL CASE HISTORIES

Hospital Number 118917: This 21 year old white male medical student entered UNH for the first time with the complaints of fever and chills for the past four days, and tiredness for the past two to three days. He had a slight sore throat for the past week. Four days prior to admission he noted that he felt feverish, had a chilly sensation and "goose pimples" all over. His feverish feeling later disappeared and was followed by a profuse sweat. He felt well for two days and then had another episode of feeling feverish, and this was followed by a chill. That evening his temperature was 101° F. For the next two days he had afternoon chills with the same temperature. He noted increasing tiredness. One day preceding admission, he noted a few enlarged suboccipital nodes, and came to the Student Health Service. Systemic review revealed that for the three to four days preceding admission he had intermittent sharp, stabbing LUQ pain; a dull, aching low back pain. He noted that his urine had been brownish for the past two days.

Physical examination revealed positive findings of a temperature of 99° F., 0.5 cm. discrete bilateral suboccipital nodes, minimal scleral icterus, grade I tonsillar hypertrophy with bilateral yellowish-gray follicular exudate and a moderately injected posterior phaynx. Bilateral 0.5 cm. discrete posterior cervical nodes were also noted. The abdomen was tender in the LUQ with the spleen questionably palpable 2 cm. below the LCM. The liver was questionably palpable at the RCM and non-tender.

In regard to clinical course: two days after admission, he was vomiting and maintained on parenteral fluids. The WBC was 8000/cmm. with 7 segs, 16 staffs, 49 lymphocytes, 18 atypical lymphocytes, 5 young forms, and 5 monocytes. Thymol turbidity was 7.3 units; cephalin flocculation 1+ in 24 hours, 2+ in 48 hours. Serum bilirubin was 3.44 mg.% direct, 6.44 mg.% total. A diagnosis of Infectious Mononucleosis with hepatitis was made.

On the fourth day, nausea and vomiting were gone; and intake was satisfactory. The sclera were now definitely icteric. Thymol turbidity was 11 units. Serum bilirubin was 6.2 mg.% direct, 9.6 mg.% total. Heterophile agglutination was 1:448 unabsorbed. On the eighth day, he was afebrile and the icterus was clearing. Cephalin flocculation was 4+ in 24 hours, 4+ in 48 hours; thymol turbidity 19.5 units; serum bilirubin 2.9 mg.% direct, 6.8 mg.% total; heterophile agglutination 1:896.

On the eleventh day, he was discharged. The thymol turbidity decreased to 16.5 units; cephalin flocculation 4+ in 24 hours, 4+ in 48 hours; serum bilirubin 0.75 mg.% direct, 2.26 mg.% total.

At one month, thymol turbidity was 10.8 units; cephalin flocculation 2+ in 24 hours, 2+ in 48 hours; serum bilirubin 0.24 mg.% direct, 0.48 mg.% total; heterophile agglutination 1:224.

At 2½ months, thymol turbidity was 6.3 units; cephalin flocculation ± in 24 hours, 2+ in 48 hours; serum bilirubin 0.16 mg.% direct, 1.68 mg.% total; heterophile agglutination 1:56.

At seven months, thymol turbidity 5.5 units; cephalin flocculation

was 1+ in 24 hours, 1+ in 48 hours; serum bilirubin 0.16 mg.% direct, 2.16 mg.% total; heterophile agglutination 1:28.

At ten months, thymol turbidity was 5.5 units; cephalin flocculation ± in 24 hours, 2+ in 48 hours; serum bilirubin 0.16 mg.% direct, 1.78 mg.% total; heterophile agglutination 1:56.

This patient had no subjective difficulty, and after a week of bed rest following his discharge, he returned to classes.

Hospital Number 4841: This 27 year old white male entered UNH for the first time with the complaints of weakness and prostration of one week duration; fever, chills, and light-headedness of six hours duration. He stated that he was in good health until one week preceding admission at which time he "caught a cold", and shortly after, developed a sore throat. He noted that he tired easier after this. The tiredness increased progressively after the past week, so that he was noticeably fatigued. On the day of admission he felt light-headed, weak, and had the sensation of being warm and then cold.

He reported to Student Health Service and following examination was told that he had a high fever and palpable spleen. He was hospitalized the same day. Physical examination revealed a temperature of 102.6° F.; the only other positive findings were very injected posterior pharynx with no membrane; a spleen palpable 4 cm. below the LCM upon inspiration. There was no evidence of posterior cervical adenopathy or icterus.

In regard to clinical course: on the first day the WBC was 5100/cmm.

with 55 segs, 21 staffs, 11 lymphocytes, 10 monocytes, 3 basophiles. Thymol turbidity 4.0 units; BSP retention 0%; serum bilirubin 0.15 mg.% direct, 1.24 mg.% total. On the third day, he had a slightly sore throat with tenderness in the right superior cervical region. A posterior cervical node was palpable on the right side. WBC was 5900/cmm. with 46 segs, 29 staffs, 18 lymphocytes, 5 monocytes. Thymol turbidity was 4.4 units; cephalin flocculation ± in 24 hours, 1+ in 48 hours.

By the fourth day, his temperature was normal. By the sixth day, his strength was much improved, appetite was good, and sore throat gone. Adenopathy was still not noted; the spleen was reported as palpable 6 cm. beneath the LCM, but it was soft and not readily palpable. At this time, review of the smears showed a few atypical lymphocytes. WBC was 11500/cmm. with 39 segs, 8 staffs, 34 lymphocytes, 4 monocytes, A heterophile agglutination done the previous day was reported as negative. The patient was dismissed with a diagnosis of probable Infectious Mononucleosis.

Two weeks after discharge, the spleen was palpable 2 cm. below the LCM. Thymol turbidity was 11.6 units; cephalin flocculation 3+ in 24 hours, 4+ in 48 hours; BSP retention 13.3%. Heterophile agglutination was 1:14.

Three weeks after discharge, the spleen was barely palpable. Thymol turbidity was 9.6 units; cephalin flocculation 2+ in 24 hours, 3+ in 48 hours; heterophile agglutination was 1:14. He subjectively felt well and returned to class with no ill effects noted.

COMPARISON OF RESULTS

In discussing the varied findings that have been presented, no attempt will be made to reveal any new facts. Only a comparison between what has been found here, and by various authors who have investigated this disease will be made.

Contratto in 1944 (10) studied 196 cases and stated that 82% had sore throat at some time during the disease. Headache often heralded the onset of the disease, he remarked, and that although true chills were infrequently seen, a feeling of chilliness was a common symptom. Fever was seen in 89%; 39% of the fevers lasted less than five days. Cervical adenopathy was seen in 76%; axillary adenopathy in 32%. Splenomegaly was noted in 41%; however, no spleens were palpable without adenopathy being present in addition. Jaundice was seen in 5%. Gastrointestinal symptoms were not common, he noted.

Read and Helwig (11) in 1945 reported findings from 300 cases which they analyzed. They noted the most frequent symptoms to be sore throat, headache, fever, and enlarged nodes in the neck. Myalgia was noted in 27%. Cervical adenopathy was found in 41%, and adenopathy was absent in only five out of the 300 cases. Splenomegaly was noted in 65%; hepatomegaly in 16%. Follicular and membranous pharyngitis were present in 48%. Jaundice was noted in 3.7% of the cases.

Kruger, et al., (12) in 1945 noted the following percentages of symptoms and findings. Fever was noted as a complaint in 87%, malaise in 55%, sore throat in 73%, headache in 24%, and cervical adenopathy

in 21%. Generalized aches and sweating were each noted to occur in 5% of cases. Pharyngitis was noted in 88%. All of the patients had adenopathy at some time during the illness, cervical adenopathy was present in 32% of them. Splenomegaly was present in 25% of the cases.

Wechsler and Rosenbaum (13) in 1946 noted that chilly sensations, fever, sore throat, malaise, headache, generalized aching and muscular pains, sweats and anorexia composed the clinical syndrome which they call the anginose group. This group corresponds to the pharyngeal group of Hoagland (1). It made up 49% of their series.

They noted that the febrile course ranged between 99.2° F. and 105° F. It lasted one to three days in all except two cases; the course lasting six days in these two cases. They did not reveal a percentage in which adenopathy was found, but only stated that the glands were small. The liver was palpable in 17%, and was described as being found a finger's breadth below the costal margin and non-tender. The spleen was palpable in 35%, and usually could be felt a finger's breadth below the left costal margin upon inspiration.

Stevens (14) in 1952 analyzed 210 cases and found that symptoms of sore throat were found in 52%, headache in 35%, fever in 34%, cervical adenopathy as a symptom in 34%. Malaise and chill were each found in 25%, night sweats were noted in 13%, generalized aching in 11.4%. Physical findings revealed were cervical adenopathy in 76%, axillary adenopathy in 46%, exudative or membranous phayngitis in 40%. Splenomegaly was noted in 43%, and hepatomegaly in 15%.

Jaundice was found to be present in 6.6% of the cases examined.

Bender (3) in 1954 studied 410 cases and found sore throat to be a symptom in 96% of the cases. Posterior cervical adenopathy was noted in 99%, or all except three cases.

Scanlon (15) in 1955 analyzed 46 cases. He noted that the presence of lymphadenopathy was almost constant, as was pharyngitis. Few of the total examined showed generalized adenopathy.

From what has been presented above, it can be seen that contrary to what has been stated by some, the basic syndrome seen with Infectious Mononucleosis is not protean in nature. This syndrome very consistently adheres to a pattern comprised of symptoms of sore throat, fever, malaise, and chilliness with physical findings of pharyngitis, posterior cervical adenopathy, and splenomegaly in a certain percentage. Generally the commonest symptoms recorded in this paper fit this pattern; however, the discrepancy most marked in comparison of physical findings is the higher percentage of hepato-splenomegaly.

In comparison of the definite and probable cases, no generalizations can be made concerning the symptoms and physical findings except that with the probable group no symptoms stand out as markedly as do sore throat, fever, and malaise in the definite group. The most marked variation in physical findings is in the probable group, where splenomegaly was recorded as being present in all of the cases. On the whole, the findings of the two groups are similar, but the over-all clinical picture is more typical of Infectious Mononucleosis in the group of definitely proven cases.

In regard to laboratory findings, the typical alterations with this disease process are the presence of an absolute or relative lymphocytosis with atypical lymphocytes found in a stained smear of the peripheral blood. Although characteristic of Infectious Mononucleosis, these changes are found with many of the known viral diseases (1) (2). While lymphocytosis is an expected finding, the most significant laboratory finding is the presence of the atypical lymphocytes (14). The diagnosis cannot be made without the occurrence of these atypical cells. However, because of the non-specificity of these findings, the heterophile agglutination titer must be positive to make a definite diagnosis. Liebowitz (16) in 1951 revealed that as stated above the abnormal lymphocyte is not pathognomonic for mononucleosis. In virus diseases, there is no qualitative morphologic difference in the appearance of these cells; but in mononucleosis there is a greater quantitative outpouring of these cells, and a tendency to persist for longer periods of time. With this disease the atypical lymphocytes may comprise up to 90% of the differential count; whereas, in the other viral diseases they are rarely found in concentrations above 10%. Liebowitz states that these cells should be called virocytes because of their frequency in relation to viral diseases.

Wechsler and Rosenbaum (13) found the typical sequence to be an initial transient leukocytosis of 10,000 to 20,000 WBC/cmm., or a normal count followed by a drop to normal or leukopenic levels. The leukocyte count exceeded 10,000 WBC/cmm. in 35.5% of the group. Leukopenia, when found, was due chiefly to reduction in the absolute neutrophile count.

Stevens (14) found the average lymphocytosis to be 65% to 70% with the peak occurring near the 15th day of illness. In 96.6% of the cases, atypical lymphocytes were present. By the eighth day, 54.7% of the cases had a characteristic blood smear. On occasions, he noted a neutropenia with a left shift to the promyelocyte stage. In this paper, the above finding of neutropenia was present in all except one of the definitely proven cases. In one case, a left shift to the promyelocyte stage was noted.

Berte (17) in his review noted that the peripheral blood varies much; usually the WBC is between 5,000/cmm. to 15,000/cmm., but it may vary between 3,000/cmm. to 48,000/cmm. with values at times as high as 63,000/cmm.

Scanlon (15) stated that the atypical lymphocytes vary between 5% and 60% of the lymphocyte count. He believes the findings on the blood smear to be the most reliable early diagnostic evidence.

Hoagland (1) (2) stated that 70% of 69 cases had blood changes in the initial smear. Lymphocytes usually composed 70% to 80% of the total leukocyte count. Other investigators (3) (14) place a great deal of emphasis upon the presence of a positive heterophile titer as necessary for the definite diagnosis because of the non-specificity of the blood picture as a supporting factor to the clinical picture. Bender (3) was willing to accept a diagnosis of mononucleosis when the smear was diagnostic and heterophile titer positive, although the clinical picture was bizarre. He did not make a definite diagnosis in the face of a positive blood picture, but absent heterophile titer under similar

clinical conditions. Hoagland (1) stated that 95.3% of the heterophile titers in his series were positive within two weeks. Wechsler and Rosenbaum (13) found the heterophile titer to become positive most frequently during the first week of illness.

In relation to the laboratory findings revealed in this paper, it can be safely stated that they are definitely typical of the findings described for Infectious Mononucleosis. It did appear that the changes, on initial examination of the blood smear, occurred in a higher percentage than reported by the investigators mentioned. The laboratory changes found with the group of probable cases are much more indefinite and non-specific, although similar to the definitely proven cases.

In commenting on the hepatic involvement that occurs in Infectious Mononucleosis, it has been noted that nearly all patients with this disease will show abnormal liver function as measured by various laboratory tests. Brown and Sims (18) showed abnormalities of one or more liver function tests in 90% of a series of 83 cases. The cephalin flocculation was abnormally altered in 85%; the bromsulfalein retention was increased in 49%. Jordan and Albright (19) in a series of 34 cases, stated that approximately two-thirds to three-fourths of the patients with mononucleosis had an associated hepatitis. They showed an elevated cephalin flocculation in 79%, altered thymol turbidity in 83%, and an abnormal bromsulfalein retention in 71%.

DeMarsh and Alt (20) showed evidence of hepatic dysfunction in all of 19 cases as indicated by cephalin flocculation and bromsulfalein retention. They stated the usual duration of hepatic

dysfunction was three to six weeks. In a few cases, it persisted to about four months.

Bennet and Frankel, et al. (21) believed that associated hepatitis was present in all cases of mononucleosis. Cephalin flocculation abnormalities occurred in 79%, thymol turbidity was altered in 81%, bromsulfalein retention was abnormal in 46%, with elevation of the serum bilirubin in 33%, of their series of 90 patients. There were one or more abnormal reactions in 90.2% of the patients. However, their criteria for abnormalities of liver function were not as strict as those used in this paper.

Watson and Johnson (22), in a series of 55 patients, stated that 70% of these patients who had subclinical mononucleosis showed alteration in either the cephalin flocculation or thymol turbidity.

Hoagland and McCluskey (23), in the latest work on this subject, attempted to prove that the hepatitis of Infectious Mononucleosis is mild and that early ambulation is unlikely to cause harm. Kass and Robins (24) in 1950 had suggested that the rarity of late hepatic complications may be due to the absence of necrosis in the hepatic lesion of mononucleosis. Hoagland (23), by means of liver biopsy, in ten cases found that the histologic pattern in the liver with this disease consisted of abnormalities in the form of lymphocytic infiltration with only minimal hepatic cell changes and without alteration of the hepatic architecture. The lymphocytic cells corresponded to the small and atypical cells of the peripheral blood and were present mainly in

the portal areas and throughout the lobules within the sinuses. In eight out of ten cases, small foci of mononuclear cells and lymphocytes were noted at random in the hepatic lobule, but the foci were unassociated with necrosis or hepatic cell displacement.

In regard to the findings concerning the alteration of liver function in this paper, approximately two-thirds to three-fourths of the definitely proven cases have abnormalities of liver function tests as shown by alteration of two or more tests. This appears to coincide well with the reported findings of the investigators mentioned. The percentage alteration of each liver function test likewise appears to coincide with the reported investigations of others. The trend of alterations in the group of probable cases is the same as with the proven cases, but the percentage of alteration of the individual tests is much less.

It should also be mentioned in discussion that the alterations of the flocculation tests are like the hematologic findings in that they are non-specific reactions to this disease process. Sterling (25), in an electrophoretic analysis of the serum proteins in mononucleosis, found that in percentage composition and absolute amounts there are diminuitions in the albumin fractions and elevations of the gamma globulin fraction when compared with normal sera. He puts forth the hypothesis that the increased gamma globulin is due to an extrahepatic source of serum globulins. Berk, Shay, et al. (26), stated that mononucleosis affects the reticuloendothelial and lymphatic structures which are closely concerned with the formation and storage of

the serum globulins. Since the morphologic alterations of the liver with mononucleosis involve minimal cell destruction, they state that it can be presumed, even though the flocculation tests are associated with alterations in the protein and lipid components of serum, that their alterations are related to the liver changes only in that these changes contribute to the serum protein changes.

The alteration of the bromsulfalein retention and elevation of the serum bilirubin can be explained primarily as a regurgitation phenomenon on the basis of lymphocytic infiltration of the liver with impaired biliary excretion resulting.

SUMMARY

An analysis of 47 cases, seen at the University of Nebraska Student Health Service and thought to be Infectious Mononucleosis, was undertaken. Of this total number, 23 cases had a definite or probable diagnosis of the disease. The triad of clinical, hematologic, and serologic criteria essential to the diagnosis was reviewed, and the manner in which it applied to diagnosis in these cases was clarified. According to these criteria only 12 cases were definitely considered to have this disease, and 11 were considered as probable cases. The analysis undertaken was done comparatively between these two resultant groups; the definite and probable cases.

Statistical charts were presented, which compared the percentage of incidence of the most frequent initial complaints, most common physical findings, laboratory findings, and abnormalities of the liver function tests found in the two groups. Sore throat, fever, and malaise were the most common initial complaints in the definite group. In the same group, posterior cervical adenopathy, splenomegaly, and fever were the most common physical findings. The laboratory findings were consistent with those found by other investigators of the disease. The incidence of alterations of the four liver function tests commonly used, was presented; and likewise, was generally typical of results described with mononucleosis.

Two case histories were presented. One represented a case of definitely diagnosed Infectious Mononucleosis with severe hepatic

manifestations and jaundice. The other case represented a probable diagnosed case of monomucleosis, in which the hematologic and serologic manifestations were not typical, but in which alterations in liver function tests were noted two weeks after discharge from the hospital.

A comparison of the results obtained in this paper, and those obtained by various authors since 1944, was presented. In regard to symptomatology and physical findings, it can be generally said that the clinical syndrome with Infectious Mononucleosis, as illustrated by the results of this analysis, is basically very definite, and not protean. In the series of definite cases, hepatosplenomegaly was more marked; and in the series of probable cases, splenomegaly was present in all the cases. In comparison of the two groups in this paper, no accurate generalizations can be made except that the over-all clinical picture in both is similar, but more precise with the group of definite cases. As stated above, the laboratory findings were consistent with those of other authors. The results of analysis of liver function tests showed that two-thirds to three-fourths of the cases in the definite group had alteration of two or more tests. This also coincides with the findings of other investigators. In the probable cases the general trend of alteration of the individual tests was the same, but the percentage of alteration was much less. The theory for alteration of these tests was proposed.

CONCLUSIONS

From the analysis that has just been presented, it is felt that twelve cases definitely represented Infectious Mononucleosis. In regard to the eleven probable cases, it is felt that these were non-specific disease entities most likely of viral etiology with a clinical and hematological picture similar to mononucleosis, but in which there was a failure to elicit the positive heterophile agglutination reaction that is seen with Infectious Mononucleosis. There is also the possibility that these represent Infectious Mononucleosis caused by a variant of the etiological agent that fails to bring about the formation of heterophilic agglutinins in the serum of those that are afflicted.

As has been stated previously, the general results of the analysis, with the exceptions mentioned, are consistent with those of other investigators.

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