

6-1957

## Infectious Mononucleosis: Medical Staff Conference

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### Recommended Citation

Mateer, John G.; Birk, Robert E.; Wilt, Edward F.; Mason, Warren B.; and Weigel, Gerard A. (1957) "Infectious Mononucleosis: Medical Staff Conference," *Henry Ford Hospital Medical Bulletin* : Vol. 5 : No. 2 , 106-118.

Available at: <https://scholarlycommons.henryford.com/hfhmedjournal/vol5/iss2/8>

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# INFECTIOUS MONONUCLEOSIS

## Medical Staff Conference

J. G. MATEER, M.D., Physician-in-Chief

### Panel

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*Dr. Birk:* This morning we are going to discuss one of the most common infectious diseases of the adolescent and young adult group, namely infectious mononucleosis. That this disease is becoming increasingly more common, or rather recognized, is noted by Farnsworth and Thorndike<sup>1</sup> in a recent article on student health. They state that at Harvard, in the academic year 1954-1955, there were 76 cases of infectious mononucleosis, 43 cases of viral hepatitis, and 11 cases of viral pneumonia in a student population of 10,300. Dr. Wilt will present the general features of this disease.

*Dr. Wilt:* This morning I would like to present some of the historical background and clinical features of infectious mononucleosis. One of the earliest descriptions of this disease was recorded in 1889 by Emil Pfeiffer,<sup>2</sup> who described a febrile illness in children characterized by generalized lymphadenopathy and splenomegaly. He called this condition glandular fever, and was careful in his description to differentiate its benign, self-limited course from the more fulminating progress of the acute leukemias. Nevertheless, in the years following his description this disease was frequently confused with the various forms of leukemia.

In 1920, Sprunt and Evans<sup>3</sup> described the characteristic peripheral blood picture of infectious mononucleosis, emphasizing particularly the increased number of mononuclear cells. They also coined the name "infectious mononucleosis".

In 1923, Downey and McKinlay<sup>4</sup> published their classical morphologic description of the white blood cells, differentiating particularly the appearance of the lymphocytes in this disease and in acute lymphocytic leukemia. However, the modern era in the diagnosis of infectious mononucleosis may be said to date from 1932 when Paul and Bunnell,<sup>5</sup> at the Yale School of Medicine, reported an increased amount of non-specific sheep cell agglutinins in the blood of patients with infectious mononucleosis. With this handy diagnostic tool, and the refinements of Davidsohn and others<sup>6</sup> differential adsorption procedure, the clinician was able to make the diagnosis of infectious mononucleosis in many cases that had previously been obscure. During the years subsequent to the introduction of this technique case reports filled the medical literature, indicating that this was truly a cosmopolitan disease found in all parts of the world. In all series, however, the highest incidence of the disease was reported in the age group 10 to 35 years.

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This is an edited report of a current staff conference of the Department of Medicine of the Henry Ford Hospital.

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## *Infectious Mononucleosis*

The etiology of infectious mononucleosis remains unknown. It is thought to be due to a specific viral agent. Nevertheless, this agent has never been isolated or identified, and, while the disease picture has been produced in monkeys by the injection of infected lymph node material, the results in human volunteers have never been so clear cut.

### SHEEP CELL AGGLUTINATIONS

Type	Serum	Adsorbed by	
		Guinea Pig Kidney	Beef Erythrocytes
I	Serum Sickness	+	+
II	Normal	+	0
III	Infectious Mononucleosis	0	+

Table I: Illustrating the differential adsorption useful in differential diagnosis.

In Table I, I have listed the three types of non-specific sheep cell agglutinens. Type I, found in patients with serum sickness, viral hepatitis, and occasionally in the presence of leukemia, has been found to be adsorbed on both guinea pig kidney and beef erythrocytes. Type II, found in normal human serum is adsorbed on guinea pig kidney alone. Type III, found in patients with infectious mononucleosis, is adsorbed on beef erythrocytes only. This phenomenon of differential adsorption may be of great help to the clinician in making the diagnosis of infectious mononucleosis when the clinical picture is obscure.

With regard to the pathology encountered in this disease, at necropsy in the few cases that have terminated fatally, there has been found generalized lymphatic tissue hyperplasia with enlargement of the mediastinal and mesenteric lymph nodes. The liver and spleen are also enlarged. Microscopically, there is found a perivascular accumulation of normal and abnormal lymphocytes in every organ of the body including the lungs, heart and kidney.

There are many varied clinical pictures of infectious mononucleosis. The classical form of the disease is characterized by a low grade febrile course associated with anorexia, generalized muscular pain, headache and pharyngitis. On physical examination the patient may have a moderate amount of supra-ocular or periorbital edema and the pharynx may be brilliantly inflamed with a dull white exudate on the tonsillar pillars or tonsils. There is generalized but particularly posterior cervical lymphadenopathy, with the lymph nodes being discrete and not particularly tender. The spleen will be palpable in about one-third of all cases on initial examination and will be felt in about one-half of all cases sometime during the illness.

The cutaneous manifestations of this disease are quite varied, ranging from a very transient, erythematous, macular eruption on the chest and shoulders which dis-

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appears in hours, to a widely disseminated, florid, morbilliform eruption which may persist for several days.

The abdominal form may present as an acute abdominal emergency, particularly as acute appendicitis. Presumably due to mesenteric lymphadenopathy, the patient may have nausea, vomiting, right lower quadrant pain, and abdominal rigidity. The diagnosis in these cases may best be made by the differential white blood count.

The neurologic manifestations also are quite varied, ranging from the mild nuchal rigidity which is a frequent presenting complaint to the overwhelming peripheral neuropathies with flaccid paralyzes of the extremities, ascending bulbar paralyzes with respiratory involvement, coma and death. There have been five reported fatalities from this type of central nervous system involvement.

The hematologic picture may be manifested clinically by evidences of a purpuric rash, ecchymoses and the presence of thrombocytopenia. It is in this particular form of the disease that ACTH and the adrenocortical steroids have recently been found valuable.

The prognosis in the uncomplicated case is uniformly good, with complete recovery without sequelae in from three to six weeks. The complications will be discussed in some detail later in the program, but I should like to bring to your attention the 16 reported fatalities of which 12 have been due to either splenic rupture or the complications of meningo-encephalitis.

The differential diagnosis, as you might well imagine, is lengthy, but in the presence of the characteristic findings and laboratory data I have described, the diagnosis should not be difficult.

Finally, a word regarding treatment. The therapy is entirely non-specific with the emphasis particularly on bed rest and symptomatic management. Bed rest should be enforced as long as the spleen is enlarged because of the danger of splenic rupture. The adrenocortical steroids have a very definite place in the management of these patients, particularly in the severely toxic individual with jaundice or thrombocytopenia. In these cases a very prompt clinical remission may be expected.

*Dr. Birk:* As Dr. Wilt has mentioned, this disease is still of unknown etiology, and therefore, everything that he has said and all that we will say from here on, may well be contested. This is true, of course, in any disease in which the etiology is undetermined. Any definite statements regarding diagnostic studies, results of specific therapy or prognosis of infectious mononucleosis must necessarily be made in a tentative way, as the non-specificity of the various diagnostic tests does not permit for definitive evaluation.

We have personally seen 17 cases of infectious mononucleosis in hospital personnel in the past year and fortunately, so far, have had no complications. However, there have been reported a great many complications of the disorder which Dr. Mason will now discuss.

*Dr. Mason:* The complications of infectious mononucleosis have been divided into eleven categories as shown in Table II, taken from an article by Dr. Jason N. Smith,<sup>7</sup> formerly of the Division of Gastroenterology. Actually not all these manifestations can be considered as complications, but rather, some are manifestations of a systemic

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### COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS

1. Neurologic — 64 cases
  2. Splenic Rupture — 21 cases — 7 deaths
  3. Hepatitis — nearly all — Jaundice 6.6% in one series
  4. Hemolytic anemia — 16 cases
  5. Thrombocytopenic purpura — 16 cases
  6. Pulmonary — 2% in one series
  7. Cardiac — 9 cases of pericarditis
  8. Abdominal
  9. Renal — hematuria 6% in one series
  10. Eye — common — papilledema in 4 cases
  11. Dermatologic — rash 8% in one series
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Table II

A listing of complications modified from Smith's<sup>7</sup> article.

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disease. Since infectious mononucleosis may involve all organs, symptoms involving other than the lymph nodes, liver and spleen may be the presenting complaint.

The first complication to be discussed is neurologic. The number of reports has been rapidly accelerating in recent years. Neurologic complications can be subdivided into six parts, the first of which is serous meningitis. It is manifested by headaches, stiff neck, and increased spinal fluid pressure. Actually this is quite common; however, only four acceptable cases are recorded. The second sub-division is meningitis which gives the same symptoms plus signs of meningeal irritation. Ten cases have been reported. The third sub-division is meningeal encephalitis which has all of the above symptoms plus lethargy, dizziness, staggering, aphagia, nystagmus, hemiplegia, convulsions and coma. The fourth sub-division is pure encephalitis of which 20 cases have been reported. The fifth sub-division is that of a Guillain-Barre like syndrome with weakness, flaccid paralysis and a high spinal fluid protein of which 18 cases have been reported plus the two cases reported from this institution. There have been four deaths of this type. The sixth sub-division is that of peripheral neuropathy. The diagnosis is quite difficult since neurological signs may be the presenting complaint. Often the diagnosis is made by accident after routine smear has been obtained.

The second major manifestation or complication is that of rupture of the spleen. Twenty-one cases of spontaneous rupture have been reported with seven deaths. There is an invasion of the fibrous structure of the splenic capsule with lymphocytes. Weakening of these structures results, and rupture may occur with minor trauma, even that of palpation. After rupture, when peritonitis begins, there may be a shift to the left of the white cells and the smear will appear more normal, thus making the diagnosis more difficult.

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The third complication is that of hepatitis. It is now believed there is some involvement in nearly all cases. Jaundice has been reported to occur in 6.6 percent of one series. The damage is thought to be of the hepatocellular type, rather than obstructive.

The fourth complication is that of acute hemolytic anemia of which 16 cases have been reported. Lack of anemia was always considered a good differential point from leukemia. It has been suggested that the enlarged spleen forms autohemolysins. The Coombs' test has been found positive in four cases and negative in one. As the heterophile titre drops the hemolysis stops and splenectomy is not necessary, although it has been done in one instance. ACTH and cortisone are effective in this complication.

The fifth major manifestation is thrombocytopenic purpura, 16 cases of which have been reported. Mild bleeding phenomena, such as epistaxis, have been commonly reported but true thrombocytopenia occurs explosively at the height of the disease. These people always recover with transfusion. Only recently it has been reported that ACTH and cortisone are effective in treating this particular complication.

The sixth major manifestation is that of pulmonary complications. Pneumonia has been commonly reported and pleural effusion has been noted in one case. The x-ray picture is said to be that of viral pneumonia while the cough is said to simulate pertussis.

The seventh major manifestation is that of cardiac complications. These are usually subclinical and benign; that is, there are non-specific electrocardiographic changes. However, nine cases of pericarditis with chest pain, friction rub and elevated RST segment with inverted T waves have been reported with no deaths.

The eighth complication or manifestation is that of abdominal involvement. This has been mentioned by Dr. Wilt and these represent manifestations of the enlarged mesenteric nodes.

The ninth manifestation is that of the renal complications. Red and white blood cells have commonly been reported, but only rarely do albumin or casts appear in the urine. In one epidemic six per cent of the cases presented as hematuria. There is no known association of these transient changes with coexisting chronic renal disease.

The tenth group is comprised of complications occurring in the eye. Oculomotor palsies are the most frequently reported. Papilledema has been reported both with and without neurologic complications. There is frequently a dry granular conjunctivitis, often unilateral and strangely enough, most often occurring on the left.

The eleventh manifestation is that involving the skin. Rashes have been reported in as high as seven percent in one series of 210 sporadic cases. The rash may be of any type, and has been described as macular, maculo-papular, urticarial, hemorrhagic, erythemamultiforme-like, and morbilliform.

*Dr. Birk:* Dr. Quinn has probably seen as many cases of infectious mononucleosis in this hospital as any other person, with the possible exception of Dr. Monto and his group. He has also reported three major neurological complications. Dr. Quinn, I wonder if you would comment on the neurological complications?

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*Dr. Quinn:* (Physician-in-Charge, Division of Infectious Disease):

In the Henry Ford Hospital 239 cases of infectious mononucleosis were indexed in the years between 1925 and 1953. Nervous system involvement was noted in only five cases; in two it took the form of an aseptic meningitis. In the other three cases an acute polyradiculoneuritis of the Guillain-Barre type developed. These were reported by Drs. Rafferty, Schumacher, Grain and myself in 1954.<sup>8</sup>

In a review of the literature reported in 1950, Bernstein and Wolff<sup>9</sup> estimated the incidence of central nervous system complications in infectious mononucleosis as probably less than 1 percent.

The types of neurologic manifestations which have been described fall into four main categories:

- a. Lymphocytic or serous meningitis
- b. Meningoencephalomyelitis
- c. Acute polyradiculoneuritis
- d. Peripheral neuritis

The two cases of aseptic meningitis were both diagnosed in the 1952 poliomyelitis epidemic when all cases with "non-paralytic poliomyelitis" were examined by blood smear and heterophile agglutinations. These patients presented minimal symptoms and signs suggestive of infectious mononucleosis.

The 3 cases reported as the Guillain-Barre syndrome were all males, and their ages were 24, 16 and 50. In one case both the heterophile agglutination and blood smear were considered diagnostic, while in the other two cases only one of these two tests was positive, the typical blood picture in one and the positive heterophile reaction in the other. All three patients demonstrated typical neurologic findings of acute polyradiculoneuritis and had increased spinal fluid protein and an absence of pleocytosis in the spinal fluid.

Two of these patients were moderately ill and one was severely ill requiring a period of ten days in the tank respirator. When last seen for follow-up, all exhibited some residual muscle weakness and disability.

We also reviewed the Henry Ford Hospital records for the indexed cases of Guillain-Barre syndrome and encountered 34 cases in the ten year period from 1943 to 1952. In four cases the illness was preceded by a "cold," three cases followed a sore throat, and in two there was a history of "flu." One case followed an acute gastroenteritis. The three cases referred to above were associated with infectious mononucleosis, and the remaining 22 cases presented no history of preceding illness.

*Dr. Birk:* Dr. Abraham, would you care to comment on the hematological complications and your thoughts concerning what Dr. Mason had to say about them?

*Dr. Abraham:* (Associate Physician, Division of Hematology):

With regard to the hematologic complications, they are often not the most striking and consequently we see perhaps less than 50 percent of the total number of cases in the hospital. Nevertheless, they justify some brief discussion.

Significant anemia is not a frequent complication, and its occurrence usually casts

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some doubt on the diagnosis. However, a few cases of infectious mononucleosis have been accompanied by hemolytic anemia.

Neutropenia may occasionally be so pronounced as to suggest agranulocytosis.

Bleeding phenomena, particularly epistaxis, hematuria, or petechiae on the skin are not unusual. Rarely, fullblown thrombocytopenic purpura is observed.

Rupture of an enlarged spleen is a striking but unusual complication. However, it does indicate the need for some restraint in repeated palpation of that organ.

In a different sense, confusion with leukemia is indeed a complication for the attending physician.

Fortunately, serious hematologic complications are rare and the prognosis in general is good from our standpoint.

*Dr. Birk:* One of the most confusing of the differential diagnostic features to be clarified is that of hepatitis in infectious mononucleosis versus infectious hepatitis. Dr. Mason has already touched upon this and Dr. Weigel will now discuss it more thoroughly.

*Dr. Weigel:* The hepatitis that is associated with infectious mononucleosis is still subject to both clinical and pathological difference of opinion. Jaundice was first reported in infectious mononucleosis by Mackey<sup>10</sup> in 1926, and it was originally considered that the basic responsible factor was lymph node enlargement impinging upon the common duct with obstruction. The work of Bang and Wanscher<sup>11</sup> then suggested that the liver was actually involved with a pathological process of a parenchymatous nature. They felt that this was pathologically indistinguishable from infectious viral hepatitis. Recently, a number of workers have agreed that while some degree of hepatitis exists in practically all cases of infectious mononucleosis, both the pathology and the therapeutic implications are different from those of true viral hepatitis.

There is general agreement concerning the clinical manifestations of the liver involvement in infectious mononucleosis and these general observations may be made. About 15 to 25 percent show hepatomegaly at some time during the course of their disease and about five percent are jaundiced. The jaundice usually appears during the second week of illness, after the patient has sought medical attention earlier because of fever, malaise, sore throat or some other symptom frequently associated with the process, as opposed to the usual patient with hepatitis who is jaundiced when first seen or within a very few days thereafter. The jaundice of infectious mononucleosis is seldom marked and usually clears in two or three days. However, cases have been reported with jaundice persisting for eight weeks. The absence of pain, the presence of fever, lymphadenopathy and splenomegaly tend to favor the diagnosis of infectious mononucleosis, but can occur in hepatitis. It is to be noted that the presence of a sore throat is the most helpful feature clinically differentiating infectious mononucleosis from infectious hepatitis.

Liver function studies are somewhat variable but it is agreed that the cephalin-cholesterol flocculation test is positive in at least 95 percent of cases. The bromsulphalein and thymol turbidity tests are very frequently positive and as much so as in hepatitis. An elevated alkaline phosphatase suggests that there is some degree of



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obstructive feature to the hepatitis and determinations considerably above the dividing line of 10 Bodansky units are not infrequent. It is generally considered that leukocytoid lymphocytes can occur with infectious hepatitis though they definitely tend to be fewer in number. A significant heterophile determination is the salient feature in distinguishing the two entities.

Pathologically, the findings by liver punch biopsy are essentially the same in jaundiced and non-jaundiced patients, and for practical purposes are present in every case of infectious mononucleosis. Hepatitis is a regularly occurring feature of the disease and not to be considered a complication. This is not surprising in view of the fact that the hepatic mesenchymal cells may be lymphocyte precursors and the etiological agent of infectious mononucleosis, whatever it may be, seems to stimulate lymphocytic production and development. The pathological features of infectious mononucleosis are the presence of large numbers of mononuclear cells in the portal areas with foci throughout the lobules and within the sinuses. About half the cases show eosinophils in the periportal exudate but neutrophils and plasma cells are absent.

The pathological features of infectious mononucleosis distinguishing it from hepatitis are on the negative side, in that there is very minimal hepatocellular damage, occurring only in areas where foci of lymphocytes within the lobules encroach mechanically upon the surrounding liver cells. Eosinophilic degeneration, which has been earmarked as characteristic of hepatitis does not occur, and there is no distortion of the hepatic architecture. In general it may be said that the hepatitis of infectious mononucleosis tends to be much more a mesenchymal and much less a parenchymal type process than is infectious hepatitis.

These pathological features have clinical application in the follow-up care of the hepatitis of infectious mononucleosis, which in general tends to be mild. There has been one case reported of cirrhosis following mononucleosis, but on closer perusal one questions whether or not this was merely a coincidental occurrence. There have been two cases of fatal liver involvement reported; but again, when one considers the vast number of cases of infectious hepatitis and the extreme frequency of liver involvement, one hesitates to attribute this liver damage solely to the infectious mononucleosis.

There would, in general, appear to be pathological support of the concept that one need not be too severe in the restriction of activity of patients who have laboratory evidence of hepatitis in infectious mononucleosis. If the patient is afebrile and otherwise asymptomatic even when jaundice is still present, it would seem logical to begin gradual ambulation. Long-term follow-ups by Hoagland<sup>12,13</sup> tend to support this. He has had no complications using a program allowing ambulation when fever and clinical symptoms have abated.

*Dr. Birk:* Dr. Haubrich would you care to comment on Dr. Weigel's presentation?

*Dr. Haubrich:* (Associate Physician, Division of Gastroenterology):

In commenting on a truly generalized disease, those of us representing the various subspecialties run the risk of casting ourselves in the roles of the five fabled blind men sent to examine the elephant. To him who felt the ear, the elephant was like a fan; the tail was likened to a rope, the leg to a tree, and so on. Infectious mononucleosis is a *generalized* disease, and it is not surprising that its manifestations are varied.

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Using "hepatitis" in the generic sense, we are reminded that inflammation within the liver may be induced by any of at least 25 distinct pathogenic organisms; viral, bacterial, spirochetal, and protozoan. Conversely, the virus of infectious hepatitis may induce disease in extra-hepatic systems, e.g., myocarditis and atypical lymphocytosis.

There are three aspects of the relationship between infectious mononucleosis and the liver which deserve emphasis:

(a) At least 80 per cent of patients with infectious mononucleosis will exhibit aberrations in so-called liver function tests, particularly in the flocculation and turbidity tests which depend upon poorly defined changes in the serum protein content and only indirectly reflect liver function. Hepatomegaly is observed in about 15 per cent and frank jaundice in about 5 to 10 per cent of patients. I am sure that the incidence of *actual* liver involvement lies somewhere between these extreme figures.

(b) Regarding the histologic distinction within the liver between infectious mononucleosis and infectious hepatitis, we may look upon the former as primarily a reticulo-endotheliosis with attendant inflammation and upon the latter as a direct injury to the parenchyma itself. Granted that it is seldom such a black-and-white situation to the pathologist examining a liver biopsy, nevertheless, I offer this as a useful concept.

(c) Finally, as Dr. Weigel has stated, the hepatitis component of infectious mononucleosis is almost invariably short-lived and benign. I am not aware of a single *bona fide* instance of lasting liver damage which can be rightfully attributed to a single attack of infectious mononucleosis.

*Dr. Birk:* In Table III, you will note listed six representative cases of the 17 that we personally have seen in the past year. These six cases were selected because they represent features of the disease which are particularly striking. I wish to point out especially the frequency of fatigue as a presenting symptom, either alone or in combination with one of the other symptoms of this disorder. It is safe to say that all patients with infectious mononucleosis complain of fatigue to a greater or lesser degree, and that it is the predominant factor in the morbidity.

The first three cases are essentially similar in that they are white, female, 19 year old student nurses. The first case is significant in that the heterophile titre is so high, that is, 1:245,376. There were also a high percentage of leukocytoid lymphocytes and very positive liver flocculation studies. This young lady was toxic for some time, and her symptoms of severe fatigue, anorexia, and malaise persisted not only for a total of 46 days, but were so pronounced that she was unable to return even to classes, and consequently was forced to lose a full year in her training. This loss of time certainly must add to the total morbidity as most of these people are in the student age group.

It is interesting to note that the second patient also had a high heterophile titre, as our titres go, with a high percentage of leukocytoid lymphocytes and that while both had very positive liver flocculation tests, neither had jaundice.

The third case is interesting in that only cervical adenopathy was present and that the degree of morbidity was somewhat less. The first three cases alone would seem to indicate that the degree of toxicity is related to the elevation of the heterophile titre. The fallacy of this is shown by the last three cases, particularly the fourth.

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### REPRESENTATIVE CASES OF INFECTIOUS MONONUCLEOSIS

Number	Sex	Age	Presenting Symptom	Days of Symptoms	Fever	Nodes	Spleen	Liver
1.	F	19	Fatigue	46	+	G	+	+
2.	F	19	Sore Throat	9	+	G	+	+
3.	F	19	Sore Throat	7	O	Cerv	O	O
4.	F	18	Nausea, Fatigue	13	+	G	+	+
5.	M	16	Fever, Headache Sore Throat	25	+	G	+	+
6.	F	26	Fatigue, Hematuria	10	+	G	O	O

Number	Sex	Age	Other Signs	Highest Heterophile	Highest % L. L.	Highest C. C.	Liver T. T.	Floc c T. F.
1.	F	19	Strep Exudate	1:245,376	73	4+	12u	4+
2.	F	19	Strep Exudate	1:7168	67	3+	7u	4+
3.	F	19	Strep Exudate	1:896	30	3+	1u	+
4.	F	18	Rash	neg.	19	3+	5u	3+
5.	M	16	Exudate Eye edema	1:1792	68	3+	3u	+
6.	F	26	Eye edema	1:3584	40	3+	5u	3+

Table 3: Six cases of the seventeen seen in past year, representing major clinical features.

This girl had 13 days of toxicity with all the other features of severe infectious mononucleosis but with negative heterophile titres and only a few leukocytoid lymphocytes on repeated examinations.

The first three cases also illustrate another important point, that is the common association of beta-hemolytic streptococcal pharyngitis and infectious mononucleosis. This association may exist with or without the typical white, membranous pharyngeal exudate of infectious mononucleosis. I would like to emphasize this point and urge that every patient with infectious mononucleosis have a throat culture. The hemolytic streptococcus, if present, should be treated adequately with penicillin.

Case three illustrates also the absence of a palpable spleen which, as previously noted, is not infrequent. Another point deserving emphasis is that once the spleen is found it would be then best left alone. Many patients have been seen initially in the clinic and a non-tender spleen and liver palpated. On subsequent examination the next day, after repeated examinations during the admission procedure, both were extremely tender, with much discomfort to the patient and increased risk of trauma.

Case number four had a classical picture of infectious mononucleosis plus a morbilliform rash for three days, despite a negative heterophile and few leukocytoid lymphocytes. Wintrobe<sup>14</sup> states that the heterophile titre is positive in only 60 percent to 92 percent of the series he has studied and that a titre of 1:64 is significant. It is interesting to note that Leibowitz,<sup>15</sup> who admits that he was probably the only exponent of excluding the diagnosis unless the heterophile was positive, recently reported three cases of infectious mononucleosis with a negative heterophile titre. He relates this to the possibility of two different but related viruses, a "non-reactive" patient, or of a test incorrectly done.

Case five illustrates the disease in a young boy, who was quite toxic for four or five days with fever, headache and sore throat before being admitted. He continued to have fever and marked malaise for another five days and, because of the increasing toxicity and high fever, he was treated with steroids. He received hydrocortisone in decreasing doses over a period of six days. It is interesting to note that his symptoms and fever completely disappeared in 12 hours and he made a very rapid and uneventful recovery.

Case five and six both illustrate one of the frequent signs of this disease which is easily missed unless looked for, that is periorbital edema. Both had marked periorbital edema, to the extent that case six was mistaken initially for primary renal disease. This patient had a history of acute glomerulonephritis at the age of six and was seen complaining of periorbital edema and fatigue for approximately a week. Initial urinalysis revealed microscopic hematuria, slight albuminuria and a few casts. Two days later, while under observation, she developed generalized adenopathy and the diagnosis became evident. The hematuria as well as the casts and albumin were present for the first two days and then disappeared entirely.

One last point is illustrated by a 24 year old white female who, in November of 1956, had 10 days of marked anorexia, fatigue, sore neck and malaise. She did not consult a physician at that time. She was seen approximately three months later complaining of fatigue, anorexia and stiff neck. Examination revealed generalized adenopathy and a palpable spleen and liver. She stated she had not felt "right" for three months. Laboratory studies were entirely negative, and she made an uneventful

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recovery after one week of bed rest and limited activity for a short time. I feel that she had a relapse of infectious mononucleosis which originated three months before, or that the "post-viral asthenia" was this long drawn out. Wintrobe<sup>14</sup> states that recrudescences are quite common and may occur in about six percent. A recent article by Koyl<sup>16</sup> describes a new disorder, "infectious reticuloendotheliosis", which is characterized by long standing fatigue and irritability and may well represent long standing post infectious mononucleosis asthenia.

As far as treatment is concerned, I must disagree wholeheartedly with the statement that bed rest is unnecessary. Treatment of the associated hepatitis by rest is not indicated, but total rest while toxicity persists does seem to promote quicker recovery and does seem to prevent further relapse. After symptoms disappear, limited activity is indicated as this also seems to reduce the total period of morbidity.

No special diet, other than a good general one is indicated, as Dr. Weigel has stated.

The use of penicillin in those patients with an associated beta hemolytic streptococcal infection is imperative. This is probably the most frequently overlooked intercurrent infection with infectious mononucleosis and needs treatment to prevent prolonged toxicity during the acute episode or further disability from the streptococcus at a later date.

As to the use of steroids, aside from their use in the severe complications where it is of unquestionable value, if the patient does not become afebrile and relatively asymptomatic after five days, the use of steroids in moderate dosage for about six days seem to promote symptomatic recovery and may prevent longstanding morbidity.

We now have some time for discussion.

*Dr. Frank R. Menagh:* (Consultant, Division of Dermatology): Are antibiotics routinely used in treatment?

*Dr. Birk:* Antibiotic therapy is not indicated unless it is for an associated infection, especially with the beta-hemolytic streptococcus, in which case adequate penicillin is indicated. If the patient is penicillin sensitive, other antibiotics, usually the tetracyclines, are used.

*Dr. Mateer:* Do you think the use of steroids in the non-complicated case causes a reduction in the total morbidity?

*Dr. Birk:* I do not feel that steroids actually shorten the course of the disease in any way except to reduce the severity of the symptoms. This may, however, promote faster recovery by increasing the appetite and so forth. Dr. Quinn, would you comment on that?

*Dr. Quinn:* We are not now able to determine whether a specific treatment is of any value in this disease because of the lack of properly controlled studies. We should set up such a study and attempt to evaluate the effectiveness of steroid therapy.

*Dr. C. E. Rupe:* (Physician-in-Charge, Medical Clinic #4): How long can the latent period be before the appearance of leukocytoid lymphocytes in the smear?

*Dr. Birk:* One recent case had a 21 day period from the onset of fatigue and anorexia to the clinical picture. She, however, had negative heterophile titres and only 13 percent leukocytoid lymphocytes at that time. There may have been a time in this 21 day period in which she had more positive findings which were not detected.

## Mateer and Panel

*Dr. Weigel:* Ninety-five percent of the cases show a positive heterophile titre, if it is going to become positive, in the first determination, and the titre most frequently becomes positive within the first two weeks.

*Dr. Birk:* The practice of drawing an initial heterophile determination in a patient with the clinical picture of infectious mononucleosis and discarding the diagnosis because of a negative result should be avoided however.

*Dr. Robert Nixon:* (Associate Physician, Division of General Medicine): I should like emphasized two points in connection with certain of the comments that have been made. First of all, patients with infectious mononucleosis may reveal initially only a mild leukocytosis with a neutrophilia without changes in lymphocytes for sometime up to a week before atypical lymphocytes make their appearance. In addition, there may not uncommonly be a premonitory eosinophilia again antedating the appearance of classical changes in the lymphocytes.

Insofar as the differentiation of the hepatitis which may occur in infectious mononucleosis from that of ordinary viral hepatitis, the following may be stated: in most instances, the peripheral smear reveals a much more marked degree of lymphocytosis and characteristically the finding of all types of atypical or leukocytoid lymphocytes in infectious mononucleosis with hepatitis, whereas, in infectious hepatitis one rarely sees more than a few, i.e., 5 percent to 20 percent atypical lymphocytes, without the marked variation in types referred to in infectious mononucleosis. Hence, in most instances, the degree and character of the atypical lymphocytes of infectious mononucleosis hepatitis is fairly easily differentiated from ordinary viral hepatitis. Of course, the other clinical and serological features will also make this differentiation clear.

*Dr. Birk:* Thank you. Our hour is up.

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