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Case studies and literature review of lupoid hepatitis : with special reference to immunologic aspects

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CASE STUDIES AND LITERATURE REVIEW OF LUPOID HEPATITIS WITH SPECIAL REFERENCE TO IMMUNOLOGIC ASPECTS

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Introduction

Lupoid hepatitis is defined as a severe chronic progressive hepatitis with a positive lupus erythematosus cell phenomenon (15). White females in adolescence or the early twenties are most commonly affected. It is not limited to age or sex; however, the disease may commence in an acute, subacute or insidious fashion and the natural course is marked by frequent relapses, often with jaundice (6,15,20,22,30). The earlier phases of the disease are characterized histologically by pronounced "inflammatory" lymphoid cell infiltrations in the liver, and the later phases by coarsely nodular (post-necrotic) cirrhosis and liver insufficiency (1,2,12, 15,17,18,29). Autoimmune phenomena are frequently associated with the disorder (18,29).

Lupoid hepatitis is part of a larger group of liver disease known as active chronic hepatitis. The criteria for active chronic hepatitis has been described by Mackay as follows (17):

1. The disorder is persistently active for at least six months usually with relapsing or continuing jaundice;
2. Active chronic hepatitis is further manifested by highly elevated levels of serum transaminase, sometimes in excess of 1000 units;
3. The elevation of serum gamma globulin levels ranges from 2.0 to 6.0 mg%;

4. Liver biopsy reveals patchy or "piecemeal" hepatocellular necrosis, regeneration, diffuse lymphoid infiltration, and fibrosis progressing to cirrhosis;
5. The serum may show various autoantibody reactions;
6. The disease, in the early stages at least, appears to be improved by immunosuppressive drugs including corticosteroids and 6-mercaptopurine derivatives.

The terminology of chronic liver disease is quite diffuse, other names applied to lupoid and active chronic hepatitis are numerous. The following are some of the more commonly used terms; "juvenile cirrhosis (31), active chronic viral hepatitis (18), chronic infectious hepatitis (12), post-hepatitis cirrhosis (18), and plasma-cell hepatitis (22). Juvenile cirrhosis refers to the most common age of incidence. Active chronic viral and chronic infectious hepatitis were terms used when the etiology was thought to be viral in nature. Post-hepatitis cirrhosis again denotes an infectious agents Plasma-cell hepatitis was coined from the histological picture of the liver.

The problems and dilemma of chronic progressive liver disease has been aptly described by Mackay using a quote from the Oxford English Dictionary (13):

> "According to ancient mythology, the demigod Prometheus stole fire from heaven for the benefit of mankind. As his punishment, Prometheus was chained to a rock haunted by a giant

vulture. His liver was devoured by this cruel bird by day, but it regenerated by night. This horrible tale bears a close analogy to the episodes of destruction and regeneration which characterize chronic persisting hepatitis."

It is the purpose of this paper to present six cases of lupoid hepatitis and to review the aspects of this disease with special reference to immunology.

In the course of this study, 500 cases of various types of hepatitis and/or cirrhosis were reviewed. This survey produced six specific cases of lupoid hepatitis using Mackay's criteria plus positive lupus erythematosus cell tests, a prevalence rate of 1.2/100 cases.

Using Mackay's criteria for active chronic hepatitis, the survey yielded 25 cases (six cases of lupoid hepatitis are included). This is a prevalence rate of 5/100 cases in this study.

Absence of a positive lupus erythematosus cell test or failure to obtain such a test may have obscured the diagnosis of lupoid hepatitis in 19 of the 25 cases of active chronic hepatitis.

Cases of various types of chronic liver disorders were reviewed in the "juvenile" age group (0-12 years). There were eight cases of chronic liver disorders yielding a prevalence rate of 1.6/100 cases. Using the above criteria for active chronic hepatitis, four (50%) of these patients could be classified as having the disease.

Case Studies

Case #1: 22-year-old white male

The patient had a history of protracted illness since 1963. He had complaints of arthritis, arthralgia, fatigue, anorexia and constipation. A diagnosis of pericarditis and pleuritis was made in June of 1965 along with the appearance of jaundice. A diagnosis of infectious hepatitis was made at this time.

Liverrenlargement was noted in October of 1965 and cortisone therapy was commenced in December of 1965. Steroid therapy was continued through February, 1966. At the time of instigation of steroid therapy serial lupus erythematosus cell tests were positive. On the basis of these tests and clinical findings, a diagnosis of lupoid hepatitis was made.

In October of 1966, the patient was again hospitalized for evaluation of the liver disease.

Physical exam revealed hepatosplenomegaly. Laboratory studies: The patients hemoglobin was 12.1 gm%, hematocrit 35.5. White blood cell count was 5,700 with a normal differential. Prothrombin time was 25 with a control of 14.5. Total serum protein was 8.7 gm; albumin 3.24 gm; total globulin 6.13 gm; and gamma-globulin was 4.87 gm. Bilirubin was 2.4 conjugated and 1.3 unconjugated. SGOT value was measured at 640 units. Alkaline phosphatase was 15.8 KA units. Several LE preps were positive.

A liver biopsy and splenoportogram were done. On the basis of the liver biopsy and clinical findings, the diagnosis of lupoid hepatitis was confirmed and long-term steroid therapy was instigated.

Case #2: Eight-year-old white female

The patient was hospitalized in May, 1966, because of increasing jaundice of three months duration.

Physical exam revealed a moderate jaundice and hepatosplenomegaly.

Laboratory studies: The hemoglobin was 14.0 mg%. A white blood cell count was 6,800 with a normal differential. Bilirubin was .7 mg direct and 1.1 mg total. The BSP was 35% retention in 45 minutes. SGOT measured 760 units. Electrophoresis revealed 7.0 gm total protein, albumin 3.6 gm, total globulins 3.5 gm and gamma-globulin was 1.81 gm. Cephalin flocculation was 4+. Several LE cell tests were positive.

A liver biopsy was performed and revealed a dense lymphoid ilfiltration with evidence of post-necrotic cirrhosis.

On the basis of clinical, laboratory and diagnostic procedures, a diagnosis of lupoid hepatitis was made.

The patient was started on a long-term steroid regimen and followed on an outpatient basis.

Case #3: 23-year-old white female

The patient has a past history of lupoid hepatitis being diagnosed in October of 1963. Since this diagnosis the patient has been on long-term steroid therapy. She was again hospitalized in July, 1966, because of upper gastrointestinal hemorrhage from esophageal varices.

Physical exam revealed no jaundice or hepatosplenomegaly.

Laboratory studies: Hemoglobin was 8.7 gm and white blood cell count was 4,200 with a normal differential. SGOT was 81. Alkaline phosphatase was 23.5 KA units. Bilirubin was .34 mg% indirect and the total was 1.1.mg%. Prothrombin time was 16.5 with a control of 13.5 seconds. BSP was 39% retention at 45 minutes. LE cell preparations revealed several suggestive tests and one positive LE cell.

A liver biopsy was performed which revealed lymphoid infiltration and evidence of post-necrotic cirrhosis.

A splenoportogram revealed portal hypertension and a end-to-side portocaval shunt was recommended.

The patient was discharged on a continuing steroid dosage and will return for the shunting procedure to alleviate the esophageal hemorrhage problem.

Case #4: 13-year-old white male

In May, 1966, the patient had nasal congestion, cough and arthralgia. This led to a period of anorexia and malaise followed

shortly by jaundice. The patient was hospitalized and a diagnosis of lupoid hepatitis was made. The patient was discharged on a daily regimen of steroids. In November if was noted that his SGOT levels were continuously elevated and he was again hospitalized for re-evaluation.

Physical exam revealed a cushingnoid appearance. No jaundice or hepatosplenomegaly were found.

Laboratory studies: The patient's hemoglobin was 16.1 gm% and the white blood cell count was 8,600 with a normal differential. Prothrombin time was 15 seconds with a control of 12. Alkaline phosphatase was 7 KA units. Bilirubin was .9 mg% total with .17 direct. SGOT was 205. Protein electrophoresis revealed; albumin 4.3 gm%, total globulin 4.7, and gamma-globulin was 3.0. LE cell tests were positive.

Liver biopsy was done and revealed chronic inflammatory cells with lymphoid infiltration and a histological picture of post-necrotic cirrhosis.

Due to the continuing liver destruction despite steroid treatment, the patient was taken off steroids and placed on a daily dosage of 6-mercaptopurine. The patient was discharged to an outpatient basis on this regimen.

Case #5: 12-year-old white female

The patient was hospitalized in August, 1964, with the complaints of jaundice and arthritis of the right knee for three months.

Physical exam revealed a marked jaundice. The liver and spleen were enlarged and there was swelling of the right knee.

Laboratory studies: Hemoglobin was 11.9 gm% and a white blood cell count was 7,000 with a normal differential. Bilirubin was 10.6 mg% direct and 19.0 indirect. Prothrombin time was 18 with a control of 14.5 seconds. Cephalin flocculation was 4+. Alkaline phosphatase was 15 KA units. SGOT was 1100. Protein electrophoresis showed a total protein of 9.4 gm%, albumin 2.44, total globulin 6.96 and gamma-globulin 4.73. PBI was 10 mcg% and BEI 3.5 mcg%. LE cell tests were positive on 4 separate occasions.

A liver biopsy was performed which revealed lymphoid infiltration with periportal cirrhosis. The histological picture was consistent with post-necrotic cirrhosis.

The patient was diagnosed as having lupoid hepatitis and "autoimmune" thyroiditis. She was discharged on an outpatient basis on a daily regimen of steroids and thyroid extract.

Case #6: 28-year-old white female

The patient was hospitalized in August, 1964, with complaints of intermittent jaundice and malaise of nine months duration. In January of that year, she had been hospitalized for two weeks and a diagnosis of infectious hepatitis had been made. She was again hospitalized in February for malaise and placed on steroid therapy.

The steroids were discontinued after five weeks and she was discharged. The present hospitalization occurred due to persistence of the above symptoms.

Physical exam revealed a markedly jaundiced female. A systolic murmur and a diastolic murmur were noted by auscultation of the heart. The abdomen was distended but no organomegaly was present. There was pitting edema of the ankles bilaterally. A generalized maculopapular rash was noted, being most prominent on the forehead, over the malar eminences and on the neck.

Laboratory studies: Hemoglobin was 12.2 gm% with a white blood cell count of 7,900 and a normal differential. Bilirubin was 15.4 mg% direct and 32.0 total. SGOT was 150 units. Prothrombin time was 20 with a control of 14 seconds. Alkaline phosphatase was 27 KA units. Electrophoresis revealed a total globulin of 4.6 gm%, albumin of 1.5 and gamma-globulin of 3.9. Repeated tests revealed LE cells.

A liver biopsy revealed plasma and lymphoid cell infiltrate with moderate fibrosis, histologically appearing as post-necrotic cirrhosis.

The patient was started on steroids, but failed to improve. 6-mercaptopurine was added to the regimen and there was a transient improvement clinically. The patient continued to deteriorate, became comatose and expired two and a half weeks after admission to the hospital.

Incidence

In the course of the literature review, it was noted that lupoid hepatitis is found predominantly in young females. However, males are also affected as illustrated by cases #1 and #4.

Figure 1 indicates sex incidence, mean age of onset and age range in a number of case studies of lupoid hepatitis conducted by various groups.

Leonhardt (11) in his studies of familial hypergammaglobulinemia, found that some members of a family of a case of lupoid hepatitis had hypergammaglobulinemia. Cavell (3) did an extensive study on families of cases of lupoid hepatitis and found a significant incidence of familial hypergammaglobulinemia. The significance of this finding is not clearly understood at the present time and is undergoing further study.

Other factors that have been studied in relationship to incidence include occupation, diet and alcoholic intake. None of these factors have been proven to have an influence on the incidence of lupoid hepatitis (14).

The mean age of the six case studies presented is 18 years 6 months with four cases being female and two male cases. The youngest case is a 12-year-old female and the oldest is a 28-year-old female.

Clinical Features

The onset and progression of lupoid hepatitis is described as the following (9):

Figure 1. Sex Incidence, Mean Age of Onset, and Age Range in a Number of Case Studies of Lupoid Hepatitis Conducted by Various Groups.

	Sex Incidence	Mean Age of Onset	Age Range	Number of Case Studies
Mackay and Wood (14)	77% female 23% male	33 years	13-74 years	22
Read, Sherlock, and Harrison (29)	50% female 50% male *	25.5 years	11-40 years	40
Taft, Mackay, and Cowling (33)	---------	31.5 years	13-50 years	17
Mackay and Wood (12)	87.5% female	20.5 years	11-30 years	12

* After age 30 years, male sex incidence predominated.

"The onset may be acute, simulating acute viral hepatitis. In others, the onset is insidious and may extend over several months or become clinically silent for an indefinite period of time. The patient then suffers chronic ill health with recurring episodes of jaundice, fever, abdominal discomfort and often joint pains."

In females, endocrine disturbances are found manifested by amenorrhea, genital hypoplasia and infertility (23). Patients tend to have hypercortisonism-like features after little or no corticosteroid therapy (9). Hypercortisonism was noted in all six cases presented in this paper which was most probably due to steroid therapy. One case had a history of menstrual irregularity.

Other presenting symptoms include mild fatigue, anorexia, pyrexia, nausea, recurrent attacks of polyarthritis and abdominal swelling (1). Some patients appear to present with a preceding illness in an organ other than the liver such as; Hashimoto's disease, diabetes mellitus, respiratory infection, or ulcerative colitis (29). Skin rashes, including the "butterfly" rash on the face characteristic of systemic lupus erythematosus (SLE); renal lesions; hematological disorders; pleurisy; lymphadenopathy; myocarditis and stomatitis have been systemic manifestations (13).

The preceding manifestations tend to implicate a multisystem disease process rather than a single specific organ disease. This supports the argument for an immunologic pathogenesis for lupoid hepatitis.

Subsequent signs and symptoms include recurrent jaundice, ascites and bleeding from gastric or esophageal varices as a result of progressing liver disease (14). Alfrey states that the majority of these patients have spider angiomata or magenta palms during the course of the illness.

In the cases reviewed it was noted that all six had the initial sign of jaundice. Pyrexia was present in three of the six cases. Spider nevi and magenta palms were present in one case. Endocrinopathies were as follows: one female was diagnosed as having an immune thyroiditis (Hashimoto"s disease), another experienced marked menstrual irregularities and a male patient was diagnosed as having diabetes mellitus.

One male patient had a history of pericarditis and pleuritis during the course of his illness.

In the six cases studied, one or more clinical manifestations of a multisystem disease were observed.

Mackay and Whittingham (18) published a study in 1967 which compares the percentage of systemic manifestations in active chronic hepatitis, lupoid hepatitis and systemic lupus erythematosus. Figure 2 represents this study along with the percentages of the casesstudies in this paper.

Dermatological, arthritic, renal, hematological and colonic manifestations appear to be the most common occurrences in lupoid and chronic active hepatitis. A large number of endocrine disorders have also been noted.

Figure 2. Percentage of Systemic Manifestations in Active Chronic Hepatitis, Lupoid Hepatitis and Systemic Lupus Erythematosus in This Study and the Case Studies of This Paper

	Skin Rash	Arthritis	Renal Lesions*	Blood Disorders**	Chronic Ulcerative Colitis
Systemic Lupus Erythematosus	90%	90%	80%	20%	0
Lupoid Hepatitis	25%	55%	20%	15%	15%
Active Chronic Hepatitis	15%	15%	0	15%	10%
Case Studies	67%	50%	0	17%	0

* Renal lesions were lupus nephritis, membranous glomerulonephritis and an atypical interstitial nephritis.

** Blood disorders were "auto-immune" hemolytic anemia or thrombocytopenic purpura.

Bartholomew (2) noted that many of his patients with lupoid hepatitis had a history of photosensitivity and drug sensitivity for months to years prior to evidence of hepatic disease. This pattern he remarked was very foreign to the concept of a viral hepatitis of which some attribute lupoid hepatitis.

Physical Findings

The majority of the physical findings have been mentioned in the discussion of the clinical features. Of these, the most consistent is jaundice. Read (29) states that all patients in his study experienced jaundice at one time or another.

According to his study the icterus is variable in degree, but usually mild or moderate (serum bilirubin 1-10 mg%).

The most consistent and striking physical findings not mentioned previously are the hepatomegaly and splenomegaly. Figure 3 shows the percentage of occurrence of these findings from several studies and the cases presented.

Laboratory Findings

Figure 4 and 5 show the routine laboratory results found in the six case studies presented.

Figure 6 and 7 are a comparison study of laboratory values of cases compiled by Mackay and Wood (14), and Page and Good (22) with the values of the cases presented.

The lupus erythematosus clot test is positive in 30% of the cases according to one study (17) and in 100% of the cases in

Figure 3. Percentage of Occurrence of Hepatomegaly and Splenomegaly From Several Studies and the Cases Presented

	Number in Case Study	Hepatomegaly	Splenomegaly
Read (29) (Active Chronic Liver Disease)	81	71.6%	76.6%
Mackay and Wood (14) (Lupoid Hepatitis)	22	90.9%	71.6%
Case Studies (Lupoid Hepatitis)	6	66.6%	66.6%

Figure 4. Common Laboratory Findings in the Six Cases Reviewed

	Total Globulin	Albumin	Gamma-Globulin	Lupus Erythematosus Clot Test	Serology
Normal Values	2.6 gm/100 ml	4.4 gm 51-65% of total	1 gm 13.6-19.6%		
Case # 1	6.3	3.24	4.87	positive x 3	negative
Case # 2	6.2	2.5	5.02	2 positive 1 negative	negative
Case # 3	6.7	2.4	3.6	1 positive several suggestive	negative
Case # 4	6.4	4.6	5.0	1 positive 2 negative	negative
Case # 5	6.98	2.44	4.79	positive x 4	negative
Case # 6	4.6	1.5	3.9	positive x 3	negative

Note: Maximum values during the clinical course were used.

Figure 5. Common Laboratory Findings in the Six Cases Reviewed

	SGOT	SGPT	BSP Retention	Flocculation Tests	Bilirubin Direct	Bilirubin Total	Alk. Phos.	Prothrombin Time
Normal Values	0-40 Units	0-45 Units	5% at 45 min	Thymol turb.0-5 Ceph. Floc. 0	0.25 mg	.1-1.2 mg	3-13 u/ 100 ml*	Quick Method 100% ± 13.5
Case #1	640	--	16%	-----	.6	.1	15.8	83.6% of normal
Case #2	760	--	43%	Ceph. Floc 4+	.7	1.1	17	87% of normal
Case #3	220	56	39%	Ceph Floc 4+ Thymol - 7	.34	1.1	23.5	83.6% of normal
Case #4	1130	606	30%	Ceph. Floc 2+	.84	15.0	40.7	62.4% of normal
Case #5	1300	190	22%	Ceph. Floc 3+ Thymol - 14.5	10.6	19.0	19.4	47% of normal
Case #6	150	170	47%	-----	15.4	32.0	30.5	58% of normal

* King-Armstrong method

---- Not done

Note: Maximum values during the clinical course were used

Figure 6. A Comparison Study of Laboratory Values of Cases Compiled by the Authors Presented With the Values of the Cases Presented in This Paper

	Total Serum Bilirubin	BSP* Retention-45 min	Alkaline Phosphatase	Prothrombin Time
Mackay and Wood (14)				
Range	1.0-17.4 mg%	0-28%	5-80 KA units	19-100% of normal
Mean	6.7	18.7	35	43%
Case Study				
Range	.1-32.0	16-47	15.8-40.7	47-87%
Mean	11.4	32.8	24.5	70.3%

* BSP values taken from Page and Good's studies on plasma cell hepatitis (22), the remaining values are from studies of lupoid hepatitis by Mackay and Wood (14).

Figure 7. A Comparison Study of Laboratory Values of Cases Compiled by the Authors Presented With the Values of the Cases Presented in This Paper

	Total Globulin	Albumin	Gamma-Globulin	SGOT
Mackay and Wood (14)				
Range	3.5-66 gm%	1.3-3.0 gm%	2.0-5.0 gm%	30-4389
Mean	5.4	2.3	3.3	716
Case Studies				
Range	4.6-6.98	1.5-4.6	3.6-5.02	150-1300
Mean	6.19	2.78	4.53	700

another (14). Various percentages for positive lupus erythematosus (LE) clot tests range from 30-100% depending on the number of tests run. An approximate average would be 50%. Many tests are not positive but are suggestive by evidence of formation of rosettes, nucleophagocytosis, and erythrophagocytosis (12,14,22). It should also be taken into consideration that the percentage of positive tests is variable due to the remissions and exacerbations of this chronic disease.

Other laboratory findings that have been abnormal include serologic tests for syphilis, Coombs' tests, the heterophile agglutination test, latex fixation, and rheumatoid factor.

Paper electrophoresis and immunophoresis show particular abnormalities which will be discussed below with the specific immunological tests.

Clinical Course and Prognosis

The clinical course of lupoid hepatitis appears to be that of a clinically "silent" progressive liver destruction finally manifesting itself by overt liver failure. Jaundice appears to be the commonest sign of this liver failure. The signs and symptoms are often described as a viral hepatitis-like syndrome (9).

The disease hallmark appears to be the induced remissions with hospitalizations and corticosteroid treatment. However, the liver disease has not been shown to be affected favorably by steroid treatment, or if so, only temporarily (14,15,29).

The liver continues to undergo progressive destruction leading eventually to a coarsely nodular cirrhosis and overt liver failure (9,19,11,14,22,28).

Read (29) in a study of 79 patients indicates the average survival time to be similar in males and females, 3.4 years in both the 12 males and 14 females who had fatal cases. Of the survivors, 17 of the 53 cases followed were alive and well after six years or longer from the apparent onset of the liver disease. Of the fatal cases, 23 of the 26 died within five years and 17 of these within four years from the onset of the disease. The five year mortality rate was 32.6%. An interesting fact was that the mean survival of the 12 fatal cases treated with corticosteroids was 3.1 years. The mean survival time of the 14 fatal cases not treated with steroids 3.5 years. It would appear from these findings that steroids not only failed to prolong the life span but may have actually shortened it. These findings are in contrast to other authors who report steroids to have a beneficial effect on survival time (14). Liver failure was the primary cause of death in 21 of the 26 fatal cases. The other five cases died of diseases unrelated to their hepatic problem.

A possible explanation for the apparent deleterious effect of steroids on survival time could be bias in patient selection. It is common practice to place moribund and refractory illnesses on more heroic means of therapy such as corticosteroids.

In a study (15) of 24 patients with lupoid hepatitis, the 12 fatal cases had an average survival time of three years. The mortality was 50%. Liver failure was the cause of death in ten of the 12 cases.

Of the 24 patients in this study, 21 received some form of steroid therapy. Of these, 15 (10 living, 5 dead) were clinically improved, one derived no benefit and in five cases the effect of treatment was insufficiently well documented to assess its value.

Mackay and Wood (14) published the following comments on corticosteroid therapy in lupoid hepatitis in 1962. In a study of 22 patients with lupoid hepatitis, 20 patients received some form of steroid treatment. Twelve of these patients received steroid treatment for more than 25% of the observation time. The survival rate for this group was 50%. Two patients were given no steroids and eight had steroid treatment for less than 25% of the observation time. The survival rate for this group was 30%. Upon this basis prolonged steroid therapy was favored.

The variables of patient selection and small series must be taken into consideration when appraising these results.

Weiden, Hasker and Mackay (17) made a comparison study of survival time of lupoid and active chronic hepatitis in 1965. The comparisons were made on two groups of 25 patients each matched as closely as possible for sex and age. It was shown that the five year survival rate for both lupoid and active chronic hepatitis was 36%.

The six patients presented in this study have the following clinical courses:

Case # 1 - This young man has had known lupoid hepatitis for the past 2½ years. He has been on almost continual corticosteroid treatment for the past year. He is currently being followed for progression of the liver disease. He is minimally restricted in his daily activities. One instance of a possible relapse, indicated by a rising serum transaminase level was averted by increasing the steroid dosage temporarily.

Case # 2 - This patient has had known liver disease for 1½ years. At the time of diagnosis the patient was placed on a continuous corticosteroid regimen. She is being followed using serum transaminase levels and closed needle biopsies of the liver to assess the progression of the disease. The liver biopsies reveal a continuing destructive process. Serum transaminase levels revealed elevated values on several occasions which returned to baseline with increasing steroid dosage. However, due to the continuing liver destruction, consideration is being given to immunosuppressive therapy. At present this child's activity is only mildly hampered by her disease.

Case # 3 - This young woman was diagnosed as having lupoid hepatitis four years ago, approximately. The patient has been on steroid therapy since the time of her diagnosis. Three years after the initial diagnosis, the patient was hospitalized due to

hemorrhage from esophageal varices. A liver biopsy at this time revealed a diffuse cirrhotic process which was leading to portal hypertension and subsequently esophageal varices. Serum transaminase levels and other hepatocellular function tests revealed marked impairment. The corticosteroid regimen was increased and the patient improved clinically. The patient was dismissed from the hospital on a continuous steroid regimen. Since this time, the patient has been living in fair health.

Case # 4 - This young child was known to have liver disease for approximately 1½ years. Steroid therapy was initiated one year ago at the time of diagnosis of lupoid hepatitis. He was on continuous steroid therapy for two months when it was noted that the serial serum transaminase levels were markedly elevated. The steroid dosage was increased and an apparent improvement ensued. One month following this episode the patient developed clinical symptoms of increasing hepatic dysfunction and was hospitalized. Serum transaminase levels were markedly elevated at this time and other hepatic function tests were grossly abnormal. The steroid medication was gradually discontinued and immunosuppressive (6-mercaptopurine) course was started. The patient's condition improved and he was discharged to limited activity at home. The immunosuppressive therapy has been continued on an outpatient basis.

Case # 5 - Approximately three years ago this young female was diagnosed as having lupoid hepatitis and was placed on continuous corticosteroid therapy. The patient suffered clinical evidence of hepatic failure nine months after time of diagnosis and was hospitalized. The steroid dosage was increased and the patient improved both symptomatically and by evidence of hepatic function tests. The patient was dismissed on a continuous elevated steroid dosage. She has been followed by serial liver biopsies and serial serum transaminase levels. Both of these methods reveal no further liver destruction. At the present time the patient leads a moderately normal life with restricted physical activity.

Case # 6 - This 28-year-old female showed symptoms of liver disease ten months prior to death. Hospitalization five months after the initial symptoms revealed a diagnosis of lupoid hepatitis. At this time, she was placed on continuous steroid therapy. The therapy was continued for five weeks and then gradually discontinued as the patient improved and was released from the hospital. However, three weeks later she was rehospitalized in hepatic failure. Corticosteroid therapy was again started. The patient continued to decline over the next four week period. A combined regimen of steroids and 6-mercaptopurine was initiated. The patient's condition improved slightly, then rapidly deteriorated resulting in death due to hepatic failure within three weeks.

Due to the short length of time elapsed for followup on these six patients it is impossible to give any estimate of mortality or five year survival.

All six cases were treated with corticosteroids. Of these six, four appeared to derive some benefit, one patient appeared to benefit from the combination of steroids and 6-mercaptopurines. One patient did not improve with steroids or 6-mercaptopurine.

It cannot be stated with certainty that these patients benefited from steroid or 6-mercaptopurine therapy due to lack of untreated controls. However, there was a high clinical correlation of remission at the time of initiation of therapy. Again lack of controls and a small survey must be considered as variables.

Liver Morphology

The gross appearance of the liver in lupoid hepatitis is that of post-necrotic cirrhosis (1,2,12,26,27,28,33). Grossly, post-necrotic cirrhosis gives the liver the appearance of a fine, coarsely nodular organ.

Fibrosis, evidence of parenchymal regeneration, occurs in an uneven manner. The reason for the non-uniformity of the fibrosis is a phenomenon known as "piecemeal necrosis"(1,12,26, 27,33). Piecemeal necrosis is a generalized, random destruction of hepatocytes throughout the liver (26). The septa that are formed by the fibrosis occur in a random manner and contribute to the nodular appearance.

This type of cirrhosis is found in a variety of liver diseases. Some of the more common are viral hepatitis, drug-induced liver injuries, and late biliary cirrhosis (26,27).

According to Popper and Shaffner (27), piecemeal necrosis of the liver is a characteristic of self-perpetuating liver disease.

Lupoid hepatitis displays hepatomegaly during the early phases of the disease, however, as the chronic destruction continues there is a decrease in the liver size due to cirrhosis (12,26,33).

Therefore, the gross appearance of the liver in lupoid hepatitis is that of a coarsely nodular cirrhosis with a generalized random distribution. Bile stasis is not present in the majority of cases (12,26).

Gross liver examination was done on case #6 of this study. The liver was small in size and coarsely nodular in appearance. From gross findings, it appeared as post-necrotic cirrhosis. Some bile stasis was present.

Histology

Lupoid and active chronic hepatitis present the following histological picture. An irregular border between the parenchyma (lobules and nodules) and mesenchyma (portal tract and connective tissue septa). Necrosis is observed in the peripheral parts of the liver anatomy. This necrosis involves both cytoplasmic

coagulation and disappearance of hepatocytes. The necrosis results in destruction of the most peripheral layer, the limiting plate. Single cells in the peripheral zone are also destroyed. Inflammatory cells are found in the portal tracts and in the area of damaged or necrotic cells. The inflammatory cells are of multiple types. The most commonly found cells are lymphocytes, plasmocytes and macrophages. Eosinophils and segmented neutrophils are found less commonly (23,24,25,26,29,31,32,34). In the areas of the lesions, designated as piecemeal necrosis, immunoglobulin-forming mesenchymal cells are noted (26,27).

The finding of both parenchymal and mesenchymal cells in the areas of destruction lead to the argument of which is most important as the cause of the ensuing cirrhosis.

Popper (27) suggests that the persisting destruction of the liver is due to the mesenchymal changes. The mesenchymal initiation of chronic liver destruction is theorized as being due to an autoimmune phenomenon. It is thought that the mesenchymal tissue in some manner causes immunologic destruction of normal hepatocytes, which in turn leads to persisting liver disease. The basis of this theory is the immunologic findings present in lupoid and active chronic hepatitis. This finding will be discussed later in the paper.

Mackay (12) on the other hand, believes that the parenchymal destruction is most important in the initiation of persisting

liver disease. He states that the mesenchymal reaction does have a role in the progression of the hepatic destruction, however.

As the liver destruction occurs, regenerative changes are also taking place. These regenerative changes involve both the adaptation of present cells and the formation of new ones. The recovery of the damaged hepatocytes is marked by excess smooth endoplasmic reticulum. This is thought to be an expression of the formation of adaptive enzymes (27,32). Regeneration results in the formation of the regenerative nodules, which are a main morphologic characteristic (25). This regeneration varies in intensity throughout the lobular nodules, but without apparent relation to the lobular architecture. The differential regeneration is responsible for the appearance of post-necrotic cirrhosis. Eventually this leads to the formation of nodules within nodules.

Popper (27) has stated that the mesenchymal reaction is far more active than would appear on histological section. He states that 10 mesenchymal cells must be formed for each hepatocyte to be in a histologic section at any giventime. Accordingly, the mesenchymal cells in itself injures the hepatic cells by competition for nutrients or other means remains to be proven.

The earliest response to liver cell injury is an increase of phagocytic cells in sinusoids, portal tracts and regional lymph nodes (27,32). These phagocytes contain PAS-positive phagosomes which are breakdown products of liver cells.

Lymphoid cell proliferation is associated with chronic liver cell injury (27). Lymphoid cells can be found in sinusoids and parasinusoidal tissue in or next to portal tracts, particularly in the areas of piecemeal necrosis. They are also found in regional lymph nodes and sometimes in lymphoid tissue throughout the body, including the spleen. The cells vary in morphology from small and large lymphocytes to cells with basophilic cytoplasm. The basophilic cells have been demonstrated to contain immunoglobulins, particularly gamma G globulin. The basophilic cells are usually found in association with the clinical finding of hypergammaglobulinemia. The production of immune globulins in the liver and their presence in the serum supports the autoimmune theory of perpetuation of liver disease. The piecemeal necrosis may suggest a delayed hypersensitivity reaction. No evidence is available to support this concept except possibly in homotransplant rejection in which a similar picture occurs (21).

Electron microscopy reveals fibroblastic proliferation and hyperactivity to occur in chronic liver disease (25). Fiber formation in the liver occurs in the portal tracts, around damaged liver cells and macrophages, and around proliferated bile ductules and capillaries. Irreversible fibrosis is said to occur when the relative number of fibers being formed is in excess of regenerating hepatocytes (27). This results in the

hepatic alteration of a lobular architecture to a nodular structure.

While acute liver injury is primarily the result of damage to the hepatocyte, in chronic liver disease both parenchymal and mesenchymal changes appear to be important. The mesenchymal response may be as important as the response of the regenerating hepatocyte in determining the severity of the illness. Popper (27) states that the mesenchymal reaction may cause further liver damage by the following means: (1) Competition with hepatocytes for nutrients; (2) Compromise of hepatocellular nutrition by fibroblastic activity; (3) Circulatory impairment due to inflammatory cells filling the sinusoids; and (4) action of lymphoid or immunocytic cells causing delayed hypersensitivity with abnormal liver tissue as the antigen. He also states that there may be deposition of complexes of excessively formed antibodies with hepatic or non-hepatic antigens.

Closed liver biopsy has been performed on all six cases presented in this study. Post-necrotic cirrhosis with piecemeal necrosis was seen in every case. Lymphoid and plasma cell infiltrates were observed in 100%.

Immunologic Histology

Mackay (12) states that the dense lymphoid infiltration of the liver represents an immunological reactivity in situ. Paronetto and co-workers (28) have demonstrated that the cells

with cytoplasmic basophilia form a gamma-globulin in the liver as well as in the lymph nodes and spleen. Further investigation (24) revealed that this was a $gamma_2$-globulin. This differs from the $gamma_1$ M globulin found in primary biliary cirrhosis or other liver diseases. The $gamma_2$-globulin fraction is elaborated by the lymphoid cells in lupoid and active chronic hepatitis. Mackay (12) believes this gamma-globulin to act as an antibody and to form antigen-antibody complexes with an unknown antigen. Paronetto and co-workers (23) have postulated that the cytotoxic effect of antigen-antibody complexes in the liver may be the mechanism of self-perpetuation of liver injury. Cohen (4) and co-workers have also by immunofluorescene demonstrated gamma-globulin formation in the liver and postulate that antigen-antibody complexes may cause persisting liver destruction. Cohen has also noted that in hypergammaglobulinemia of non-hepatic origin very few hepatic cells contain gamma-globulin.

Thus, it appears that in post-necrotic cirrhosis from lupoid or active chronic hepatitis a specific type of gamma-globulin is produced within the liver. The gamma-globulin produced has been shown to have its origin in the basophilic cytoplasm of the lymphoid or plasma cells. It is postulated that the gamma-globulin reacts with an unknown antigen to form antigen-antibody complexes. These complexes in turn may be the cause of persisting liver disease by damaging otherwise sound hepatocytes.

Immunologic Laboratory Findings

The phenomenon from which this disease entity derives its name is the lupus erythematosus cell test. The finding of a positive lupus test in a high percentage of the active chronic hepatitis cases led Mackay and co-workers to call this disease lupoid hepatitis. The LE-cell phenomenon is produced by a gamma-globulin with an affinity for nucleoprotein (11). These globulins have been found localized to the sites of lesions in kidneys, on the surface of red cells in hemolytic anemia in systemic lupus erythematosus and in the LE-cell itself (33). These phenomena are highly suggestive of antigen-antibody reactions occurring at these sites. These particular globulins have been named anti-nuclear antibodies due to their specificity for nucleoprotein (13). It appears highly unlikely that the specificity of these reactions and the frequency are due to random non-pathogenic happenstance. Not all cases have a positive test and there has been reports of positive lupus cell tests without liver disease (7).

Popper (27) postulates that the lupus cell test is due to mesenchymal activation resulting in formation of peculiar globulins which have this affinity for nucleoprotein.

The preceding finding has been labled antinuclear factor by Doniach (5). She has demonstrated that in all instances the reaction is a globulin reacting to a nuclear component of the cell. From this finding a test known as the anti-nuclear factor

test (ANF test) has been devised. This test involves using various organ extracts as antigens and demonstration of reaction of the antigen with a globulin by immunofluorescence.

Autoantibody Reactions

A significant discovery was made by Johnson and co-workers (9) in 1965. They were able to demonstrate a new immunologic finding utilizing gastric tissue of rats as an antigen. Immunofluorescence revealed an antibody to smooth muscle (SMA) in cases of lupoid hepatitis.

Ironside supported this work by excluding a possible source of non-specific reaction to the high serum-globulin levels in lupoid hepatitis (8). He utilized sera from patients with diseases in which there is a selective increase in one or more of the immunoglobulins. It was found that immunofluorescence occurred in gastrointestinal and vascular smooth muscle of rat and human origin with lupoid hepatitis sera only. It was also found that the staining properties were confined to the fraction containing the 7-S globulins.

Another method of utilizing the autoantibody reaction is the autoimmune complement fixation reaction (AICF) test. This test utilizes complement fixation, indicated by immunofluorescence with tissue homogenates as an antigen to the globulins of the sera. The use of this test is to demonstrate non-organ-specific cytoplasmic antibodies (5).

The results of the studies in Figure 8 show that ANF and AICF are not specific for lupoid hepatitis, rather points to autoimmune

Figure 8. Results of ANF, SMA, and AICF tests by Various Studies

	# of Cases	ANF	SMA	AICF
Doniach (5)				
Active chronic hepatitis	43	77%	67%	30%
Matched controls	43	2%		
Primary biliary cirrhosis	41	46%	50%	85%
Cryptogenic cirrhosis	32	38%	28%	31%
Systemic lupud erythematosus	10		0	
Mackay (17)				
Active chronic hepatitis	20	40%		
Lupoid hepatitis	22	73%		
Systemic lupus erythematosus	33	100%		
Nutritional cirrhosis	18	10%		
Johnson (9)				
Lupoid hepatitis	16		68%	44%
Systemic lupus erythematosus	16		0	44%
Normal controls	25		0	
Mackay and Whittingham (18)				
Lupoid hepatitis	34		82%	
Active chronic hepatitis	19		48%	
Systemic lupus erythematosus	20		0	
Mackay and Wood (15)				
Lupoid hepatitis	12			25%
Active chronic hepatitis	20			10%
Nutritional cirrhosis	27			4%

phenomena occurring in these diseases. The results of the SMA test provide the diagnostician with a much more specific means of discovering lupoid hepatitis. This evidence also suggests that lupoid hepatitis is a separate entity rather than a manifestation of another disease.

Other tests classified as autoantibody reactions include; rheumatoid factor, tanned red cell hemagglutination test, and the Coombs' reaction.

Studies (5,9,10,14) show that the prevalence of positive tests for rheumatoid factor, tanned red cell hemagglutination and the Coombs' reaction are approximately equal in lupoid hepatitis, active chronic hepatitis and systemic lupus erythematosus. None of these tests show specificity for any single disease.

Johnson and co-workers (10) have been able to demonstrate an antibody which appears to be directed at the bile canaliculi outlining each liver parenchymal cell. This is significant due to the fact that this is the first tissue - specific antibody isolated that is directed at the liver. However, Doniach (5) has demonstrated the same antibody is found in biliary cirrhosis and cryptogenic cirrhosis. Thus, the hepatic antibody is not specific for any single disease entity. The finding of this hepatic antibody does, however, strengthen the support for an autoimmune basis for lupoid hepatitis because of the organ-specificity.

It is of particular interest to note that the antiductile antibody found in these liver diseases have also been found frequently in chronic ulcerative colitis (24). There may be some association of this antibody with the occasional finding of ulcerative colitis in patients with lupoid or active chronic hepatitis.

In summary, production of specific gammaglobulins have been demonstrated to occur in lupoid and active chronic hepatitis. Antigens that react with these gammaglobulins have been found in thyroid, gastric, renal and smooth muscle of the vasculature. An antibody-antigen reaction has been shown to occur in the bile caniculi of the liver; however, this reaction is seen in other types of liver disease. At the present time, no liver specific antigen-antibody reaction has been demonstrated to occur only in lupoid or active chronic hepatitis.

An interesting fact has evolved during the search for autoantibodies. Ironside (8) in his effort to evaluate Johnson's (19) finding of SMA noticed that stromal elements, renal glomeruli capillary walls in particular, reacted specifically with the antisera being tested. Whittingham and Mackay (19) elucidated on this finding by running a study comparison of immunofluorescence of renal glomerular cells in lupoid, active chronic hepatitis, primary biliary cirrhosis and systemic lupus erythematosus. It was found that 61% of 34 cases of lupoid hepatitis sera reacted

immunologically to renal glomerular homogenate. Active chronic hepatitis showed a positive result in 35% of 19 cases. Primary biliary cirrhosis and systemic lupus erythematosus cases, six and 20 respectively, had no positive reactions.

Doniach (5) has demonstrated that sera from cases of primary biliary cirrhosis, reacts with homogenates of renal tubular homogenate. This finding has been substantiated by Whittingham and Mackay (19).

The finding of an immunologic complex in renal glomerular cells of patients with lupoid hepatitis is significant. Silva (31) has demonstrated renal glomerular lesions in seven of 12 (58%) patients with lupoid hepatitis. The glomerular lesions resembled the lesions described in early "lupus nephritis." Silva concludes from this evidence that the liver is only the predominant target in lupoid hepatitis and that many other systems may be affected. Whittingham and Mackay (19) contend that the autoimmune globulin found in the glomerulus in lupoid hepatitis is the result of a reaction in situ. They believe that the antigen-antibody complex found in systemic lupus erythematosus is formed remotely and lodged accidentally in the renal glomerulus. The reasoning for this being that the lupoid hepatitis globulin reaction is specific for glomerular cells, whereas, the antigen-antibody complexes of systemic lupus erythematosus are not.

Immunoglobulins

Hypergammaglobulinemia is one of the hallmarks of lupoid hepatitis. A diminution in the albumin fraction is also a common finding.

Zlotnick and Rodnan (35) have elaborated on these findings. Immunophoresis technique has revealed a number of more specific abnormalities in alpha and beta globulins.

The $alpha_2$ fraction, which appears normal on paper electrophoresis, showed striking changes on immunophoresis. A decrease in $alpha_2$ haptoglobulin and an increase in $alpha_2$ macroglobulin was found. The decrease in haptoglobulin is also seen in nutritional (alcoholic) cirrhosis. An increase in $alpha_2$ macroglobulin is observed in scleroderma and rheumatoid arthritis, but not seen in any other types of liver disease.

The $beta_1$ complexes revealed a decrease which appears to be a characteristic feature of lupoid hepatitis. This finding has, however, been described in some cases of fatal hepatitis of viral origin also. The $beta_1$ A globulin is decreased and the $beta_1$ C globulin appears to be absent. An explanation given for the absence of $beta_1$ C globulin is transformation to $beta_1$ A globulin or aging of the sera. The decrease in $beta_1$ A globulin is characteristically seen in cases of systemic lupus erythematosus.

An increase in $beta_2$ A and $beta_2$ M globulins was found. These increases have been reported in a variety of conditions and are not specific for liver disease.

In summary, the following findings have been found in the proteins of lupoid hepatitis by immunophoresis. There was a decrease in albumin, $alpha_2$ haptoglobulin, $alpha_2$-beta lipoproteins, and beta A globulins. An increase was observed in $alpha_2$ M, $beta_2$ A, $beta_2$ M and gammaglobulins.

The increase in gammaglobulin correlates well with the finding of $gamma_2$ globulin (7 S gammaglobulin) complexes that are found in various tissues of the body by immunofluorescence.

Associated Diseases

Certain diseases that have been postulated to have an autoimmune basis have been found in association with lupoid and active chronic hepatitis.

The Coomb's-positive hemolytic anemia has been observed in several cases of lupoid hepatitis (29).

Ulcerative colitis is seen occasionally in lupoid hepatitis (22,29). In Reads (29) study of three patients with both diseases, it was shown that the symptoms of ulcerative colitis appeared after there was clinical evidence of chronic liver disease. This suggests that the cirrhosis was not the result of the colitis.

Acute rheumatic fever, chronic rheumatic heart disease, and rheumatoid arthritis and spondylitis have been seen with cases

of lupoid or active chronic hepatitis (29). Page and Good (22) reported on cases of lupoid hepatitis where acute rheumatic fever preceded the onset of the liver disease.

Renal lesions of the glomerulonephritis type have been observed in cases of lupoid hepatitis (31,33).

The occurrence of Hashimoto's disease has been demonstrated in lupoid and active chronic hepatitis (29). A histological finding revealed prominent lymphocytic infiltration in the portal zones of the liver as well as in the thyroid. The similarity of the two lesions might indicate a dual autoimmune basis.

A true case of systemic lupus erythematosus and lupoid hepatitis in a single individual has not been demonstrated. However, characteristics of systemic lupus erythematosus are often seen in cases of lupoid hepatitis. On the other hand, cases of systemic lupus erythematosus rarely present with chronic progressive liver disease resembling lupoid hepatitis.

Etiological Aspects

1. Persisting Viral Infections - Viral infections have been postulated as a possible cause of the persisting liver disease seen in active chronic hepatitis. Methods of proving this theory are hampered due to the inability to isolate or detect the virus responsible for hepatitis. Several observations, however, tend to rule against persisting viral infection

as the etiology of chronic progressive liver disease. First, most viral infections are of short duration and confer lasting immunity. One viral infection which is prolonged is that of herpes simplex. However, with herpes infection there is not continuing damage, but rather a state of complete symbiosis for most of the time. Secondly, large scale surveys of soldiers who suffered from acute viral hepatitis reveal very few cases of active chronic hepatitis (13). This suggests that the virus of hepatitis does not cause persisting disease.

2. Derangement of Vascular Architecture - Chronic persisting liver disease has been attributed to derangement of vascular architecture. Growth of regenerative liver nodules tend to distort and compress venous and capillary channels, and shunts may develop between the portal and hepatic veins (25). Regenerative nodules are thus at a definite circulatory disadvantage, which would explain the persisting ischemic necrosis and progression of the disease. Mackay and co-workers (13) on the other hand, state that it is their experience that the episodes of necrosis are maximal in the early stages of chronic hepatitis when fibrosis and nodulation are minimal and circulatory derangement is not demonstrable. On this evidence, they find it difficult to accept that ischemic necrosis can be the major cause of persisting destruction.

3. Bacterial Toxins - Bacterial toxins have been thought to be contributing factors to chronic persisting liver disease.

An analogy has been made to chronic blood-borne pyelonephritis in which renal damage and bacteremia are associated. Hepatitis may similarly result from the combination of pre-existing liver damage and portal bacteremia. The occasional coexistence of chronic hepatitis and chronic ulcerative colitis is noteworthy, because of the possibility of portal bacteremia occurring in chronic ulcerative colitis. However, it is thought that the episodes of liver necrosis cannot entirely be attributed to bacterial toxins (13,26).

4. Autoimmunity - The most current and popular explanation of chronic persisting liver disease is on an autoimmune basis. The major proponents of this theory are Mackay and Wood. The excess of serum gammaglobulin in chronic hepatitis has been shown to originate within the liver. It is believed that this intrahepatic gammaglobulin synthesis is part of an autoimmune process occurring in the liver. Other findings which support an autoimmune basis are the numerous immunologic reactions and autoantibodies that are frequently demonstrated in active chronic liver disease.

Mackay (12) and Popper (26) attribute the progressive damage of liver disease to cellular activity as in homograft rejection, rather than to the circulating autoantibodies. There is little evidence that circulating autoantibodies or the antigen-antibody complexes have cytotoxic properties.

The present theory of persisting liver damage as proposed by Mackay is based on the "forbidden clone" theory of Burnet (12). This theory is also known as the clonal selection theory. A forbidden clone is described as a clone of cells capable of immunological activity with the tissues of the host. It is thought that every individual possesses such clones throughout his life time. The "forbidden clones" are postulated to arise by somatic mutation during embrylogical life and in post-natal life by mutation among normal antibody-producing cells. A normal individual is thought to possess forbidden clones, however, these are eliminated by the body's homeostatic mechanisms. These forbidden clones are thought to become pathogenic when there is an imbalance or overabundant contact with excess antigen or stimulation by unknown causes. The excess stimulation may be the <u>initial</u> viral hepatitis or other unknown factors. In any event, the forbidden clones become apparent due to lack of normal homeostatic controls. The cells of the specific clones mediate a delayed sensitivity response such as the tuberculin sensitivity reaction. This reaction results in a homograft rejection response. This mechanism was formerly termed "cell bound antibody," but now is described in terms of "immunologically competent cells (I.C.C.)." The importance of the circulating autoantibodies in this type of liver disease is that they indicate that immunologically competent cells of the same specificity are also present in the body (12).

Lupoid hepatitis and active chronic hepatitis, therefore, are seen as the colonization of the liver by forbidden clones of immunologically competent cells which have become established following an imbalance of the normal homeostatic mechanisms of the body. The factors which initiate the homeostatic imbalance reamin unknown.

Further support of this theory has come from Cohen (4). It has been shown that immunologically competent cells are concentrated in the liver in lupoid or active chronic hepatitis and in post-necrotic cirrhosis by the fluorescent antibody technique. The experiment demonstrates gammaglobulin formation by "reticuloendothelial cells showing transition to plasma cells," whereas control cases showed few if any such cells. The concentration of cells producing gammaglobulin was correlated with the severity of liver destruction.

Immunosuppressive drugs appear to give a clinical improvement in cases of lupoid hepatitis (36). This finding supports the theory that an immune mechanism is the basis for the persisting hepatic destruction.

Popper (26) supports the immune mechanism as the basis of continuing liver destruction; however, his views differ slightly from those of Mackays. Popper believes that the initiation of the immune response begins in the mesenchymal tissue of the liver instead of the parenchymal tissue. He believes thatthis immune

response results in immune reactions which are not directed against hepatic tissue specifically. He attributes the actual progressive liver damage to antigen-antibody complexes that are subsequently formed. This differs from Mackays viewpoint which attributes the hepatic damage to autoantibodies directed to the liver. Popper relates this theory as a self-perpetuation theory whereas Mackay's viewpoint is called an autoimmune theory. Mackay has also referred to his theory as the "autoclasia" theory.

Popper's theory provides an explanation of the finding of other organ autoimmune phenomena which are encountered in lupoid hepatitis.

Conclusion

Lupoid hepatitis is a disease belonging to the active chronic hepatitis group. This type of liver disease is characterized by a slow, erratic progressive liver destruction leading to a post-necrotic cirrhosis and eventually hepatic failure.

The disease is associated with a variety of systemic manifestations that are not the result of the liver involvement.

Many immune phenomena are observed to occur in lupoid hepatitis. Histologically, it has been demonstrated that specific immune globulins are produced by certain types of cells within the liver. Various autoantibodies have been found in the sera of these patients. These antibodies have been directed against organs other than hepatic tissue. A hepatic-specific autoantibody

has been shown to occur in lupoid hepatitis and certain other liver diseases thought to be of an autoimmune origin. Non-specific immune reactions occur as evidenced by immunofluorescent laboratory tests. These nonspecific immune reactions occur in other non-hepatic diseases which are thought to have an immune basis.

Corticosteroids and immunosuppressive drugs appear clinically to have a beneficial effect on the disease. However, no evidence has been brought forth that these drugs cause a prolongation of the life-span.

Various theories as to the pathogenesis of lupoid hepatitis have been brought forth. At the present time, the most promising explanation is that of an autoimmune disease. This type of phenomena best explains the chronic, progressive course of the disease.

Further study appears to be indicated in the isolation of possible liver specific autoantibodies and clarification of the mechanism of actual persisting damage to the liver. Control studies of the beneficial effects of corticosteroids and immuno-suppressive drugs related to prolongation of the life span are warranted.

Summary

Six cases of lupoid hepatitis are presented in various stages of the disease. Incidence, clinical signs and symptoms, laboratory

findings, clinical course and mortality are discussed. Gross and microscopic histology are presented with special reference to findings relating to immunology. Various immune tests are discussed and compared with diseases other than lupoid hepatitis. The finding of autoantibodies and their relation to the disease process is presented. The relationship of other possible autoimmune diseases to lupoid hepatitis is brought forth. The pros and cons of possible etiologies of chronic progressive liver disease are presented with special detailed reference to the current autoimmune theories.

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