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Familial portal cirrhosis of the liver : presentation of three cases in one family

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FAMILIAL PORTAL CIRRHOSIS OF THE LIVER: PRESENTATION OF THREE CASES IN ONE FAMILY

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FAMILIAL PORTAL CIRRHOSIS OF THE LIVER: PRESENTATION OF THREE CASES IN ONE FAMILY

Portal cirrhosis of the liver is a subject much discussed and its etiology much debated. The blame for its development has been placed variously on conditions ranging from malnutrition to gluttony; thru a broad spectrum of ingestible substances and micro-organisms. Several writers (*) have noted its occurrence in siblings, this condition becoming known as "Familial Cirrhosis of the Liver". The purpose of this paper will be to review three cases in one family and present a study of what is known of this condition in an effort to ascertain its etiology.

PRESENTATION OF FIRST CASE:

M. T., a white, 8 year old female, was brought to M. D. with the complaints of irregularity of appetite, weight loss, and being generally "run Down". The patient's past history was considered non-contributory. Her childhood diseases were not recorded. On examination the patient was found to have hepato-splenomegaly and was referred to the Mayo Clinic. There the liver was reported to be considerably enlarged and the spleen

(*) References at the last of the bibliography

to extend to the superior border of the pelvis. Splenectomy was done there and the patient was returned to her home in good condition. She went to school and participated in all activities.

Approximately 10 months later her abdomen began to enlarge and was tapped, yellow fluid being obtained. She had no pain, jaundice, or other complaints. Two weeks later her abdomen became very tense and she had some pain along with a bronchial infection. The patient was admitted to Lincoln General Hospital at this time, 10-6-36. Examination revealed her to be acutely ill and somewhat cyanotic. Her respirations were fast and labored, her pulse 120, and her temperature 102.4° orally. Her abdomen was markedly enlarged and superficial venous distention was present over the trunk. Her legs were swollen. Gentle abdominal pressure was not painful. The splenectomy scar was well-healed. There were many rales in the chest, but no sign of heart abnormality was found. The impression at that time was: 1--cirrhosis of the liver with ascites; 2--bronchitis with bronchopneumonia. Urine exam was essentially negative except that bile was reported present. Urobilinogen was positive in 1:20 dilution (within normal limits). The blood findings are listed below:

Hb 9.9 gm/100cc
RBC 3.63 M/cu. mm.
WBC 38, 700/cu.mm.
Differential

Seg	59
Staff	10
Young	1
Myelo	2
Lympho	20
Mono	3
Eos	1
Baso	0
Immature lympho	4
Megaloblasts	2
Reticulocytes	0

The patient's course went progressively downhill, her temperature varying from 103.4° to 99°, being around 100° shortly before demise. Pain in her abdomen had to be relieved by codeine terminally. The patient died on 10-14-36 at age 10. The immediate cause of death was not recorded. The final diagnosis: 1--Banti's Disease; 2--bronchopneumonia.

PRESENTATION OF SECOND CASE:

G. T., a white, 88year old male was brought to M. D. with the complaints of a capricious appetite and recurrent abdominal pain for a period of 6 months. He had some abdominal tenderness but no fever. Approximately 2 months previously a large liver and spleen had been noted on examination which had not been recognized in an examination one year before. The patient had had recurrent nosebleeds for 2 months prior to seeing the M. D. with these complaints. The patient had

had a tonsillectomy and adenoidectomy four years before this time at which time his bleeding time was 1 minute and his coagulation time was 13 minutes.

The patient was admitted to the Lincoln General Hospital on 5-3-38. On examination his cardio-respiratory was reported as negative. The liver was palpated three fingers below the right costal margin and was firm and tender. The spleen was palpated two fingers below the left costal margin. There was a spider angioma beneath the left eye. The remainder of the examination was negative. A BSP retention test was done on 5-17-38 and showed 40% dye retention. An appendectomy was done at this admission from which recovery was uneventful except for occasional nosebleeds. Report of findings at operation were: "Liver enlarged --pale--markings distinct--firm and rubbery. Gallbladder grayish and distended. Spleen enlarged 2-3X extending well b elow the left costal margin--not adherent". Diagnosis at this time was "Banti's Disease".

The patient was admitted again on 5-26-38 for splenectomy. The physical examination done at this time was essentially the same as before except that the pallor formerly present was thought to be more pronounced.

Pathological report on the spleen following splenectomy was "...Splenomegaly with reticulum cell hyperplasia--(Banti's Disease)...". The course following this operation was uneventful.. Laboratory studies showed:

Blood: Hb 9.8 gm/100cc
Rbc 4.5 M/cu.mm.

Urine: Essentially negative. Urobilinogen was positive for 1:20 dilution (within normal limits). Bile was not found to be present in the urine.

The patient was discharged with suggested bedrest. Diagnosis: Banti's Disease.

Later the same year the patient developed ascites and died shortly at age 8. No autopsy was done.

PRESENTATION OF THIRD CASE:

C. T., a white, 4½ year old female was sent to Mayo Clinic for examination following the death with cirrhosis of her second sibling. The patient had been a well-developed, well-appearing child up to this time. At examination, hepato-splenomegaly was noted and liver was described as "possibly" more firm than normal. Hb 13.1 gm/100cc., WBC 9,200/cu.mm. X-ray of the chest, flocculation test for syphilis, RBC fragility and Takata-Ara test were all done and reported as negative. Serum bilirubin was reported as 1 mg. with a normal of 1.05 to 2.0 mg. BSP retention was found to be within normal

limits. Splenectomy was suggested.

The patient was admitted to Lincoln General Hospital on 9-3-38 where the findings were the same as at the Mayo Clinic. In addition, 2 spider angiomata were noted on the right elbow and hand. Splenectomy was done at this admission. The spleen was reported by the pathologist to be enlarged but not otherwise abnormal. At operation the liver was described as smooth, firm, and of a normal brown color, extending to just below the right costal margin. No blood tests were.done. Urine findings were within normal limits. Diagnosis at this time was "Familial Cirrhosis of the Liver".

At the time the patient had a tonsillectomy and adenoidectomy five years later, the bleeding time was 1 minute, 10 seconds; the coagulation time was 6 minutes, 30 seconds; the prothrombin time was 84% of normal; and the ESR was 15 mm./hr.

The patient was readmitted to the hospital approximately 5½ years following her splenectomy, on 1-29-44 with complaints of increased susceptibility to colds and infections and a progressive listlessness for three years. She had had common intermittent periods of nausea and anorexia for three months. Frequent vomiting, dizziness, back- and leg-ache, and

questionable jaundice had been present for two months. Abdominal fullness had been present for a short time b efore admission. On physical examination the patient did not appear to be sick but was listless. Spider angiomata were present on her face and body. The liver was palpated 9 cm. below the right costal margin in the mid-clavicular line. All other findings were within normal limits. The patient was placed on a 2000 calorie diet, including 100 grams of protein and essentially no fat. Choline chloride was administered 100 mg. qid. During the hospital stay the liver decreased somewhat in size, nausea decreased, the appetite improved and the ascites lessened. The blood findings remained relatively constant:

Hb 11 gm/100cc.
RBC 4 M/cu.mm.
WBC 25,000-40,000/cu.mm. with an essentially normal differential count.

Other laboratory findings were:

Date	TSP	Albumin	Globulin
1-31-44	6.45 gm/100cc	3.96 gm/100cc	2.49 gm/100cc
2-10-44	5.6	3.5	2.1
2-17-44	7.1	3.2	3.9
4-13-44	9.5	2.7	6.8

During the hospital stay the patient developed some bone pain but nothing could be demonstrated radiographically. She was discharged 4-15-44 and her

condition was described as "improved". The diagnosis remained the same.

The patient was readmitted on 5-23-44 with the same complaints as at last admission. The physical examination revealed the same findings. During this hospital stay her sclerae b ecame definitely icteric. The patient became generally uncomfortable with gas and pain in her right epigastrium which bothered her intermittently. She commonly had nosebleeds and her course was generally downhill. Hb 9.8 gm/100cc, RBC 3.55 M/cu.mm., WBC 3400/cu.mm. The patient was dismissed on 7-2-44 and died at home of anesophageal hemorrhage on 7-9-44at the age of 10 years, 6 months.

Autopsy revealed the external physical findings mentioned. The peritoneal cavity contained 1200 cc of clear yellow fluid, and 500 cc of the same were in the pleural cavities. Congestion of the superficial vessels of the abdominal viscera and the epicardium was noted. The liver weighed 1250 gm. Its surface was studded with yellowish nodules maasuring up to 0.5 cm. The surface was hard and fibrotic "giving a typical appearance of portal cirrhosis". There were no adhesions of the liver to other organs. The portal vein was found to be thickened and contained no thrombi. The lower esophageal veins showed marked dilatation

with congestion and slight superficial ulceration of the mucous membrane. One ruptured esophageal varix was found to be present and there was approximately 500 cc of hemolyzed blood in the stomach. The pancreas, kidneys and heart had a "waxy" appearance. There was a generalized visceral lymphadenopathy with a brownish-yellow discoloration of the nodes. There was no accessory spleen present.

Microscopic examination revealed an atypical bronchopneumonia. The liver showed marked periportal and interstitial fibrosis with atrophy of cells. Marked subacute and chronic inflammatory cell infiltration of connective tissue of the periportal spaces was noted. There was precipitation of bile salts in the liver cells with resulting pigmentation and numerous bile thrombi. This was described by the prosector as a picture typical of portal cirrhosis. No evidence of parasites or ova was found in the liver tissue. The gastrointestinal tract demonstrated a picture of subacute and chronic enteritis, which suggested to the prosector that this represented more than a terminal event. The bone marrow showed diffuse hyperplasia especially in the myelocytic series. This was thought to be related to the splenectomy done early in life. In the lymph

nodes the sinusoids were markedly dilated and the reticulum prominent. The lymphoid tissue was gathered into follicles. All the lymph nodes had striking resemblance to splenic tissue.

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The condition of portal cirrhosis of the liver has several synonyms which have proved inadequate for one reason or another. They are "Laennec's Cirrhosis", "diffuse nodular cirrhosis", "atrophic cirrhosis", "hobnailed liver", and "alcoholic cirrhosis". The pathological picture of this condition is characterized by marked alteration of the architectural pattern. The normal lobular arrangemint of the liver becomes diffusely and completely distorted by irregular degeneration and destruction of hepatic cells, accompanied by fibrosis and irregular regenerative hyperplasia of hepatic cells and bile ducts. In addition to disturb ances of the various functions of the liver there is obstruction of the portal blood channels in the liver, with chronic passive hyperemia of tissues drained by the portal circulation. This results in distension of collateral channels of venous return which bypass the liver, some of which may rupture and result fatally. The increased portal pressure also increases the diffusion gradient

from the capillaries in the regions drained by the system causing ascites and interstitial fluid or edema (these 2 conditions are also related to the abnormal salt and protein levels). While usually reduced in size and weight (often less than 1800 gm.), the liver size may be normal or even considerably enlarged with weights up to more than 3000 gm.

The most characteristic feature is the diffuse development of small brown-yellow nodules, usually between 1 mm. and 1 cm. in diameter, separated by irregular thick b ands of connective tissue of pale gray color. The surface is roughened by the projecting nodules. Microscopically, bands of connective tissue divide the hepatic cells into irregular lobules of variable size. Various inflammatory cells infiltrate the distorted lobules and various stages of fibrosis, degeneration and regeneration are seen. (1)

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Familial Cirrhosis of the Liver had been discussed as being an entity since 1892 when Jollye (2) reported the occurrence of hepatic cirrhosis in siblings, a boy, age 11, and a girl, age 10. Both of these children developed all of their symptomatology within 6 months of their respective deaths. Both had ascites,

leg-swelling and jaundice. Post-mortem was done on the girl and the only significant findings were a large lobular liver and marked proliferation of intrahepatic bile ducts. There was nothing in the family history to suggest heredity to be a factor. The only things that these children had in common besides parentage were having had measles and a fancy for drinking vinegar. Jollye suggested that their cirrhosis had developed following and secondary to their measles infection.

Though Hollye was the first writer to have made comment about a familial tendency to this condition, Howard (3), in 1887, reported two similar cases in a brother and sister of approximately the same ages. Judging from his rather extensive coverage of the literature previous to that time from which he reports 63 cases of juvenile cirrhosis, his are the first cases of juvenile cirrhosis striking two members of the same family reported in the English literature.

Since Jollye's article there have been some 13 families reported in the English literature which have been afflicted with juvenile cirrhosis exhibiting a familial tendency. All of these show generally the same picture. The ages of the affected persons

vary from a few months (4) to age 21 (4), but the great majority fall in the narrow age range of 8 to 11 years. The symptomatology of each of the cases is very similar to that presented by Jollye. Brenneman (6) states the condition may progress with or without symptoms which are indefinite and then suddenly show acute hepatic injury. Lassitude, anorexia, nausea, vomiting, vertigo, infantilism (7), emaciation, debility and periods of apparent improvement may all be seen. Death may commonly be associated with intercurrent infection, gastrointestinal hemorrhage and uncommonly cerebral hemorrhage. Things commonly seen are fever, epistaxis, spider angiomata, 2° anemia, and convulsions; while jaundice, ascites, and swelling of the legs are almost invariably present. Splenomegaly and hepatomegaly are variable but are present generally at some stage of the condition. From the time of onset the course of the disease is characteristically brief, lasting from a few weeks to, at most, 2 or 3 years.

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The etiology of many or most portal cirrhoses is vague at best. Once the condition has occurred, a way has not been found that will reverse the course. Thus, the treatment is primarily aimed at slowing or stopping its progress, or just minimizing the symptomatology. In the case of the familial condition, however, if once considered, were the etiology known,

rational prophylactic therapy might be instituted in an effort to forestall occurrence in another child.

As has been formaerly stated the gamut of suggested etiologies is wide. The word "familial" in the name of the condition might suggest that this is a congenital disease (fr. Lat. cum, together + genitus, born; i. e., present at birth). It is known that juv-enile biliary cirrhosis, the more common type of juven-ile cirrhosis (8), is most commonly secondary to con-genital defect. This relationship of portal cirrhosis is not so definite. Merely the presence of more than one member of the same family contracting the disease seems good circumstantial evidence in favor of heredity, however, the relative rarity of family history of the condition mediates against this. Chapman and Barber (9) in their report of b rothers with the condition mention that their mother had a sister who was per-sistently delicate, undersized and anemic, and whose liver and spleen were enlarged in childhood. She dev-eloped severe hematemesis and died in her teens. The pathological diagnosis was never made but was certainly suspicious. Sarma (10) found instances in his study in which not only a number of children from the same parents died of the desease but cousins as well.

Two possib ilities of hereditary etiology have been discussed. Farina and Ferrari (11) raised the question of heredity in 1950 and attributed its transmission to changes in genotype, rather than to cirrhogenous environmental factors. They verified in their own minds that this gene appears in recessive form though sometimes it appears to be dominant. They state that it is invariably characterized by an identical genotype. They feel that in a limited number of cases, however, when the familial cirrhosis is associated with familial Rendu-Osler-Weber's disease (hereditary telangiectasis), that the possibility of a pleiotropic gene (one with more than one effect) may be considered. This latter condition is the case in the other suggested possibility of hereditary etiology of familial cirrhosis, an abberant form of Wilson's disease ("Progressive lenticular degeneration" or Hepatolenticular degeneration").

Wilson's disease has never been absolutely established as being an inherited condition though some consider it to be transmitted by either a pleiotropic or a recessive gene (12). This condition is characterized by a portal cirrhosis of the liver and progressive bilateral degeneration of the putamen and

caudate nuclei and to a lesser extent, the globus pallidus. A commonly, but far from invariably, associated symptom of this disease is a brown pigmented ring of what is thought to be a breaksown product of hemoglobin which is found at the corneo-scleral junction, the Kayser-Fleischer ring(12). This has been used incorrectly as the factor which ruled out Wilson's disease in differential diagnosis of familial cirrhosis. Due to the marked tendency for this condition to be familial (reports suggest familial cases to be 8 times as common as single cases (12)), Bramwell (13) suggested that 4 of his cases of familial cirrhosis which progressed rapidly might constitute a "forme fruste" of Wilson's disease which progressed so rapidly that neurological symptoms did not have time to develop. His study, however, is not well corroborated with evidence of the necessary brain pathology. Neurological symptoms commonly seen in familial cirrhosis are not those characteristically seen in Wilson's disease, i. e., those related to extrapyramidal dysfunction (12). Nor are they those of peripheral neuropathy as are occasionally seen in cirrhotic adults and which are thought to be secondary to vitamin B deficiency (6). They are convulsive in character.

There are three conditions which have been thought to enter into the etiology of this condition which are in the form of physical defects or malformations. The first was described as "dysbiotrophy" by Weber (14) in 1936. He explains this as a constitutional defect in the hepatic cells which diminishes their power of resistance to toxins and causes them to decay prematurely. Other conditions he attributed to "dysbiotrophy" were hemophilia (congenital hypoprothrombinemia, a sex-linked gene), familial hemolytic icterus (now known to be hereditary), the lipodystrophies and glycogen storage disease (probably due to enzyme deficiencies), and others including allergic peculiarities.

The second of these conditions is hereditary angiomatosis (Lindau-Von Hippel's disease) which is described by Mitchell and Nelson (15) as on of the two causes of congenital portal cirrhosis (the other being Wilson's disease). This condition is characterized by increased numbers and tortuosity of blood vessels and large thin-walled veins found, among other places, over the surface of the liver. This has been seen in conjunction with juvenile cirrhosis of the liver but has not been reported in the known cases of familial cirrhosis.

The third of these conditions was called "fibroid diathesis" by Howard (3) in 1887. Characterized by a general tendency to connective tissue formation leading to, among other things, cirrhosis, this condition has not been seen in pathological diagnosis in familial cirrhosis.

Polyhydramnios has been mentioned as a cause of fetal cirrhosis (16) but has not b een reported in familial cirrhosis.

Cirrhosis has been reported in association with erythroblastosis fetalis, congenital hemolytic anemia and sickle cell anemia (15), especially the first (17), (18), (19). Cirrhosis in erythroblastosis is thought by György (20) to be linked with some yet unidentified phase of the Rh antigen-antibody reaction. None of these have been demonstrated in cases of familial cirrhosis however. Gerrard (21) stated in 1952 that there was no evidence to support the thesis that familial hepatic cirrhosis is a sequel of Rh iso-immunization, though it has been shown to lead to infantile cirrhosis (22).

The last likelihood of congenital etiology found in the literature is that of infectious hepatitis of the mother during pregnancy with placental

transfer of the virus and subsequent infection of the fetus and development of cirrhosis. This has been reported by Bellin and Bailit in 1952, and presumptive evidence of placental transfer of the virus has been presented (8). Zondek and Bromberg described infectious hepatitis in 29 pregnancies in 1947 (23) with no infected infants. There have been no cases of infectious hepatitis during pregnancy related to familial cirrhosis.

Non-congenital causes of juvenile cirrhosis include infection and dietary abnormalities as the most common. Others considered are metabolic disorders, tumors, Banti's disease, and a condition known as "generalized cytoplasmic inclusion disease".

Infectious hepatitis is a viral disease commonly considered in relation to development of cirrhosis of the liver. Lucke (24) has stated that infectious hepatitis rarely if ever terminates in cirrhosis. However, a majority of sources state that this disease is commonly the primary antecedent of cirrhosis (25). Krarup and Roholm (37) claim to have demonstrated "all sorts of transitions" between acute hepatitis and fully developed cirrhosis. Block (25) thinks that many reported cases of liver infection of

"unspecified nature" (25), (27) are most probably truly cases of infectious hepatitis. Most of the cases of reported familial cirrhosis have had no history of infectious hepatitis, however.

Chronic infection of the liver was, in former times, a more common cause of cirrhosis. Such diseases as syphilis and tuberculosis used to account for a significant number of cases of cirrhosis of the liver. Howard (3) reported in his series of 63 cases of juvenile cirrhosis collected in 1887 that tuberculosis and syphilis were each responsible for 11%(28). They probably account for a rather small number in these days when those entities are becoming so uncommon. Portal cirrhosis is probably not a common manifestation of syphilis in childhood (6).

Acute infections of the liver are considered to occur in several ways. Moon (29) and others (15) mention infection of the liver associated with enteritis while Potter (30) and others (15) have noted infection via the umbilical stump. Coccal infections of the liver are reported (15), (31) as are those caused by colon bacilli (32) leading to cirrhosis in children. Of the parasitic infestations that have been found to lead to cirrhosis, malaria and kala azar are the least uncommon. (15, 31).

The exanthemata appear to require some attention as a class. Though it is misleading that such a hish percentage of children contract measles and scarlet fever, these diseases are thought by many to be the primary cause for cirrhosis in some children (3, 15, 29, 33, 34). In the cases reviewed for this writing of familial cirrhosis a large percentage of the patients hadhad a history of having had measles, scarlet fever (scarlatina), or both, and in many the close relationship of these diseases and cirrhosis is to be noted. No studies reported have compared the incidence of the exanthemata in children afflicted with, and not afflicted with juvenile cirrhosis.

Also found in a very large percentage of the cases reviewed and all of those presented was a history of fever and definite evidence of infection associated with the development of the cirrhosis. Fever was commonly present in Howard's review of 63 cases (3). Abt, in 1919, (35) pointed out that the common febrile crises noted in juvenile cirrhosis suggested an infectious basis for the condition. However, it is difficult to determine for sure that the febrile conditions were not developed parallel to or secondary to the cirrhosis. In most cases the febrile episodes appeared to precede

the development of symptomatic cirrhosis suggesting some infectious relationship.

Dietary abnormality has long been thought to be an antecedent to cirrhosis of the liver. Interestingly enough, before the twentieth century it was thought that an overly stimulating diet would lead to cirrhosis (3,35). One source states: "Overeating acts primarily as a stimulant to hepatic tissue and theoretically brings as an after result cirrhotic changes analogous to those of interstitial nephritis which is frequently excited by a diet too largely nitrogenous."(35) (It has only recently been reported by Schwartz and others (36) that patients treated with high protein, high carbohydrate diets may become intolerant of certain nitrogenous substances and develop a syndrome resembling incipient hepatic coma.

Dietary deficiency now is considered to play a large part in the development of many cases of cirrhosis. Many reports from India, where juvenile cirrhosis is very common, mention dietary deficiency as the primary consideration in the etiology (32, 36). Lahiri (32) suggests a subacute infection (colon bacilli, as a rule) superimposed upon an already damaged liver due to dietary deficiency accounts for the et-

iology of a large percentage of the juvenile cirrhosis in India. Kwashiorkor, or malignant malnutrition, is a condition seen in Central Africa, India, and the West Indies which leads to fatty infiltration of the liver and thence to cirrhosis (15). Malnutrition, however, does not appear to be present in the cases of familial cirrhosis reviewed.

Many substances, both inorganic and organic, are known to be toxic to liver tissue (15, 38). None of these are commonly in a place accessible to children with the exception of alcohol and some rare things which have been indicted in specific cases of juvenile cirrhosis in variously distributed foreign lands (15, 39). There is an interesting report from Denmark of jaundice in hogs which seemed to be associated with production of more cases of jaundice in more rural than urban folk.....this being apparently associated with cirrhosis (40). Reed (41) suggests that the infantile liver is extremely vulnerable to toxins. There have been several articles reported suggesting a toxic effect of galactose on children (42). One of these describes 3 children in one family with this condition. It was found that taking milk from one infant resulted in his marked improvement after 2 siblings had died

following a typical course of cirrhosis.

In conditions of cirrhosis in childhood certain metabolic abnormalities must be mentioned if for completeness only. The lipoid storage diseases such as Niemann-Pick's and Hand-Schuller-Christian's diseases are quite rare in childhood (42). Gaucher's disease is said to characteristically give a picture of a "femalt Jewish child who dies at an age of less than three years" (43). None of these have been noted in the reported cases. Hemochromatosis must also be considered (38, 40). Schindler and Kindschi (38) suggest consideration of aberrations in protein and carbohydrate metabolism and disturbed adrenal function.

Tumors of primary or matastatic origin may lead to cirrhosis but these are rare in children (44) and have not been noted in the reported cases.

Banti's diseases or syndrome is a slowly progressive condition of splenomegaly associated with portal cirrhosis of the liver. It has been confused with other juvenile cirrhoses as it was in two of the cases presented here. In Banti's disease, however, the splenomegaly is generally considered to be primary. Histologically a hyperplastic picture is usually present as opposed to the congestive one which develops

secondarily in portal cirrhosis of other etiology. This has not been the pathological diagnosis in any of the eases reported.

Wyatt and others (45) reported in 1950 on a condition which they termed "generalized cytoplasmic inclusion disease" in which inclusions are found in the cytoplasm of liver cells associated with cirrhosis. This report has not been well corraborated elsewhere and its signifidance here is difficult to evaluate.

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SUMMARY

The value of determining the etiology of "Familial Cirrhosis of the Liver" lies in the fact that, once suspected, prophylactic therapy might be given with an eye toward avoiding its occurrence in another child. If the condition were found to be transmitted hereditarily the problem would then have to be handled something like, for example, hemophilia. In this condition the parents should be informed of the situation. The Possibilities of their having an affected or non-affected child should be discussed, and consideration should be given to their not having more children.

The question of heredity is suggested by the familial occurrence. However, there have been only 2 instances in which a history of any cirrhosis has been elicited in members of a family outside of siblings. This finding is also to be noted in Wilson's disease where the condition is not generally reported in relatives outside of siblings. Bramwell's thought that this might be a "forme fruste" of Wilson's disease could only be borne out by the finding of suggestive brain pathology at autopsy in a case of familial cirrhosis. The problem then would become one of determining the cause of Wilson's disease.

Certainly, however, the likelihood of some inherited tendency, primarily of the order of a Mendelian characteristic, must be seriously considered. It is unlikely that it is of the form of the gross congenital structural abnormality where seldom are two members of the same generation affected. The question of incompatible parental genetic types goes beyond the scope of this paper. Liver biopsy, single or serial, in asymptomatic members of the affected generation (e. g., C. T., the third case presented here) might be of great value.

Infection, whether it is the initiating factor, the precipitating factor, or a secondary occurrence, is apparently almost omnipresent in each case of this condition. The time of appearance of fever usually is noticed within a few months of the terminal episode. This time interval is probably not long enough for the development of the full-blown cirrhosis that is commonly found at autopsy. It should b e remembered in addition that portal cirrhosis does not arise from a single insult to the liver substance but from repeated destruction of the liver parenchyma. (If the hepatic lobular reticulum is affected, however, the resulting fibrosis appears to be much more marked

(15).) This mediates against any short-lasting acute infection. Probably the only type of infection which would allow the asymptomatic course which is so commonly seen up to the time of the short terminal episode is a very low grade type. It might be expected that this would show some definite signs before that.

The close relationship of the ages at which the siblings die, even though they may die years apart should be considered. This fact would be against the likelihood of there being an especially virulent organism being transmitted among siblings. This would tend to make one consider something which might be ritual in the affected family such as some food allowed the children at a certain stage in their life and which is probably repetitive (conforming to the requirement of repeated destruction of hepatic tissue for the development of cirrhosis). The only thing which has been mentioned along this line is the report which suggested the toxic effect of galactose. This might well be an example of just the type of injury involved.

In most of the cases reviewed the diet has not been reported to be so markedly deficient as to suggest this as the etiology of the majority of cases.

Among all the likelihoods considered, the

most plausible seems that of an inherited Mendelian characteristic which appears to be recessive. Along this line, question of incompatible parental genetic types remains unanswered. This inherited characteristic probably potentiates the action of some factor, probably a common substance which is toxic to the compromised liver. In most cases the infection commonly found is probably secondary to the lowered resistende of the patient.

During the brief reign of chemotherapeutic agents and antibiotics little has been written on this condition. This era eventually may contribute much to the knowledge of the subject.

I wish to express my gratitude to Dr. Frank Tanner of Lincoln General Hospital, Lincoln, Nebraska for his aid in procuring the case histories presented.

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CONCLUSION

1. Three cases of portal cirrhosis of the liver in siblings of ages 10, 8, and 10, respectively, are reported.
2. The pathology of portal cirrhosis is presented.
3. The history of knowledge of Familial Cirrhosis of the Liver is presented and the general course of the disease is discussed.
4. A review of the literature concerning the possible etiology of the condition is presented and these possibilities are discussed.

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