1955

Liver involvement in infectious mononucleosis

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1955

Omaha, Nebraska

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INTRODUCTION

Peterson (1) reports that in the original description of the disease called glandular fever published in the late nineteenth century, Pfeiffer mentioned enlargement of the liver as one of the physical findings and shortly thereafter, Snapper and co-workers first described jaundice in patients with infectious mononucleosis. Since that time, a considerable amount of investigation has been recorded in the literature concerning the liver in infectious mononucleosis and numerous significant aspects have been revealed. The subject is of special interest because the disease is common, although a large number of cases go unrecognized or are passed off as an upper respiratory tract infection, "the flu", or some other condition, and the high incidence of hepatic dysfunction present some time in the course of the illness. These features, in turn, bring forth two important problems. Firstly, those cases which present themselves with jaundice and clinical and laboratory evidence of impaired liver function offer a diagnostic problem involving a wide variety of diseases, notably infectious hepatitis. Secondly, such cases cause difficulty in therapy and management. If an incorrect diagnosis is made and improper therapy instituted of if inadequate therapy is used even in the correctly diagnosed case, prolonged and unnecessary debility results. A similar, perhaps more difficult problem in therapeutics arises in the

patient with mononucleosis who shows laboratory evidence of hepatic damage but no clinical evidence of icterus. There are, however, other facets to this subject. The question of the etiology of jaundice and liver abnormalities in the disease, the types, results and significance of the liver function tests used in connection with it, and the pathology involved are important topics of discussion in themselves. These will also be dealt with in this paper.

The material to be used here has been assembled from the medical literature without the addition of new cases related to the subject. Almost all of the significant, available reports written in English and also some of the abstracted foreign literature concerning the liver in infectious mononucleosis have been reviewed for this discussion.

JAUNDICE AND HEPATOMEGALY IN INFECTIOUS MONONUCLEOSIS, STATISTICAL DATA AND CLINICAL ASPECTS

A review of the cases of jaundice occurring in association with infectious mononucleosis will now be presented with special reference, when available, to such points as its onset in relation to the onset of the disease, its duration, its overall incidence in mononucleosis, and the palpability and tenderness of the liver in jaundiced and non-jaundiced cases.

Although hepatomegaly and clinical jaundice have been observed in mononucleosis for many years, no valid conclusions were drawn

as to its actual incidence in the illness until 1934, at which time Nyfeldt, according to Peterson (1), reported a series of 33 cases with jaundice in about 12 per cent. The following year McKinlay (2) recorded a group of 55 patients with mononucleosis in whom jaundice was observed in 10 per cent. To better establish the incidence of clinical icterus the larger series should be investigated. Halcrow and associates (3), from 296 cases of infectious mononucleosis, found but one instance of jaundice. Contratto (4), in a study of the disease among 196 Harvard students between 1935 and 1943, observed jaundice in ten cases or about 5 per cent. In these, the icterus occurred from five to fourteen days after the onset of the illness and lasted less than two weeks in most patients. No enlargement or tenderness of the liver was demonstrated. The majority of the icteric patients experienced anorexia, nausea, and vomiting for a day or two. The urine contained bile, but the stools showed no alterations in color, and itching of the skin was not present. Press et.al. (5), in reviewing 96 cases, found jaundice in 5.2 per cent but 27 per cent showed hepatomegaly. Their cases of jaundice according to Press, "cleared gradually, signs of improvement appearing in the second week of the disease." In 300 patients with mononucleosis analyzed by Read and Helwig (6), there were 3.7 per cent displaying icterus, while among the entire group 15.7 per cent had demonstrable enlargement of the liver.

Milne (7) reported 111 acceptable cases of mononucleosis in 1945 in which three had jaundice, however, one had pre-existing chronic biliary infection. Six others "appeared jaundiced" but showed normal icteric indices. Apparently the largest series of cases reported on this subject was presented by Wechsler et.al. (8) in 1946. Their study concerned an epidemic among 556 individuals of the army personnel at Fort Bliss, Texas. Jaundice of varied degree was seen in 6 per cent and in these patients lasted up to 48 days. The liver was palpably enlarged in 17 per cent, usually being located one fingersbreadth below the right costal margin and non-tender, but occasionally it would be found as far as four fingers-breadth below the rib margin. With such enlargement, jaundice was almost invariably present. Between the years 1921 and 1946, Gardener and Paul (9) found 137 cases of infectious mononucleosis. Five per cent showed jaundice, "usually in the first or second week of the disease." Hepatomegaly was manifest in 13 per cent. Bennett (10), in presenting 90 cases in 1950, stated that jaundice was observed in about 12 per cent, whereas an "abnormal liver" i.e. an enlarged and/or tender liver was found in 34 per cent.

Smaller series of cases have been recorded by several groups of workers. Leavell and McNeel (11) found one case of icterus in their 57 patients with mononucleosis. In 34 cases, Mathisen (12) found fourteen with enlargement and tenderness of the liver but

only six with clinical jaundice. Of twelve cases of the disease, Farely (13) observed four instances of hepatomegaly and one case which displayed jaundice. In a similar number of patients with mononucleosis, Berk et.al. (14) demonstrated liver enlargement in five, while two individuals were jaundiced. Numerous isolated cases and very small groups of patients having jaundice in association with infectious mononucleosis have been recorded in the literature throughout the years, but these do not concern us here since they are of little value in establishing statistical data. Some of them, however, will be used later to illustrate various other points.

Before summarizing the foregoing material, one important consideration should be observed, namely that the diagnosis of infectious mononucleosis was properly established in the above groups of cases so that an accurate evaluation of the overall incidence of jaundice can be established. In almost all instances reviewed, the diagnosis was based on the usual criteria i.e., (1) the clinical picture, (2) lymphocytosis and atypical "mononucleosis cells" in the peripheral blood, and (3) a positive heterophile antibody titer. In a few groups, the diagnosis was established by the first two criteria alone or by the heterophile test alone. Such diagnosis are valid in almost all cases but in a small percentage this does not hold true. That a heterophile antibody titer

was used, positive in high enough dilution to eliminate other conditions which might cause confusion, can hardly be disputed in the vast majority of patients discussed in the above material. Nevertheless, the guinea pig kidney absorption test which practically removes all doubt of a diagnosis of mononucleosis was infrequently performed. It is believed, however, that from the standpoint of correct diagnosis the aforementioned groups of patients are satisfactory enough to draw conclusions as to the incidence of jaundice and other clinical findings referable to the liver in mononucleosis. One word about the jaundice which is rather a remote point of error. The icteric coloration was generalized in all cases described and was practically always borne out by laboratory studies.

To better establish the overall incidence of clinical jaundice in infectious mononucleosis, I have totaled the number of patients reported by each investigator or group of investigators and also their number of jaundiced individuals. In doing so, itis found that of 1,951 cases of mononucleosis 100 patients, 6r 5.1 per cent, were found to have clinical icterus. The overall incidence of hepatomegaly was similarly determined. In 1,433 cases where the various investigators made note of liver enlargement, 240 patients, or 16.6 per cent, were found to have hepatomegaly. It can thus be seen that the latter occurs about three times more frequently than does jaundice. It should also be pointed out that these figures

fairly well approximate those observed in the larger individual studies. The liver enlargement in infectious mononucleosis is usually not marked, but the organ may be palpable up to four fingerbreadths below the right costal margin. It is noted that even though enlargement of the liver may be present by clinical determination, the organ is not necessarily tender although it frequently is. It can also be concluded that jaundice in infectious mononucleosis may make its appearance in either the first or second week of the disease and be of variable degree. It usually lasts less than two weeks but may remain up to 48 days.

Very little information has been recorded concerning the age and sex of those showing jaundice in mononucleosis. Most of the patients listed in the above studies were young adults, in whom the incidence of infectious mononucleosis without icterus is known to be most common. However, since as Lawrence (15) states the illness may occur in any age group, from infants as young as seven months to adults in their seventies, we might feasibly expect to see icterus likewise in all age groups. No sex preponderance has been recorded. It has been thought that negroes are less commonly afflicted with thise disease than are the white race, but I have been unable to find any data concerning whether this applies to the incidence of jaundice. Practically all the series presented and discussed above concerned members of the white race.

LIVER INVOLVEMENT IN INFECTIOUS MONONUCLEOSIS IN PATIENTS WITHOUT CLINICAL JAUNDICE

As can be ascertained from the above section, the liver, from a clinical standpoint, is involved in mononucleosis more often than the incidence of icterus would lead us to believe. If this is true, what is the frequency of hepatic involvement in this disease, even in the absence of jaundice, and what is its nature as determined by laboratory studies? Such questions will be answered below. Of course, a small per cent of the patients in the following studies were icteric, but this does not alter the significance of these studies in investigating theproblem of hepatic damage in non-jaundiced individuals. In a sense, this is actually a help because it shows how similar many of the liver function tests may be in the icteric and non-icteric patients.

Carter and Maclagan (16) in 1946 reported on nineteen cases of mononucleosis in which jaundice was present in only one instance. Positive colloidal gold curves were found in 95 per cent while 58 per cent displayed positive thymol turbidity tests. They found only one case in which there was urobilinogen in the urine. They felt that the degree of positivity of the gold tests correlated directly with the height of the white blood count and the heterophile antibody titer, a finding not generally supported by other investigators. DeMarsh and Alt (17) studied nineteen cases without jaundice and found some degree of hepatic damage in all cases as

evidenced by the cephalin-cholesterol flocculation and bromsulfalein retention tests and found abnormal albumin-globulin ratios in two of ten cases tested. They established a correlation between the severity of the symptoms and the degree of liver damage. The usual duration of dysfunction as measured by the laboratory was six weeks, but in three cases it persisted for three to four and one-half months. In 1947, Gall (18) analyzed 34 cases with clinical jaundice in one patient and a "subicteric hue" in two others. In 22 of 26 patients that were tested, the cephalin flocculation was two plus or more. Only five had abnormal alkaline phosphatase tests. In all but one of fifteen, the thymol turbidity was over four units and nine of twenty had an icteric index over twenty units. In eighteen of 28 patients, two or more tests were abnormal and in the remaining ten, at least one test was abnormal. Thus, in 32 of 34 patients studied, there was evidence of impaired liver function. Gall concluded that there was no evidence of biliary obstruction and that liver involvement in mononucleosis is the rule rather than an incidental finding.

Cohn and Lidman (19) studied fifteen cases among white male soldiers with no past history or present evidence of jaundice. They found impairment of liver function in all patients as demonstrated by more than one test. Serum bilirubins were uniformly normal and none of the patients were jaundiced yet all showed

bilirubinuria at some time during the course of the disease. These workers found the thymol turbidity test to be the best indicator of hepatic dysfunction, with values up to 14.3 units being found. Often, however, it did not yield maximum evidence of hepatic damage for one to two weeks after studies were initiated, while other tests were showing improvement. It was the last test in their series to approach normal limits as patients entered the recovery phase. The bromsulfalein retention test varied from 11 to 43 per cent at the height of the disease. Seven of eight patients showed elevations of the alkaline phosphastase test and one of five a reduction in the esterified fraction of the serum cholesterol. In two of five cases, the intravenous glucose tolerance test was abnormal, showing evidence of hepatic parenchymal disease. Two patients were found to have brief, slight reductions in prothrombin activity. Electrophoretic analyses of sera from six patients showed in general, protein distributions which are characteristically found in early cases of hepatitis i.e. a slight decrease in the concentration of serum albumin, some increase in alpha and beta globulins, and a rather marked increase in gamma globulins. Cohn and Lidman also observed a rough correlation between the severity of the disease and the degree of hepatic involvement and concluded that in most instances serial studies were necessary to detect hepatic dysfunction.

In 1948, Evans (20) reported on nineteen cases of infectious mononucleosis without jaundice. He found abnormal cephalin flocculations in 95 per cent whereas in 22 cases of uncomplicated upper respiratory infections, the test was normal. Sixty-eight per cent of those with mononucleosis showed later and more transient changes in the thymol turbidity and 43 per cent showed an elevated serum alkaline phosphatase. All serum bilirubin examinations were normal. Two cases, one jaundiced and one not, were analyzed for alterations in serum proteins by electrophoresis. By such methods, a marked increase in the percentage of beta and gamma globulins were found together with a slight decrease in alpha globulins and a slight to moderate decrease in serum albumin. Brown (21) reviewed 83 cases of mononucleosis in 1949. Although he made no mention as to the number of jaundiced patients in his group, he found that 85 per cent had cephalin flocculations of three plus or more and 92 per cent had two plus or more. Forty-nine per cent had abnormal thymol turbidities, 38 per cent showed elevated icteric indices, 34 per cent displayed increased urobilinogen in the urine, 13 per cent had decreases in prothrombin concentration, and 62 per cent were found to have increased retention of bromsulfalein.

Further work on the alterations in serum proteins in this illness, as studied by electrophoretic methods, was done by Sterling (22) who found, in his seven cases, deviations in both

the jaundiced and non-jaundiced patient. The chief abnormalities seen were diminutions of the albumin fractions and elevations of the gamma globulin fraction. That the latter was not due to the presence of heterophile antibodies was proved by repeat examinations on sera from which these antibodies had been absorbed with no additional changes in electrophoretic patterns being found. Less pronounced and less frequently observed alterations were elevations of the alpha-1-globulin and beta globulin fractions. The alterations in the serum proteins were considered as possibly related to hepatic dysfunction, although as Sterling went on to say, "The cephalin cholesterol flocculation and the thymol turbidity tests may merely reflect directly the abnormalities of the serum proteins. The concomitance, however, of occasional hyperbilirubinemia, frequent elevation of the alkaline phosphatase activity....., makes plausible the association of disturbed hepatic function and the alterations of the serum proteins."

Jordon and Albright (23), in reporting on 24 cases of infectious mononucleosis of which two patients were jaundiced, found abnormal thymol turbidities in 83 per cent, cephalin flocculations of two plus or more in the 48 hour test in 79 per cent, significant bromsulfalein retention in 71 per cent, elevated urinary urobilinogen in 56 per cent, increases in the alkaline phosphatase in 38 per cent, and elevated serum bilirubins in 18 per cent (i.e. readings

over 1.0 mgm. %). The albumin-globulin ratios were normal in eighteen cases tested, serum cholesterol values were within normal limits in eleven patients on which this test was performed, and prothrombin times were unaltered in sixteen cases tested. They found the maximum number of laboratory changes developed during the second and third weeks of the disease and that abnormal thymol turbidity and cephalin flocculation values persisted for over two months in 25 per cent of cases. They could find no correlation between the abnormal liver function tests and the signs and symptoms of hepatic involvement or with the height of the heterophile antibody titer. By doing serial studies of liver function, these investigators estimated that between two-thirds and three-fourths of all patients with mononucleosis have associated hepatitis.

In 1951, Watson (24) recorded a study of 51 cases of infectious mononucleosis seen in an epidemic among medical students at Long Island College of Medicine in 1949. Although no clinical instances of jaundice were observed, 39 patients showed abnormal thymol turbidities and cephalin flocculations, seven of which persisted for twelve months and seven for 22 months. Only one positive bromsulfalein test was seen. Watson concluded that it was unlikely that abnormal liver function studies were due entirely to alterations in the serum proteins without particular elaboration on this point. Hsia and Gillis (25) found 26 cases of this

disease among children, all apparently non-icteric. In each patient, one or more liver function tests were positive. Sixty-five per cent had elevations of the thymol turbidity test, 73 per cent showed abnormal cephalin flocculations, 77 per cent were found to have increased thymol flocculations, and 86 per cent of the cases displayed significant colloidal gold responses. Only one case showed an elevated serum bilirubin. A second group of five patients with mononucleosis were found to have no definitely abnormal liver function tests.

Bennett et.al. (11) discovered the following alterations in tests of hepatic function among his study of 90 cases of mononucleosis in which eleven individuals were clinically icteric.

Test performed	No. of patients tested	Percentage abnormal
thymol turbidity	78	81 %
cephalin flocculation	43	79
alkaline phosphatase	38	57
bromsulfalein retention	52	46
Van den Bergh	76	33
Watson test for urobilin	60	32
cholesterol level	13	16
albumin-globulin ratio	44	9.5

He summarized his findings, stating that one or more abnormal reactions were observed in 90.2 per cent. It was also pointed out that the thymol turbidity was the first test to become abnormal and the last to return to normal. In seven patients, at least one function test was positive, after an elapse of three months and

four were found to have abnormal tests five to nine months after becoming clinically asymptomatic. One patient displayed an abnormal test after 39 months. Bennett believes that all cases of mononucleosis should be considered as having an associated hepatitis.

In forty cases analyzed by Peterson (1), among which only one showed jaundice, the following results were demonstrable.

Test performed	No. of patients tested	Percentage abnormal
alkaline phosphatase	12	76 %
urinary co-proporphrin	23	70
bromsulfalein retention	33	62
urinary urobilinogen	40	55
thymol turbidity	40	47
total serum bilirubin	40	40
cholesterol esters	10	40
thymol flocculation	18	39
one minute bilirubin	40	38
cephalin flocculation	40	34

Peterson failed to elaborate much upon his results except to point out that hepatitis without jaundice in this illness is extremely common. He states that liver function tests "showed a return to normal in a short period of time."

Rapaport (26) studied hepatic function in nineteen patients ill with mononucleosis and found abnormal tests in seventeen. The cephalin flocculation and the thymol turbidity tests, according to Rapaport, were equally sensitive in the detection of abnormal liver function. In only nine instances was there "clinical evidence" of hepatic involvement.

Several isolated case reports and studies dealing with small numbers of patients concerning liver function tests in mononucleosis have been recorded in the literature. These, however, lend but little information as compared with the larger group reports.

Before drawing conclusions from the foregoing material, it is necessary to analyze the reports of the various investigators in general. In the first place, do such tests as the thymol turbidity and the cephalin flocculation actually measure abnormalities of hepatic function or do they merely reflect minor alterations in certain components of the serum proteins? Shay and co-workers (27) simultaneously performed three tests (thymol turbidity, cephalin-cholesterol flocculation, and colloidal gold curve) on the sera of 167 normal individuals and various disorders and concluded that these tests, particularly the thymol turbidity, were true measures of hepatic disease. Further studies which clearly show a correlation between abnormal liver function studies and hepatic disease as proved by microscopic examination will be presented in the following section. Some workers, however, disagree with this concept. For example, Iverson and Flemming (28) state that "the thymol turbidity test is hardly a test of hepatic function, but is rather to be regarded as an indication of changes in serum proteins in consequence of different viral infections." They base their beliefs upon a study of 373 cases of various viral diseases in which they

found positive thymol turbidity reactions in 71 per cent of their patients with measles, in 73.5 per cent of individuals with infectious mononucleosis, and in 75 per cent of patients with acute hepatitis. Negative results were observed in tonsillitis, scarlet fever, serous, purulent and tuberculous meningitis, pneumonia, and acute gastro-enteritis. They demonstrated a certain resemblance between the curve of the positive thymol turbidities and the antibody titers in infectious disease. They conclude that the thymol turbidity (and probably related tests such as the cephalin flocculation) are useful in the diagnosis of mononucleosis but not in the diagnosis of hepatic damage. It would seem to the author, however, that the liver function tests at least reflect liver damage if not exactly measuring the severity of the destruction. This will be further discussed in the next section in which studies which demonstrate abnormal function tests in patients with hepatitis proven by microscopic study.

One of the chief points of argument in the matter of liver function tests and hepatic disease in mononucleosis is that of values used for normals in these tests. Some investigators, for instance, regarded a one plus cephalin flocculation as abnormal, while others used only three or four plus readings as pathological values. This might be explained upon the basis that different standards are used in various laboratories, and hence the normal

and abnormal ranges can only be determined by the individual laboratory performing the particular test. Yet, this remains a significant problem. The difficulty is further observed in other tests such as the bromsulfalein retention test, in which variable amounts of dye are injected by a certain laboratory and readings then made after the elapse of inconstant periods of time. Similarly, the normal ranges of the serum cholesterol and esters are very wide and often difficult to interpret. The thymol turbidity and the alkaline phosphatase tests, nevertheless, remain fairly well standardized as far as normal values are concerned. From the data presented above, it appears to be rather well established that the thymol turbidity is of value in demonstrating liver involvement in mononucleosis.

What then do the liver function tests in infectious mononucleosis reveal as to the nature of the hepatic abnormalities? From the laboratory standpoint alone and without detailed explanation of what the various tests are designed to show, it is quite obvious that, in general, parenchymal liver damage, namely a hepatitis, is the pathological conditinn present. It is also apparent that the vast majority of cases of mononucleosis show some indication of an associated hepatitis, at least by laboratory studies, and perhaps all patients with this illness would show such a condition if serial tests were performed. In general, the liver

function tests show alteration rather early in infectious mononucleosis as would be expected from observations previously noted in which jaundice was found to begin during the first or second week of the illness. The tests usually return to normal in a few weeks but may remain abnormal for many months. This would tend to indicate that at least from a laboratory standpoint a chronic hepatitis may result in infectious mononucleosis, although this is relatively uncommon and not necessarily symptomatic.

To say which liver function test would be of most value in this illness and in what per cent of cases a test is likely to be abnormal is difficult to ascertain because of the rather marked variability reported from series to series. Futhermore, in some cases one test may be normal while on the same patient, a simultaneously performed similar test may be abnormal. Nevertheless, it can fairly safely be concluded that the tests most likely to be positive in any given case of infectious mononucleosis are the cephalin flocculation in up to 90 or more per cent, the thymol turbidity in 80 or more per cent and the bromsulfalein retention in up to 70 or more per cent. The alkaline phosphatase and other tests have been used with variable results. The serum colloidal curves have been used by a few investigators with fair results. Electrophoretic studies, while not used as diagnostic aids, have shown interesting aspects in the levels of the components of the

serum proteins. The most prominent changes observed in this disease are elevations in the gamma globulin fraction and decrease in the albumin fraction. The value of using tests of hepatic function in infectious mononucleosis is probably not that of establishing the presence of a hepatitis since it is quite well established that this is almost a universal finding. There is even considerable dispute as to whether these tests are useful in determining the severity of the liver damage. They probably do serve a purpose in determining the duration of therapy in the individual case as will be discussed later. Moreover, such tests are helpful in distinguishing mononucleosis from other infections such as certain bacterial or viral types of tonsillitis and other respiratory infections in which hepatic involvement is only rarely or never seen.

PATHOLOGY OF THE LIVER IN INFECTIOUS MONONUCLEOSIS

Probably the first record of the pathology of the liver in mononucleosis was reported in 1930 by Glanzman (29) who cited a thesis written by Du Bois the previous year concerning an autopsied fatal case of a 26 year old male with "monocytic angina" (a term used in the older literature for infectious mononucleosis) in which the liver was found to contain small groups of monomuclear infiltrations in the portal spaces with some areas of necrosis and disappearance of hepatic cells. Nine years later Thomsen and

Vimtrup (30) presented data on two of six fatal cases of mononucleosis. In the first case, the liver appeared grossly hyperemic with normal markings. The portal lymph nodes and the nodes along the common bile duct were swollen. Microscopically, the liver was described as normal except for many lymphocytes in the periportal tissues. The liver in the second instance was grossly normal. On microscopic study, abundant infiltration with mononuclear cells in the periportal spaces were observed. In 1942, Jersild (31) added post-mortem data concerning a fatal case of mononucleosis in which he breifly described the liver as not remarkable.

The same year Kilham and Steigman (32) performed a punch biopsy of the liver on a patient who had become deeply icteric by the fifth day of his illness. Microscopic examination was done by Professor J. H. Dible of the British Postgraduate Medical School who reported as follows: "The sections show a well-marked focal acute hepatitis. The maximum change is seen in the portal tracts of the lobules where there is a loss of liver cells and a well developed histocytic reaction with some early proliferation of bile ducts. There are also isolated foci of similar histocytic reaction in other parts of certain of the lobules and the sinusoids show an excess of cells, some of which are Kupffer cells and others resemble monocytes. The glycogen content of the hepatic cells is well preserved and the general appearances suggest

that an earlier phase of necrosis has preceded the present histocytic reaction. The reticular pattern of the lobules is disturbed in the affected portal zones, but there is no true fibrosis."

Van Beck and Haex (33) in 1943 biopsied the liver of a jaundiced patient and reported results similar to those listed above. A second biopsy on the same patient done three and one-half weeks later was practically normal except for increased lymphocytes in the triangles of Kiernan. One year later Ziegler (34) reported a case in which the patient died from splenic rupture. The patient had had a tender, though not clinically enlarged liver. No mention was made as to the presence or absence of jaundice and none to the gross appearance of the liver. His findings were essentially the same as those of Kilham and Steigman. In addition, Ziegler more clearly described the location of the cellular infiltration by stating that it was most extensive in the perilobular areas and particularly the portal areas, although there were scattered areas of infiltration which showed no particular relationship to the lobular structure of the organ. Indeed, the picture resembled leukemia under the low power of the microscope but with the oil immersion lens, Ziegler stated that the findings were "distinctive." The infiltrate was found to consist of numerous Kupffer and mononuclear cells with occasional neutrophils and eosinophils. Although considerable numbers of cells of the

lymphocyte series were seen, mature lymphocytes were scarce. Edema of the sinuses and swelling of the small bile ducts were observed. In the foci of infiltration, destruction and disappearance of liver cells were found with some mitotic figures and swelling of other hepatic cells. No vascular congestion was seen. Ziegler concluded that jaundice in mononucleosis could be explained by the presence of a "diffuse focal hepatitis" and that whether or not jaundice developed depended upon the extent and intensity of the hepatic involvement.

Bang and Wanscher (35) studied four cases of mononucleosis in 1945 by aspiration biopsy of the liver. All four patients were clinically icteric. In addition to parenchymatous degeneration and infiltration in the portal areas, they observed an increase in interstitial connective tissue but no actual parenchymatous necrosis. They believe that the changes are like those in infectious hepatitis but with "less pronounced parenchymatous and a little more severe interstitial changes." They state that the proliferation of small lymphocyte-like cells in the sinusoids most undoubtedly represents growth of cells belonging to the reticulo-endothelial system but that this is not a finding characteristic of the disease. Further new observations were those of small biliary thrombi and of bile pigment contained in some of the liver cells. It is pointed out that by the subacute

character of the microscopic picture. The inflammatory process must have been proceeding for sometime before manifesting itself in jaundice. The cause of the process is though by these investigators to be due to the specific agent of the disease.

In 1946, Fisher (36) examined the livers of the two fatal cases of mononucleosis and found "lesions in the liver similar to those of Van Beck and Haex." Grossly, the organs were soft in consistency with the cut surface showing a gray, mottled appearance and indistinct markings. The same year Allen and Kellner (37) reported the post-mortem findings of a case which had shown no icterus or hepatomegaly. In addition to discussing many of the findings listed previously, they pointed out that although most of the infiltrate was perilobular just as many of the infiltrating cells were scattered widely without characteristic location. The predominant cell was seen to be a large mononuclear type with an oval or rounded nucleus and containing vacuolated cytoplasm. No regeneration of liver cells was noted. In 1947, Bicker and coworkers (38) reviewed two fatal instances. The livers were somewhat enlarged, weighing 2,100 and 2,600 grams. One appeared grossly normal. However, the other received no mention from the gross standpoint. They presented no new microscopic information except that they observed mononuclear cells of the atypical variety immediately beneath the endothelium of the veins of the

portal radicles and occasionally lying free in the sinusoids of the lobules. The same year Peters et. al. (39) observed mononuclear cells in the adventitia and subintima of the veins in a fatal case of infectious mononucleosis.

Davis and associates (40) biopsied the liver in a patient with the disease as a procedure incidental to splenectomy for rupture of the spleen. This was done fifteen days after the onset of the illness in a non-icteric individual. They demonstrated cloudy swelling of the liver cord cells but no other findings that have not been mentioned before. In 1948, Custer and Smith (41) published an article analyzing nine fatal cases of mononucleosis, four of which had already been discussed by other investigators. Their findings were similar to those reviewed above but in addition, they found round cell infiltration of the capsule of the liver which consisted of both normal and abnormal lymphocytes. Considerable variability in the degree of the peripertal infiltration was seen. However, no necrosis of parenchymal cells was present except in one case in which portal vein thrombosis followed splenectomy. No biliary obstruction existed in their cases. They stated that the liver lesion is essentially a periportal hepatitis and pointed out "the majority of cells in the lymphocytic infiltrates of the connective tissue and perivascular collars are metaplastic rather than inwandering i.e., that they

are formed in situ and from stem cells of the reticulo-endothelial system." Other conclusions were that the milder cases of the illness were not characterized by hepatomegaly and that the rapid enlargement of the liver could cause abdominal pain.

Dolgopal and Husson (42) in 1949 found the liver of a patient who died from mononucleosis to weigh 1,900 grams and show moderate congestion. The patient had displayed no jaundice during his illness. The parenchyma was markedly friable, however, no other remarkable findings were recorded. The same year Bertrand (43) reported on punch biopsies done in five cases without jaundice or evidence of hepatic disturbance, performed during the height of the disease. He stressed that the presence of large numbers of mitotic cells and localized nests of lymphocytes in the lobules were distinguishing features, separating the microscopic appearance of mononucleosis from infectious hepatitis. One biopsy was repeated five months later and revealed persistance of the localized areas of lymphocytic infiltration.

A significant study was reported in 1949 by Glayne (44) who performed serial liver biopsies on a case of mononucleosis complicated by hemolytic anemia. The patient was jaundiced with a palpably enlarged but non-tender liver; he was symptom free in about three weeks after the onset of the disease, and his liver function studies returned to normal in about nine weeks. The first biopsy

revealed a granulomatous reaction with fibrosis and atypical reticulo-endothelial proliferation. The scaring, however, could have represented some damage that had occurred before the immediate episode, or possibly the severe hemolytic anemia could have been a factor. The liver function tests at this time disclosed severe, diffuse hepatocellular damage plus some obstructive element. On the second biopsy, much less infiltration was observed. Scant areas of necrosis were seen but no foci of fibrosis of any significance. Simultaneously performed liver function studies showed a definite trend toward improvement. Further biopsies revealed additional improvement with only isolated patches of infiltration and occasional necrotic liver cells being present. The latter was characterized by hyaline degeneration of the cytoplasm and pyknosis of the nucleus. The hepatic function tests likewise gradually returned to normal, although the increased thymol turbidity persisted during regeneration.

In 1950, Ainley (45) reported a fatal case of mononucleosis which showed extensive centrilobular necrosis and lymphocytic infiltration. An interesting contribution was added by Leibowitz (46) the same year who described an instance of cirrhosis of the liver following infectious mononucleosis. The entire case is somewhat too long to be entirely reviewed in this paper. Suffice it to say that it concerned a 24 year old white male who supposedly had

"catarrhal jaundice" but was found icteric six weeks later and possessed a heterophile antibody titer in a 1:800 dilution and an enlarged, tender liver. Three years later he was found to have an enlarged, painful liver and scleral icterus, and three months thereafter a biopsy of the liver showed the typical pattern of cirrhosis. Several points lead the author to suspect some error here despite the positive heterophile which never reaches this height in other diseases. That cirrhosis did occur probably cannot be disputed. It is more likely, however, that it resulted from initial liver damage followed by extensive period of alcoholism and malnutrition. Such a history was actually established, and the two latter factors are suggested by Leibowitz as contributory causes. Futhermore, we have no way of knowing the condition of the liver before the patient acquired his alleged mononucleosis. It seems difficult to explain how the liver could be "hard and irregular" at the time the initial diagnosis of "catarrhal jaundice" was made unless the patient had had pre-existing hepatic disease. Irregularity of the liver surface is certainly not a characteristic finding in hepatitis, at least to palpation. Moreover, this patient apparently never had lymphadenopathy or atypical lymphocytes in his peripheral blood; the only actual lymphocytosis was observed three years after the onset of the disease. Zimmerman (47) recently pointed out that in his studies he had not seen cirrhosis

of the liver following infectious mononucleosis nor had he found valid reports of such a phenomenon in the literature.

Kass and Robbins (48) recorded a fatal case in 1950 with death coming as a result of a ruptured spleen. The liver was found to weight 1,280 grams. It had a slightly distended capsule and indistinct markings with a friable parenchyma. No portal lymphadenopathy was present. Although some hepatic cells stained deeply acidophilic and some contained fat droplets, usually solitary, no necrosis was observed. Both the extra- and intra-hepatic biliary systems were patent. They point out that the literature shows few instances of prolonged hepatitis and no acceptable instances of frank chronic hepatitis. It is suggested by them that "the rarity of severe late hepatic complications may be due to absence of necrosis in the hepatic lesions of infectious mononucleosis."

In 1951, Kalk and Vlbricht (49) performed liver biopsies on seven patients ill with this disease, three of whom were jaundiced. They added nothing new to the pathological findings already recorded. However, they believed that "the parenchyma was, in contrast to infectious hepatitis, completely or almost completely unaffected." Marshall and Mellingen (50) added the post-mortem examination of a patient who had shown hepatomegaly and marked icterus. Grossly, the liver was enlarged and hilar lymph node en-

largement was also present. Microscopically, they found moderate perilobular fibrosis and infiltration, especially periportal, with lymphocytes, questionably atypical lymphocytes, and a few giant cells. The liver cells showed cloudy swelling and some areas of necrosis; hyperplasia and regeneration were both noted, although neither was pronounced. They believed that some of the liver damage was the result of lymph node enlargement.

One of the most important studies, particularly from a clinical pathological viewpoint, was presented in 1952 by Wadsworth and Keil (51). They analyzed ten patients ill with mononucleosis by liver function tests and biopsies at varying intervals of time after the onset of the disease. Their study would suggest an explanation for the discrepancy in previously reported histologic findings in mononucleosis. They commented, "as might be expected, the histologic features appear to depend upon the time interval which has elapsed since the onset of the disease, upon the severity of the infection and, to some extent, upon the presence or absence of jaundice." Only minimal changes could be found in the liver during the first five days. These consisted of slight lymphocytic infiltration in the periportal zones, eosinophilic degeneration of hepatic cells, evidence of regeneration of liver cells, and activity of the Kupffer cells. These processes gradually increased and reached a peak between the tenth and thirtieth days.

Other findings seen, particularly during this period, were hepatic cell destruction, multiple nucleation of parenchymal cells, some periportal fibroblastic proliferation, retention of bile in some canaliculi, lymphocytic infiltration in sinusoids, vacuolization in various cells of the lobules, occasional neutrophils in the parenchyma and sinusoids, and multiplication of bile ducts. It was also during this time that Rupffer cell activity and periportal infiltration were most pronounced and although these features had subsided considerably at the end of sixty days, they were still present in the protracted cases. Some evidence of isolated degeneration and regeneration was observed as long as 225 days after onset.

Even though these workers tried to correlate the histologic findings with the clinical course of the disease and the laboratory data they found that "the degree of anatomic change does not parallel the degree of abnormality of the liver function tests." This is plainly seen in their data which show no particular correlation between the degree of abnormality of the cephalin flocculation and thymol turbidity tests and the intensity of the disease process in the liver. Although two of the patients were icteric, they did not show the most marked changes in either the tests of liver function or in microscopic pathological alterations, but showed more changes than the average.

In summary of the salient features of the pathology in the liver in mononucleosis, it must be emphacized the findings are, as pointed out by Wadsworth and Keil, dependent upon the time interval, the severity of the illness and probably the presence or absence of jaundice. Therefore, it becomes somewhat difficult to summarize pathological findings. Nevertheless, a review will be made with some notation to the interval of time.

Grossly, the liver may be normal in size and appearance or enlarged, with congestion, friability and loss of markings. Probably there are various gradations in gross pathology. Portal and periportal lymph nodes may or may not be enlarged. Doubtless these findings have a direct relationship to the time elapsed between the onset of the illness and the date of the examination and also to the severity of the reaction.

Microscopically, the liver during the first days of the disease apparently shows only minimal changes. The height of the process, as established by Wadsworth and Keil, is between the tenth and thirtieth days at which time, the most striking feature is a cellular infiltration, especially in the portal areas. The infiltration consists chiefly of mononuclear cells, regarded by some as "atypical" and an in situ product of the reticulo-endothelial system, and Kupffer cells. Occasional neutrophils, eosinophils and mature lymphocytes, however, are also present.

Some infiltration may be noted in widely scattered areas with no relationship to the liver architecture. Mononuclear cells may be observed in the adventitia and subintimal tissues of the veins and occasionally in the sinusoids. Considerable disagreement exists concerning the findings seen in the hepatic parenchyma. While it seems fairly well established that acidophilic degeneration of liver cells occurs, the question of whether necrosis and regeneration of these cells takes place is not well settled; both have been reported by various investigators. Parenchymal cells may contain mitotic figures (again evidence of regeneration) and may show such changes as cloudy swelling and vacuolization and may contain fat droplets. Periportal fibroblastic proliferation has been described, and thrombi in the small bile ducts and bile in hepatic cells have been noted. Although isolated degenerative and regenerative changes have been observed in liver cells as long as 225 days after the onset of mononucleosis, it is doubtful that chronic, symptomatic hepatitis exists and probably cirrhosis of the liver does not follow this illness.

It can finally be said that the periportal hepatitis of infectious mononucleosis is almost impossible to differentiate microscopically from that of infectious hepatitis. Its cause is probably related to the agent causing the disease, which is thought by most workers to be a virus. It is obvious to conclude that the

pathology in the liver, namely the hepatitis, is the cause of the jaundice when this is seen, in contrast to the old theory that blockage of the bile ducts by enlarged lymph nodes was responsible. Laboratory tests of hepatic function reveal a hepatitis sometimes with an obstructive component and in this respect reflect the microscopic picture in the liver. However, the pathological findings do not necessarily parallel the degree of abnormality of the liver function tests.

DIFFERENTIAL DIAGNOSIS

Instead of discussing the many different symptoms and signs with which an individual case of mononucleosis may present, the author will try to limit this portion of the discussion to those who show clinical evidence of jaundice since these cases are particularly difficult from a diagnostic standpoint and are more the concern of this paper.

In brief summary, the icterus, if present, during mononucleosis usually beings in the first or second week of an illness ushered in by a variable list of symptoms which according to Read and Hellwig (7) most often include sore throat, malaise, headache, fever, anorexia and soreness in the neck. The most common signs reported by these workers include lymphadenopathy, often generalized but especially cervical in location, pharyngitis and/or tonsillitis, enlargement of the spleen, stomatitis and/or Vincent's

angina, skin rash, and hepatomegaly. It can be seen that with a combination of jaundice, hepatomegaly with or without certain of the above listed symptoms, a difficult problem in diagnosis may occur. Probably the most difficult task lies in trying to distinguish between mononucleosis and infectious hepatitis. (Whether jaundice is present or absent in mononucleosis, the problem still exists, because it is well known that icterus in infectious hepatitis may be absent.) Peterson (1) discussed this problem at some length. He stated that "clinically, the one symptom that is most valuable in differentiating the two conditions is sore throat. Most all patients with infectious mononucleosis will complain of a moderate to severe sore throat during some period of the illness, whereas, this is not a very outstanding sign in infectious hepatitis. As far as physical signs are concerned, this is also a valuable guide." He also pointed out that "lymph node enlargement is distinctly more common and more marked in infectious mononucleosis than in infectious hepatitis. However, the difference is not too striking." He goes on to say that while various investigators have found splenomegaly in infectious hepatitis in from 13 to 21 per cent of the cases, he has found splenic enlargement in 48 per cent of his series of patients with infectious mononucleosis. He states that this latter figure is comparable to other observers who report its occurrence as

ranging from 34 to 50 per cent, conversely, according to Peterson. The liver is probably much more often enlarged in viral hepatitis than mononucleosis. He mentions that Zimmerman, however, found the liver to be enlarged in only 69 per cent of a series of patients with infectious hepatitis in which 90 per cent were jaundiced. This would still be considerably more frequent than that in mononucleosis, in which, as was established previously, the incidence of hepatomegaly is about 16 per cent. Almost all workers, however, agree that tenderness in the liver area is nearly always present in infectious hepatitis, whereas, this sign is less commonly seen in mononucleosis.

Peterson further observed that while the clinical features of the two diseases may overlap considerably, the laboratory is of valuable help in distinguishing the two entities. He states that patients with both illnesses "show the atypical or leucocytoid lymphocytes of Dawney, types I, II, and III--mostly type II. However, patients with infectious mononucleosis have a much greater number and at some stage in the disease practically always show an absolute lymphocytosis with large numbers of leucocytoid lymphocytes, whereas, patients with infectious hepatitis only develop a relative lymphocytosis. It has been found in experimentally induced infectious hepatitis in human beings there is only a relative lymphocytosis with the greater number of atypical

lymphocytes at the fourth to the fifth day after the onset of fever. In infectious mononucleosis, the lymphocytosis usually is not transient but increases in degree as the disease progresses and usually remains absolute after the symptoms have subsided."

"The heterophile antibody titer," Peterson stated, "is equally as helpful as the lymphocytic reaction in differentiating the two conditions. It is practically always positive in infectious mononucleosis if enough determinations are obtained, whereas, we have never found it to be positive in infectious hepatitis. Others also have been unable to find an elevated heterophile titer in infectious hepatitis. Eaton and associates noted a moderate increase in titer of antibodies to sheep red blood cells in some patients with infectious and homologous serum jaundice. These antibodies, however, were of true Forssman type, absorbed by guinea pig kidney, thus unlike those of infectious mononucleosis."

Commenting on the tests of hepatic function, Peterson noted that "the liver profiles of the patients with infectious mononucleosis have for the most part, characteristics of those seen in infectious hepatitis." ....."The tests that were most frequently positive in the patients with infectious mononucleosis are in general the same tests that one finds positive in the greatest percentage of patients with infectious hepatitis."

It is also brought out that the same differences which exist between mononucleosis and infectious hepatitis would apply to homologous serum jaundice. With this condition, however, there is often a history of innoculation and the onset of the illness is typically insidious and afebrile; urticaria and arthralgia are often seen.

Clough (52) in an editorial published in 1948 came to almost the same conclusions as Peterson. He stated that the differential diagnosis between the two diseases is particularly difficult when it is observed that in mononucleosis pharyngitis may be mild or absent and enlargement of the peripheral lymph nodes may be minimal with the predominant symptoms being malaise, anorexia, and gastro-intestinal disturbances with or without fever. Furthermore, he pointed out that "Barker et. al. have reported that these cells"--i.e. atypical lymphocytes in infectious hepatitis--"may constitute 60 per cent of the leukocytes. Bizarre lymphocytes, therefore, do not furnish a reliable criterion for the differentiation of the two diseases in an individual patient. An increase in heterophile agglutinins, however, has not been reported in infectious hepatitis. Although this is not always demonstrable in significant titer in infectious mononucleosis, when present, it furnishes the most reliable means of differentiating the two diseases."

A further statement concerning the use of the Paul-Bunnell test has been made by Berk and co-workers (15). They referred to a study made by Gambescia and Knowlton among 500 soldiers with viral hepatitis, in which only sixteen or 3 per cent developed titers of 1:56 which were reduced to 1:7 or to zero by absorption on boiled guinea pig kidney. Berk and associates stated that "it appears, then, that a significant rise in sheep cell agglutinins must occur but rarely in infectious hepatitis. Though a heterophile antibody titer may be taken as evidence favoring mononucleosis over hepatitis, it is incorrect to assume that a low titer establishes hepatitis over mononucleosis. The maximum heterophile antibody titer in infectious mononucleosis may be delayed in its development. Hence, serial studies over a period of weeks is essential before concluding that sheep cell agglutinins are not increased. Even so, there remains a not insignificant number of patients with what appears clinically to be mononucleosis who are sero-negative. The percentage of cases with negative agglutination tests has been reported to vary in different series from 0 to 57 per cent. Even with the use of confirmatory absorption studies, Dempster found only 26 per cent of his cases to be definitely sero-negative."

Another entity to be considered in jaundiced patients suspected of having mononucleosis is that of leptospirosis. The following

information concerning it is taken from an extensive survey by Bertucci (53). This condition is quite rare in the United States, only somewhat over 100 cases having been reported in this country in the literature by 1944. Many cases, however, are though to go unrecognized. This is a bacterial infection caused by Leptospira icterohaemorrhagica and rarely by L. canicola. Rats constitute a natural reservoir and a source for human infection. The incubation period is from four to nineteen days. The illness is characterized by high fever, chills, megalgia, conjunctival infection, jaundice, hepatomegaly, various respiratory symptoms, hemorrhagic tendencies, arthralgia, prostration, disturbance of heart function and varying degrees of renal failure. In the first or septicemic stage, the illness may resemble mononucleosis, however, conjunctival injection is seen in 50 per cent of patients with Weil's disease and the fever tends to be higher and the patient more ill. After three to seven days, the hepatic stage occurs which lasts for a week to ten days. Here, a hepatitis occurs in all cases and is moderately severe in about 60 per cent. The liver is enlarged and tender with jaundice being very common. Points that help to distinguish leptospirosis from mononucleosis in this period are the following features: in leptospirosis, the spleen is enlarged in only about 10 per cent, the patient is very toxic, hemorrhagic tendencies occur in over 50 per cent and

no skin rash appears as occasionally does in mononucleosis. Perhaps the most significant point is that in Weil's disease generalized lymphadenopathy is not part of the characteristic picture.

In the next or uremic stage, findings occur in leptospirosis which would be extremely uncommon in mononucleosis. Throughout the previous stages some albuminuria occurs, but in this period rather large amounts of albumin are passed in the urine and oliguria is common. Moreover, the urinary sediment frequently contains red cells, white cells, and granular casts. Following this is the convalescent stage which lasts one to three weeks but relapses occur in as many as 25 per cent. (The above course of this disease, of course, applies to the untreated case.)

If any confusion exists between this entity and mononucleosis, some help can be obtained from the laboratory. In leptospirosis, the causative agent can be detected in the first week of the illness, especially during the first few days by direct examination of the blood in about 23 per cent of cases. The organism can be cultured from the blood and occasionally from the urine, particularly during the tenth to the twentieth days of the disease. Specific agglutination tests may also be performed but are useless before the ninth or tenth days. When the agglutination titer is high, i.e. over 1:300, after the fourteenth day it is diagnostic.

A negative reaction after thirty days eliminates this illness as a cause of symptoms. Naturally, the examination of the blood smear and the use of the heterophile antibody test would be of great help here also. The liver functions again serve no useful purpose in distinguishing mononucleosis from Weil's disease, for Chenin (54) reports that in the latter illness these tests show evidence of parenchymatous liver damage. Thus, the same tests altered in one disease would be similarly abnormal in the other.

From this point, one is left with several different diseases in which icterus may occur and on occasion might be confused with infectious mononucleosis and associated jaundice. Martin (55) pointed out that cholecystitis with jaundice may present a problem. However, the age of this patient with this condition is usually greater than that of the individual with mononucleosis and often gives a history of previous, similar episodes. Moreover, symptoms of right upper quadrant pain and colic of rather severe nature with signs of muscle spasm and often a palpable mass in that area typify cholecystitis. Furthermore, the leukocytosis in this condition consists of an increase in neutrophils, whereas, that in mononucleosis is the result of lymphocytosis. The presence of the "atypical lymphocytes" and the positive heterophile titer, if its positivity becomes manifest early, are distinguishing features of mononucleosis.

While lymphocytic leukemia is sometimes difficult to distinguish

from mononucleosis without icterus, the presence of jaundice in the latter disease practically excludes the possibility of leukemia. Wintrobe (56) states that jaundice in leukemia is very unusual. Then too, although as Goldbloom and Lieberson (57) and Wallerstein and Madison (58) have observed, thrombocytopenia may occur in mononucleosis and even anemia may exist, as discovered by Gloyne (44) and numerous other workers, these conditions are quite uncommon in mononucleosis but the rule in the acute or subacute lymphocytic leukemia. If any doubt remains, the Paul-Bunnell test is the surest means of distinguishing the two illnesses.

Martin (55) has stated that when jaundice occurs in syphilis a problem may occur in trying to differentiate this entity from mononucleosis with icterus, particularly when enlargement of the nodes develops in the leutic and a subsequent skin rash appears. Further confusion is added by the fact that occasionally a false positive Wasserman reaction is seen in mononucleosis. However, the history of exposure, the primary lautic lesion, the uncommoness of syphilis during the present time, plus the use of the blood smear and the heterophile antibody test should serve to separate the two diseases.

Another interesting, though rare condition, which has caused some recent difficulty in the differential diagnosis, is that of severe sensitivity to the drug para-amino salicylic acid. Lichenstein and Cunnemger (59) found eight such cases in a group

of 3,000 patients treated with this compound. Clinically, the condition is very similar to mononucleosis. The illness begins 23 to 27 days after the drug is started with fever up to 105°, chills, headaches, and generalized aching, nausea, vomiting, burning of the eyes and increased lacrimation, erythematous and macular rashes, severe pruritis, cervical and occasionally axillary and inguinal lymphadenopathy. Atypical lymphocytes of Downey types I and III were found in the peripheral blood and constituted from 1 to 21 percent of the cells. Neutropenia and eosinophilia (11 to 55 per cent) were, however, common. Heterophile titers were repeatedly negative. Liver function tests showed abnormalities not unlike those of infectious mononucleosis. The condition was fairly easily detected by skin tests for sensitivity to PAS and prompt improvement followed ceasation of the drug.

Numerous other conditions in which jaundice is a manifestation might be considered here, however. The diagnostic points of these illnesses are, for the most part, well enough established that confusion between them and infectious mononucleosis rarely exists. Suffice it, then, to briefly mention such entities, in which jaundice may be present, as general sepsis, lobar pneumonia, tuberculosis, malaria, and yellow fever. The important fact to be remembered is that when an illness occurs in which jaundice

is present and mononucleosis might be suspected, a careful examination of the peripheral blood and a heterophile antibody test are definitely in order. Indeed, it has been advocated by De Vries (60) that a heterophile titer be obtained in every case of jaundice. The same would of course apply to non-icteric patients in whom infectious mononucleosis is strongly considered.

To summarize, the different diagnoses which should be considered in the suspected case of infectious mononucleosis with jaundice are many; however, the disease that causes the most confusion is infectious hepatitis. But why be concerned as to the precise diagnosis in these instances when it is true, as will be discussed in following section, that both are treated similarly? Perhaps it is chiefly an academic exercise to distinguish the two, however, it is of some importance to note that the reported deaths in mononucleosis are not due to liver damage with the possible exception of a case presented by Marshall and Milligen (50) in which the patient reportedly died of "hepatic and renal failure." In infectious hepatitis, on the otherhand, death may occur, usually according to Capps (61), the incidence is low (about 0.3 per cent) but in special groups the fatality rate has been as high as 20 per cent. To proceed, then, the more common occurrence of sore throat and pharyngitis, lymphadenopathy, and splenomegaly and the less common findings of hepatomegaly and

liver tenderness in mononucleosis, are sometimes helpful in determining the clinical diagnosis. While "atypical lymphocytes" occur in infectious hepatitis, they are usually of small number, and typically, there is no absolute lymphocytosis in central distinction to mononucleosis. The heterophile antibody titer, is, however, the most reliable means of distinguishing between the two conditions and also serves to eliminate numerous other illnesses, among which are leptospirosis, cholecystitis, lymphocytic leukemia, syphilis and PAS sensitivity. These conditions have been briefly discussed above.

THERAPY AND MANAGEMENT

Because hepatitis is so common in infectious mononucleosis and is believed by Cohn and Lidman (20) and numerous other investigators to be responsible for the chronic course of the illness and the occurrence of relapses, which according to Gardener and Paul (10), are found in 6 per cent of cases, proper management of this illness becomes important.

Cohn and Lidman (20) have this to say concerning the therapy: "As soon as the hepatitis complicating infectious mononucleosis was discovered, therapy routinely used at this hospital for infectious hepatitis was instituted. This treatment consisted essentially of rest, diet, and a high intake of vitamin B complex in balanced form. The diet consisted of carbohydrate 400 grams,

protein 150 grams, and fat 35 grams. The protein was high in methionine, and included casein and egg white. The fats were rich in unsaturated fatty acids and low in cholesterol. Supplemental feedings of casein in skimmed milk were given. The vitamin B complex was included in the diet as whole Brewer's yeast. This type of diet has been recommended for the prevention and treatment of hepatic injury in man. In a previous outbreak of infectious mononucleosis observed at this hospital, non-specific therapy was employed. It was observed during that outbreak, before the therapy outlined above was instituted, that patients, even after complete subsidence of the infection, experienced retarded convalescence with marked asthenia, anorexia, and easy fatigability, which persisted in some cases for months after discharge from the hospital. These symptoms persisted in spite of the fact that the patients had been hospitalized for as long as two to four months. In the present series, the treatment outlined above shortened the period of hospitalization by an average of six weeks. In addition, at the time of discharge from the hospital, the patients were asymptomatic, Asthenia, anorexia, and poor exercise tolerance were absent. Every patient discharged was able to undergo physical examination required in the Convalescent Medical Service Program without undue fatigue. All patients on whom it was possible to carry serial studies to completion have

demonstrated a return to normal hepatic function with the exception of one case." (Their study was based on fifteen cases of the disease.)

Wechsler et.al. (9) advocates a similar regimen when icterus is present, i.e., one consisting of a low fat, high carbohydrate diet, multi-vitamin capsules, bed rest, abundant fluids, and other symptomatic measures. He reports no beneficial results with the use of sulfa therapy in mononucleosis. Demarsh and Alt (18) believe that all cases of infectious mononucleosis should be treated similar to viral hepatitis. They consider bed rest to be the most important measure and question whether a high carbohydrate and protein diet is actually beneficial. Moreover, they state that sulfa drugs should be avoided because of their possible toxic effects upon the liver. Bennett (11) states that active therapy should be given to patients until such time as the reactions to liver function tests return to normal. His policy is to place the patients at absolute rest in bed, and on a diet consisting of high carbohydrate, high protein, and moderate fat, with vitamin supplements and lipotropic substances as indicated. During periods of anorexia and poor food intake, parenteral administration of hypertonic dextrose solutions and amino acids are used. After the liver function tests have returned to normal, he permits his patients to gradually resume normal activity but continues to

follow them with "screening liver function tests" several times a year to evaluate the late results of the illness and its possible effects on portal cirrhosis.

Kaufman (62) has summarized a large portion of the literature concerning the therapy of mononucleosis and believes that those ill with severe hepatitis should be managed exactly as those who have infectious hepatitis. He points out that the avoidance of alcoholic beverages for several months following the illness helps prevent recurrences of hepatitis and the development of chronic liver disease. His summary of therapy is as follows: "(1) There is no specific therapeutic agent for infectious mononucleosis. (2) Sulfonamides and penicillin may benefit a complicating Streptococcal throat infection. (3) Convalescent infectious mononucleosis and scarlet fever sera have given dramatic results in some seriously ill patients. (4) Human plasma and gamma globulin occasionally appear to be beneficial. (5) Aureomycin and chloromycetin seem effective in some cases when started early in the disease." It should be noted, however, that the convalescent sera mentioned here have been used in only a small number of cases; the same applies to the use of plasma and gamma globulin. Futhermore, whether such substances as these and also aureomycin and chloromycetin are beneficial in the hepatitis of infectious mononucleosis is not clear.

Other investigators, among whom are Hsia and Gillis (25),

also believe that the therapy of mononucleosis should be identical to that used in viral hepatitis. What, then, is the proper management of infectious hepatitis if it is applicable here? Many of the metoids have already been discussed; however, it would be well to review the program used by Capps and Barker (63) who performed a planned study in therapy upon 8,000 patients having infectious hepatitis, together with control groups. Their cardinal principles of treatment are three, the first of which is bed rest. They have found that exercise will produce an exacerbation in those with active hepatitis. This bed rest should be as strict as possible, although bathroom privileges are allowed for all but the seriously ill. It should be maintained for at least three weeks. Other criteria before ambulation is permitted are a return of the liver to its normal size and the disappearance of hepatic tenderness, absence of symptoms, such as diarrhea, cramps, headache and anorexia, a normal serum bilirubin for one week, (if it is slightly elevated, the direct Van den Bergh must be negative) and finally, the bromsulfalein retention should be under 10 per cent in one hour, (with 5 mgm./Kg. used as a dose of the dye), and preferably under 5 per cent. Also, if available, the cephalin flocculation test should be two plus or less in 24 hours and alkaline phosphatase under 4.0 Bodansky units. If only one finding is positive, the patient should be kept in bed

one extra week and a test of ambulation then performed. As mentioned by Capps and Barker, this is rather a drastic procedure for widespread civilian useage. Moreover, the use of liver function tests for the determination of ambulation is not upheld by all investigators; however, the clinical criteria aforementioned are valuable.

Their second principle is that of proper diet. They point out that "there is ample evidence that a diet high in protein is most desirable in acute liver injury. We believe that for the present there is insufficient evidence concerning the harmful effects of fat to warrant more than moderate restriction. However, an excess of fat other than butter fat in the diet is poorly tolerated and may result in severe anorexia." They relate that when malnutrition is present or when there is prolonged anorexia and failure to eat, it is desirable to administer protein in the form of plasma or amino acids by vein. For the average case, a diet of protein 200 grams, fat 65 grams, and carbohydrate 300 grams is recommended. They feel that the addition of methionine or casein has not produced clear cut results, probably because in man there is rarely a sufficient degree of deficiency in these substances to allow for a demonstrable effect in the small-sized groups in which it has been employed.

The third principle of treatment is the avoidance of additional

liver trauma. These workers state that "an already injured liver is extremely sensitive to toxic agents which would ordinarily have little effect. This is especially true during the prodromal and early icteric stages where maximal degree of acute liver cell damage is present." Among the common casues of additional trauma are surgical operations, secondary infections, and exposure to various toxic substances, particularly alcohol. They recommend local or spinal anesthetics in cases of surgical emergencies and discourage the use of saline purges and cathartics. Since opiates and short-acting barbituates are probably detoxified in the liver, these substances should be used with extreme care. They agree that the sulfa drugs should not be used because of their toxicity to the liver. According to them, bile salts are without benefit and may be harmful. Thiamin is likewise used with caution.

In analysis and summary of the treatment of mononucleosis, it seems quite well agreed that the hepatitis of mononucleosis should be managed similarly to that of infectious hepatitis. One unanswered question is whether all cases of mononucleosis, in view of the fact that probably everyone has some hepatitis, should be treated specifically for hepatic involvement. From the above material, it appears that in general, only those with "severe hepatitis" are treated. However, it is often difficult to determine the severity of the liver reaction because function tests do not

uniformly reflect the degree of damage. It would, therefore, seem best to depend more on the clinical picture and response and to follow those clinical criteria established by Capps and Barker before normal activity is resumed. Measures to be used in therapy, directed specifically for the hepatitis of infectious mononucleosis include strict bed rest, an adeuate diet, high in protein and carbohydrate with supplements, both oral and intravenous as necessary, and avoidance of further injury to the liver.

SUMMARY AND CONCLUSIONS

A survey of the literature concerning the liver involvement and disease in infectious mononucleosis has been presented. It was found that from a clinical viewpoint alone hepatic disturbance is fairly common as evidenced by an incidence of hepatomegaly of 16.6 per cent; the enlarged liver is not necessarily tender but frequently may be. Jaundice, however, is present in only about 5 per cent of the cases. It usually appears in the first or second week of the illness, is of variable degree, and typically persists for less than two weeks. From the laboratory standpoint, the liver is damaged in probably every case of mononucleosis if studies are carried out serially. Hepatic function tests reveal a pattern of parenchymal disease or hepatitis, occasionally with an obstructive component. These studies become altered rather early in the illness but usually return to normal in a few weeks; in some instances, they remain abnormal for several months, suggesting a chronic hepatitis, which is uncommon and perhaps of doubtful occurrence clinically. The laboratory tests most often abnormal are the cephalin flocculation, the thymol turbidity, and the bromsulfalein retention. Since hepatitis in mononucleosis is practically universal and because there is considerable disagreement as to whether or not these tests reflect the degree of liver damage, it would appear that their value lies in using them to distinguish

mononucleosis from similar appearing diseases in which hepatic involvement is rarely or nevery seen. The tests are used by some to determine the duration of therapy.

The pathology in the liver in this disease is now quite well established. Grossly, the liver may be normal in size and appearance or enlarged, congested, and friable. Microscopically, the findings are those of a periportal hepatitis, characterized by a periportal infiltration, chiefly of mononucleear cells, regarded by some as "atypical", and Kupffer cells. Although various types of degenerative changes have been observed in the parenchymal cells of the liver, the question of whether actual necrosis of these cells occurs is not settled; presumably it does happen. The pathology appears to follow a time curve, meaning that a peak of changes in the liver is reached between the tenth and thirtieth days of the illness with a gradual increase in severity of reaction noted prior to this time and a gradual decrease thereafter. Moreover, the changes seen in this organ are seemingly dependent upon the severity of the illness and possibly upon the presence or absence of jaundice. Isolated changes in the liver have been seen microscopically for as many as 225 days after the beginning of the disease, however, it is likely that cirrhosis of the liver does not occur following mononucleosis. The cause of the hepatitis is thought to be the specific agent of

the disease, presumably a virus.

The various diagnoses which should be considered in a suspected case of infectious mononucleosis with jaundice were discussed with particular stress placed upon distinguishing infectious hepatitis from mononucleosis. It was emphacized that the presence of sore throat, pharyngitis, lymphadenopathy, and splenomegaly are more common in mononucleosis, whereas, hepatomegaly and liver tenderness were more often seen in infectious hepatitis. Moreover, an absolute lymphocytosis with a large percentage of "atypical forms" together with a high titer of heterophile antibodies almost always is present in mononucleosis at some stage of the disease and these tests, particularly the Paul-Bunnell tests, serve to differentiate between the two entities. Several other diseases which could cause difficulty in diagnosis were briefly discussed such as leptospirosis, cholescystitis, lymphocytic leukemia, syphilis, and PAS sensitivity.

It has been decided by most investigators that infectious mononucleosis should be treated similarly to infectious hepatitis, but whether all cases of mononucleosis should receive the same therapy, particularly in regard to the duration of treatment, is a question not clearly answered. At least those who are seriously ill clinically as a result of hepatitis are advised to remain at bed rest for at least three weeks without resumption of normal

activity until symptoms are absent and the liver has returned to normal size and is free of tenderness. The use of liver function tests to determine ambulation is also a disputed problem. Other therapeutic measures to be instituted are the use of a high protein and carbohydrate diet with moderate fat, supplements of vitamins and intravenous fluids as necessary, and avoidance of further liver injury.

No specific section was allowed for the discussion of the prognosis of mononucleosis with hepatitis; however, this subject, which was presented in various parts of the paper, will be summarized at this time. While complete recovery in this illness within three weeks is the rule under proper management, inadequate therapy can lead to prolonged debility and relapses. There is some doubt whether a true chronic hepatitis may follow infectious mononucleosis, although there is certain laboratory and even pathological evidence to indicate that it can. Cirrhosis of the liver, however, does not appear to be a sequel to this illness. The mortality is probably not influenced by the presence of a hepatitis.

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