Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

CHOLANGIOLITIC CIRRHOSIS

Volume XVII | Friday, November 16, 1945 | Number 6

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

Volume XVII | Friday, November 16, 1945 | Number 6

INDEX

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William A. O'Brien, M.D.

I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
Nov. 17 - Nov. 23, 1945
Medical Visitors Welcome

No. 90

Saturday, Nov. 17

9:00 - 9:50 Pediatrics Grand Rounds; I. McQuarrie and Staff; W-205 U. H.

9:15 - 10:20 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515 U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221 U. H.

11:30 - 12:20 Anatomy Seminar: Origin of the Contralateral Connections of the Lemniscus with the Globus Pallidus; A. T. Rasmussen; I.A. 226.

Sunday, Nov. 18

11:00 - 1:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Monday, Nov. 19

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

12:15 - 1:15 Pediatrics Seminar; Irvine McQuarrie and Staff; 6th Floor Eustis.

12:30 - 1:20 Pathology Seminar; Demonstrations of Biopsies from the Liver in Hepatic Diseases; Robert Hebbel; 104 I. A.

12:30 - 1:20 Physiology Seminar; Reciprocal Innervation and Co-Contraction in Cortically Controlled Movements; J. F. Bosma; 214 M. H.

4:00 - School of Public Health Seminar; Some New Materials and Processes Causing Occupational Hazards; L. W. Foker; Students' Health Service, 6th Floor.

Tuesday, Nov. 20

9:00 - 9:50 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 104 I. A.

3:15 - 4:15 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U.H.

4:00 - 4:50 Surgical-Physiology Conference; Therapeutic Splenectomy; Drs. Merendino and Watson; Eustis Amphitheater.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgen Diagnosis Conference; Solveig M. Bergh, T. B. Merner.

Wednesday, Nov. 21

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515 U. H.

9:00 - 10:30 Pediatrics Staff Rounds; W-205 U. H.

9:00 - 10:50 Neuropsychiatry Seminar; J. C. McKinley and Staff; Station 60 Lounge, U. H.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Possible Bronchogenic Carcinoma; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Physiology Chemistry Journal Club; Staff; 116 M. H.

4:30 - 5:20 Neurophysiology Seminar; Postural Reflexes; Herbert S. Wells, Sibyl Beckett; 113 MeS.

Thursday, Nov. 22 -- Thanksgiving.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater.

12:30 - 1:20 Physiological Chemistry; Biochemistry of Nucleic Acid; Cyrus P. Barnum; 116 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

4:30 - Bacteriology Seminar; 214 M. H.

5:00 - 5:50 Roentgenology Seminar; M-515 U. H.

Friday, Nov. 23

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 12:20 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department; U. H.

11:50 - 1:15 University of Minnesota Hospitals General Staff Meeting; Endogenous Encephalitis (Uremia, Porphyria, Eclampsia, Burns); A. B. Baker, David Daly; New Powell Hall Addition Amphitheater.

1:00 - 2:20 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-206, U. H.

1:30 - 2:20 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff; Todd Amphitheater, U. H.

There will be a meeting of the Minnesota Pathological Society Tuesday, November 20, 1945, 8:00 P.M. in the Med. Sci. Amphitheater.

II. CHOLANGIOLITIC CIRRHOSIS

C. J. Watson
F. W. Hoffbauer
R. B. Howard

The problem of relationship of hepatitis to cirrhosis of the liver is an exceedingly important one, especially in view of the marked increase in incidence of hepatitis during the war, as discussed at the outset. The majority of investigators favor the view that some cases of hepatitis become chronic in nature and develop diffuse cirrhosis.[1,2,3,4,5,6,7] This is not to be confused with the so-called toxic or postnecrotic cirrhosis, or healed acute yellow atrophy[8,9], the occurrence of which has been generally accepted as a sequel of a very severe hepatitis, a relationship especially well documented by Bergstrand.[10] Some pathologists,[11] while accepting the latter type, are not convinced that any relationship exists between epidemic or sporadic hepatitis or so-called catarrhal jaundice on the one hand, and diffuse cirrhosis of the liver on the other. Nevertheless, evidence has been accumulating for a number of years which strongly supports such a relationship. Jones and Minot[6], in a thorough study of catarrhal jaundice reported in 1923, refer to the development of cirrhosis after several months of jaundice. In speaking of this transition Jones and Minot expressed the following belief: "Serious complications outside of the biliary tract appear to be rare. The term 'complication' has been used in the above discussion in reference to certain untoward occurrences observed in the course of apparently typical cases of infectious jaundice. The advisability of such a term may be questioned by some who may believe that the original diagnosis is at fault. We believe, however, that the above cases warrant the use of the term 'complication'. The first two cases with the infectious cirrhosis occurred in the same family within a week of each other and ran an identical course. The last two cases developed in the midst of well-recognized epidemics, and at the start differed in no way from other cases observed in these epidemics. The final outcome alone differed from the results seen in the other epidemic cases. The serious results reported occurred, we believe, in well authenticated cases of infectious jaundice, were not coincidental, and were probably complications of the original infection."

As Eppinger[1] points out the usual case of acute hepatitis recovers completely within a few weeks but there are cases in which the jaundice does not disappear, and in which after 6 months or a year the clinical picture is that of "biliary" cirrhosis, i.e., jaundice, enlarged firm liver, spleen commonly palpable and firm, ascites usually absent. Eppinger would reserve the designation biliary cirrhosis for those cases in which so-called "catarrhal" jaundice persists and gradually exhibits more and more of the features of cirrhosis. From a clinical standpoint this form of cirrhosis is most compatible with that originally described by Hanot[12]. According to Karsner[9] Hanot's cirrhosis is probably comprised by the conditions described by Lichtman[2], Klemperer[13] and Rössle[14], under the following designations, and, according to Karsner, the following histologic differences:

Lichtman:	Non-obstructive cholangitic biliary cirrhosis	(Evidence of (cholangitis (and fibro-
Klemperer:	Chronic intrahepatic obliterating cholangitis	(sis in portal spaces.
Rössle:	Cholangiolitic or cholangiotoxic cirrhosis	Intralobular fibrosis and cellular infiltration

Karsner[9] mentions an example of the latter variety which he studied. This was in a male 32, a periodic alcoholic who had had repeated attacks of what appeared to be acute hepatitis over the course of 10 years. There was jaundice, enlargement of the spleen and liver but no ascites, in other words a clinical picture corresponding with Hanot's cirrhosis. At autopsy the liver weighed 4100 gms. and exhibited "cholangiolitic biliary" cirrhosis. If one can judge from the microphotographs in Karsner's

paper, this was not a fatty cirrhosis. It may be noted again, with respect to the question of repeated attacks of hepatitis, that these are well known and that one attack does not necessarily confer immunity. The question is whether in such instances one is dealing with a continuous chronic disease having latent periods and exacerbations, or whether a new infection has occurred. Both, of course, might be of importance.

The following three cases have afforded an opportunity to study the clinical course of the disease and to secure material for histological study. Observations on two of the cases were made by other physicians who have kindly made their records available. Our appreciation for this courtesy is acknowledged.

Case 1.

, female, age 48, This patient was first studied on the Medical Service of the University of Minnesota Hospitals between the 9th of April, 1943 and the 1st of June, 1943. In Sept. 1944 she was readmitted for a period of one week of observation. Her third admission began the 16th of April, 1945; she was discharged on June 2, 1945. At the time of the first admission the patient complained of weakness, epigastric discomfort, and occasional bouts of diarrhea. Review of her history disclosed that she had had jaundice more or less continuously since the age of 15. This was characterized by recurrent episodes of deeper jaundice with dull aching right upper quadrant pain. The patient did not use alcohol in any form; her dietary intake was normal.

In 1912 this patient, then 15 years of age, was severely jaundiced during an illness which was characterized by high fever and a prolonged period of disability. Her sister also had jaundice at that time although her symptoms were milder in nature. As nearly as can be ascertained this illness was a severe form of infectious hepatitis (acute catarrhal jaundice). In 1932 during her fourth and last pregnancy the patient was more markedly jaundiced during the last 7 months; anorexia and nausea were prominent. In 1936 she consulted Dr. M. O. Oppegard of Crookston, Minn., who has kindly made available his observations and surgical findings. Examination at this time revealed that the liver was much enlarged and firm; splenomegaly was noted but there was no evidence of ascites. X-ray studies revealed a nonfunctioning gall bladder. After a period of observation cholecystectomy was decided upon, as offering the patient some hope of relief of the recurrent discomfort. At operation, Dr. Oppegard found an enlarged liver exhibiting a definite hobnailed surface. The spleen was enlarged to about three times its normal size. The gall bladder was found to be thick walled and firmly adherent to the fossa; it contained no stones. A biopsy of the liver was made and a cholecystectomy was performed. The patient made an uneventful recovery and appeared for a time to be relieved of some of her distress. The liver biopsy section was made available to us through the courtesy of Dr. Kano Ikeda, pathologist at the Miller Hospital, St. Paul, Minn. A photomicrograph is to be shown as a lantern slide; the pathologist's description appears later in the text.

One year later, in 1937, the patient was subjected to a second operation at which a Talma-Morrison omentopexy was performed by Dr. J. F. Malloy at Thief River Falls, Minn. The report of this operation was made available to us by Dr. Edward Bratrud of Thief River Falls. It was found that the liver was enlarged, the right lobe extending to the iliac crest; the spleen was enlarged to one and one-half times the normal size. The patient's recovery was uneventful after this operation. She continued, however, to have varying degrees of jaundice. The patient was able to perform most of her household duties being incapacitated only during periods of more marked jaundice and distress.

In 1943, during the first period of study by us, the outstanding features on physical examination were the massively enlarged liver and the presence of minimal icterus. Ascites was not demonstrable, nor were any spider nevi observed. A faint but definite factor hepaticus was repeatedly discernable; this was confirmed by several observers. A clinical diagnosis of Hanot's cirrho-

sis was made. Numerous liver function tests were carried out in serial fashion at this time. These revealed obvious evidence of hepatic functional impairment. During this first period of hospitalization, the patient received the "liver diet" and supplements of choline and cystine for a period of six weeks. Although subjective improvement occurrfd, no significant change in liver function was noted as measured by serial tests. She was allowed to return home on the same diet, but without the cholincystin. The diet was supplemented by yeast powder and vitamin B complex. This regime was followed for the ensuing year; frequont clinic visits permitted further clinical and laboratory observations.

In September, 1944, the patient experienced a severe attack of right upper quadrant pain associated with nausea and vomiting, chills and fever. The pain was sufficiently severe as to require morphine for relief. Jaundice increased at this time and for a short period, acholic stools were noted. The patient was readmitted to the hospital 10 days after this episode. The acute phase had subsided. This episode was entirely similar to what Naunyn and Umber[15] observed in certain cases of cirrhosis and designated as "cholangitis cirrhotica". The cause was assumed to be a secondary (hematogenous) infection of the intrahepatic bile ducts as a sequel to the biliary stasis produced by the fibrosis in the portal spaces. The possibility exists, however, that such episodes in some cases are simply exacerbations of the original hepatitis. The history in case 1 would lend support to such a theory, proof of which would have to depend upon demonstration of the presence of the virus. Physical examination disclosed a more marked degree of jaundice (total serum bilirubin of 4 mg. per cent) and a moderate degree of hepatic tenderness. Other findings, clinical and laboratory, were much the same as before. The blood cholesterol level was 440 mg. per 100 cc. Urobilinogen was constantly present in the urine in abnormal amount. Duodenal drainage failed to reveal any pus cells or crystals. A mild normocutic and normochromic anemia had developed since her previous admission. After a week in the hospital, the patient was allowed to return to her home.

In April, 1945, the patient again returned to the hospital for her third admission. At this time the jaundice was quite intense, and she complained bitterly of pruritus. Physical examination revealed marked jaundice. The nutrition was well maintained. Excoriations of the skin were prominent. Neither spider nevi nor palmar erythema were noted. A definite foetor hepaticus was again observed. The liver measurements were essentially as in 1943 (9 cm. in right midclavicular line, 15 cm. in the midline, and 8.5 cm. in left midclavicular line). The edge of the spleen was palpable 4 cm. below the left costal border. The patient was afrebrile; the leucocyte pattern was normal. The mild anemia (hemoglobin 10 grams) was still normocytic and normochronic in type. X-ray examinations again revealed the enlarged liver, but no calculi were seen. Esophageal varices were visualized at this time by the roentgenologist, although in 1943 careful study had failed to reveal them. The results of various laboratory studies during this last admission again revealed evidence of liver damage.

The patient was treated by means of bed rest; she received a diet containing carbohydrate 350 grams, protein 150 grams, and fat 88 grams. This is an increase of 38 grams, of fat per day over the previously mentioned liver diet and represented an increased allotment of butter and cream. Recent observations have convinced us that the increased palatability of such a diet more than outweighs any possible deleterious effect of the increased fat. In addition to vitamin supplements, both orally and parenterally, the patient received 5 grams of methionine in a liter of 10 per cent glucose as a daily intravenous infusion. No appreciable change in her condition was noted after two weeks. The pruritus was well controlled, however, with 1 mg. of a di-hydroergotamine preparation given by injection every third day. No untoward effects were noted in this or in other patients in whom this product has been used.

Since the remote possibility of a common duct calculus or an inflammatory

stricture could not be excluded surgical exploration was requested. On May 8, 1945, Dr. Richard Varco explored the biliary tract; the liver was definitely hobnailed and had the gross appearance of a cirrhosis. The common bile duct was not dilated, no stones were encountered and a probe was readily passed into the duodenum. External biliary drainage was established by means of a catheter inserted into the remaining stump of the cystic duct.

The patient experienced prompt relief of her pruritus. She was released from the hospital on June 1, 1945, to be followed in the outpatient clinic.

Dr. J. S. McCartney's reports of the histologic findings in the two liver biopsies from this case, are as follows:

1936 - "This piece of liver tissue shows portions of many lobules. There is a definite increase in connective tissue and new bile duct proliferation in the portal spaces, but no evidence of fatty metamorphosis is seen. The portal cellular in filtrate is largely composed of lymphocytes and plasma cells, the latter being especially prominent." Conclusion: Early cirrhosis of the liver.

1945 - "This piece of liver tissue shows portions of many lobules. The lobules vary greatly in size. No central veins are seen. The increase in the portal connective tissue is quite marked with only a minimal amount of new formation of bile ducts and a moderate degree of leucocyte infiltration. The increased portal tissues are quite vascular. In the liver lobules themselves there are fairly numerous bile thrombi which are in part centrally situated and in part at the periphery." Conclusion: Cirrhosis of the liver.

The patient got along well and was free of pruritus until 7-11-45, when following irrigation of the catheter, she developed chills and fever which persisted. On 7-15-45 she had 4 hematemeses and was brought to the University Hospitals. Examination at this time revealed a blood pressure of 88/56, pulse 100. Marked jaundice was present. The remainder of the examination was essentially as before except the spleen was larger than it had been previously. The stool was light colored at this time. The day following admission the patient became comatose and did not respond. Initially, she received 1500 cc. of whole blood and therafter received 400 cc. plasma, 1500 cc. of 10% dextrose I.V. and 1000 cc. of Dietene with 10 Gm. of methionine via nasal tube daily. She showed a rather remarkable response to this form of therapy and on 7-21-45 she responded to questions and felt quite well. However, 4 days later, esophageal bleeding again occurred. Esophageal tamponade was attempted and temporarily halted the bleeding. However, she again lapsed into coma, her blood pressure dropped despite administration of blood and she expired on 7-27-45.

Autopsy revealed moderate pulmonary edema; an enlarged liver, weighing 3050 grams, greenish in color and presenting a typical hobnailed surface; and pale granular kidneys. Esophageal varices were present, and there was blood in the stomach and intestines.

Case 2.

, housewife, age 51. The patient was admitted to the Medical Service of the University of Minnesota Hospitals on Sept. 15, 1944. Her illness commenced with nausea and vomiting about July 4, 1944. At this time she felt cold and thought she had some fever, but there were no definite chills. Within a few days she became jaundiced and noted that the urine was dark and the stools light in color. The jaundice deepened and was associated with itching from the outset. There was no pain at any time, nor any history suggestive of gall stones. With the onset of nausea and vomiting a marked anorexia developed, especially characterized by distaste for fatty foods. The patient suffered a weight loss of 20 pounds prior to admission to the hospital. She stated that the jaundice and itching had become somewhat less but that the vomiting persisted.

Examination revealed moderate jaundice with numerous excoriations of the skin. The liver edge was easily palpable 1-2 cm. below the right costal

margin. It was not tender. The spleen was not palpable. Examination of the blood revealed a hemoglobin of 9.45 gm. per cc., erythrocytes 4,090,000, leucocytes 5050 - 8350 with from 52 to 79 per cent neutrophiles, usually less than 60. The sedimentation velocity was 64 mm. in 60'. The results of the composite liver function study are shown in Table 1. This reveals distinct, although variable, evidence of functional derangement in the presence of regurgitation jaundice; (bilirubinuria and increased 1' serum bilirubin). It may be noted on the basis of the feces urobilinogen, that the element of obstruction or exclusion of bile from the intestine was relatively slight. The stools at this time, of course, were no longer acholic in appearance.

Liver biopsy was done on 10-3-44, at the time of peritoneoscopy, using a modified Silverman needle as described elsewhere[16]. The appearance of the surface of the liver was normal. The piece of liver obtained consisted of portions of 7 or 8 lobules. In the main the liver architecture was relatively normal. In one area, a small amount of periportal fibrosis and lymphocytic infiltration, was observed. Scattered bile thrombi, together with occasional atypical, multinucleated liver cells, were also seen. At this time the patient had been in bed and receiving the "liver diet" for 18 days. The serum bilirubin on 10-6-44, three days later, had decreased to: 1', 1.3 mg.; total, 2.5 mg. per 100 cc. It may be noted that a cholecystogram on 10-7-44 revealed a nonfunctioning gall bladder without evidence of calculi. The itching had disappeared and the patient felt considerably better. She was allowed to go home on 10-12-44 with instructions to continue rest, to adhere to the "liver diet" and to take vitamin B complex, two capsules 3 times daily. She returned on November 1 stating that she felt very well. The liver and spleen were not palpable. There was still slight icterus, however, and if anything, the serum bilirubin had risen slightly: 1', 1.2 mg.; total, 2.8 mg. per 100 cc. The patient was again seen on November 29 still feeling very well but slightly jaundiced. She was readmitted to the hospital February 6, 1945. At this time she still exhibited a mild jaundice. Pruritus had become severe and the patient's appetite was poor. Physical examination failed to reveal any appreciable change; the liver was not enlarged, the spleen was not palpable. Neither palmar erythema nor spider nevi were seen. X-ray examination of the esophagus failed to reveal any evidence of varices. A composite liver function study (Table 2) revealed little change from that of her previous admission. A moderate reduction of hippuric acid formation is noted, and the total cholesterol is seen to be increased over that of the previous admission. The patient was offered a high protein, high carbohydrate diet but ate very little. Ten grams of methionine in 1000 cc. of distilled water containing 10 per cent glucose was given intravenously daily, for 7 days, without noticeable benefit.

Despite the evidence favoring aparenchymal type of liver involvement, the possibility of a silent common duct stone could not be excluded with certainty. Therefore, on March 6, 1945, a laparotomy was performed; the gall bladder and bile ducts were found to be entirely normal. A cholangiogram was made and no obstruction in the extrahepatic biliary tract was discovered; the biliary tree in the liver was well demonstrated. Liver biopsy and cholecystostomy were performed. The latter procedure was done with the purpose of interupting the enterohepatic circulation of bile-salts in the hope of relieving the severe pruritus. As a matter of fact the patient did experience marked relief from the operation. In addition to relief from the pruritus the appetite improved and the patient gained weight. Subsequently, the tube which had been in the gall bladder, came out, and following this the patient's itching recurred.

The liver biopsy on March 6, 1945 revealed the following histological changes: "the capsule was not thickened; all of the portal spaces were enlarged but none had coalesced; there was a mild increase of the portal connective tissue and a marked increase in the number of the ducts with rather marked increase in the number of lymphocytes. The liver cell cords show no appreciable change;

no bile thrombi were seen." Dr. McCartney's conclusion was "mild cirrhosis".

Table 1.

Initial Liver Function Analysis - Case 2.

Serum Bilirubin	
1 minute value	- 2.4 mg. %
total value	- 4.2 mg. %
Serum Albumin	- 3.6 gm. %
Serum Globulin	- 3.1 gm. %
Blood cholesterol (total)	- 370 mg. %
Serum phosphatase	- 22 Bodansky units
Cephalin-chosterol flocculation (48 hrs.)	- 3+
Nippuric acid excretion (i.v. method)	- 0.6 gm.
Urine urobilinogen per 24 hours	- 6 mg.
Feces Ehrlich reaction (per 100 gm.)	- 210 Units.

- - -

Table 2

Second Liver Function Analysis Case 2

Serum Bilirubin 1 minute value	2.4 mg. %
Serum Bilirubin total	4.8 mg. %
Serum albumin	3.6 gm. %
Serum globulin	2.8 gm. %
Blood cholesterol (total)	460 mg. %
Serum phosphatase	7 Bodansky Units
Cephalin-cholesterol flocculation (48 hrs)	4+
Hippuric Acid excretion (i.v. method)	0.4 gm.
Urine urobilinogen per 24 hours	7 mg.
Feces urobilinogen per 24 hours	150 mg.

- - -

Case 3.

, male, age 65. St. Joseph Hospital. The data for this case was supplied by Dr. John Briggs of St. Paul, Minn. Dr. Steven Barron performed the autopsy examination and furnished the material for microscopic study.

This 65 year old male was first admitted to St. Joseph's Hospital, St. Paul, on Dec. 28, 1944. His chief complaints were jaundice and pruritus. The patient's illness began in Sept. 1944 when following an upper respiratory infection he developed extreme anorexia, weakness and vague abdominal distress, characterized by belching, distension and flatulence. In mid November he first noted that his urine was dark in color and that the stools were light. Early in December he began to complain of pruritus and several weeks later detectable jaundice appeared. Weight loss of an indefinite amount had occurred.

The patient's past history was noncontributory save that he had suffered from migraine headaches for many years. There was no history of alcoholism.

Examination of the patient revealed a well developed and fairly well nourished male of the stated age. The skin and sclera were deeply jaundiced and pruritus was evident. An indefinite mass was noted in the right upper quadrant of the abdomen. The remainder of the physical examination was reported as normal.

Laboratory studies at this time revealed a hemoglobin of 82%; the leucocyte count was 4500 and the differential pattern was normal. Urinalysis revealed a trace of albumin, a trace of urobilinogen, and a positive test for bile. The icteric index was initially reported as 26 units, it later rose to 72. Bromsulphthalein test revealed 25% retention of the dye. Hanger's flocculation test was 4+.

X-ray studies of the gastrointestinal tract showed no evidence of intrinsic pathology in the stomach, small or large bowel. A cholecystogram revealed a non-functioning gall bladder.

Because of the increasing jaundice and the persistent acholic stools, an extrahepatic form of biliary obstruction was suspected. On Jan. 19, 1945 surgical exploration of the biliary tract was performed. The liver was found to be mottled and greyish. No stones nor

masses were palpable in either the gall bladder, the bile ducts nor in the pancreas. A cholecystostomy and a choledochostomy were performed.

Following the operation there was an apparent clinical improvement manifested by an increased appetite. Bile drained freely from the tubes and the icteric index dropped to 32 units. The total serum proteins and the A/G ratio, measured postoperatively were normal. The patient was maintained on a diet of 350 grams of carbohydrate 150 grams of protein and 90 grams of fat. Supplemental vitamins were added and liver extract was given parenterally. The patient left the hospital in the middle of February and the dietary regime was continued at home.

One month after discharge the jaundice began to increase in severity. By April the icteric index was 93 units, and the stools were acholic. Repeated determinations for urobilinogen showed very low values in the feces. The liver was now enlarged and readily palpable. The patient complained of constant right upper quadrant pain of an aching character. His condition remained essentially the same throughout the summer of 1945.

On Aug. 25 he was readmitted to ths hospital shortly after he had suffered an attack of severe abdominal pain. This was followed shortly by weakness, pallor, and prostration. Examination revealed the abdomen to be distended; a mass was palpable in the right upper quadrant. Shortly after admission the patient became comatose. Later he had repeated episodes of hematemeses and melena. The coma deepened and the patient failed to respond to supportive measures. Death occurred on the third day of hospitalization, Aug. 28, 1945. The total duration of the illness was 11 months.

At autopsy a retroperitoneal hemorrhage extending around the right kidney was found. A loop of the jejunum was distended and hemorrhagic. Large venous clots were present in the mesentery of this loop. The liver weighed 2460 grams; the external surface was granular. The parenchyma was firm and cut with a gritty sound. The gall-bladder was attached to the surgical scar of the anterior abdominal wall. No stones were present in the gall-bladder or bile ducts. There was no stricture of the latter. The pancreas was normal.

Microscopic examination of the liver sections was reviewed by Dr. McCartney as follows:

Biopsy of liver: Jan. 1945. This section shows parts or all of about 15 lobules. A slight, but definite, increase of the portal tissues is present. The increase is chiefly of the connective tissue. There is only a slight degree of leucocytic, mainly lymphocytic, infiltration. The bile duct increase is only minimal. The central veins are in their normal positions. Numerous bile thrombi are scattered through the lobules and tend to be mostly at the centers of the lobules. Bile is present in some of the liver and endothelial cells. Part of the liver cells are finely granular and part have a solid eosin staining cytoplasm. Scattered liver cells are necrotic. No fatty metamorphosis is noted. Some small foci of polymorphonuclear leucocytes are found. Conclusion: Epidemic hepatitis.

Section of liver from postmortem Aug.-1945. This section shows marked distortion of the architecture. The portal spaces are enlarged and partially coalescent. The enlargement of these spaces is about equally divided between connective tissue and bile ducts. Only a slight degree of leucocytic infiltration is found in the portal tissues. Only very few central veins are identified in their normal positions. In or near a number of portal spaces are foci of clear or pale liver cells with large central bile stained masses. Numerous large bile thrombi are scattered thru the liver cords. Bile staining of liver and endothelial cells is prominent. Neither necrosis nor fatty metamorphosis of liver cells is found. Conclusion: Cirrhosis of the liver.

In case 1 of this series, certainly the most remarkable insofar as the question of transition of infectious hepatitis to cirrhosis is concerned, the history indicated a continuous chronic

disease of 34 years duration following the initial acute episode. As a striking instance of individual variation it may be noted again that the sister, who had also suffered from infectious jaundice 34 years previously, recovered completely and has had no further jaundice nor manifestations of liver disease. Bloomfield[7] was particularly impressed with the concept of a latent chronic form of hepatitis gradually progressing to a clinically manifest cirrhosis of the liver, and cited numerous cases apparently exhibiting such transitions. Steigmann and Popper[17] likewise regard chronic hepatitis and cirrhosis as identical and describe two cases of unusually prolonged acute hepatitis in which laparotomy with biopsy revealed clear cut evidence of developing cirrhosis. The histologic changes described agree well with the concept of a cholangiolitic cirrhosis which is perhaps the best term to designate briefly the type of cirrhosis developing after hepatitis. Axenfeld and Brass, in an extensive study of epidemic and sporadic hepatitis carried out with the aid of liver biopsy and reported in 1942[5], conclude that cholangiolitic hepatitis represents a subacute or subchronic stage of the disease, and that in some instances definite transition to cirrhosis of the liver is observed.

Bloomfield's cases, in the main, were instances of ordinary portal cirrhosis and the majority were in alcoholics, only 10 per cent giving a history of previous episode of jaundice. Of the 386 cases of cirrhosis reported by Ratnoff and Patek[18], 25, or 6.5%, had had previous episodes of jaundice, and no attempt was made to determine the type of jaundice experienced. Two hundred and seven or 54% of these cases were chronic alcoholics, and it may be assumed that a fatty liver and hence an intermediate fatty cirrhosis was the usual sequence of events in the development of the portal or atrophic cirrhosis which was observed. Eppinger[19] stated that 14% of 269 males and 12% of 107 females with cirrhosis had a previous history of "catarrhal jaundice".

In an attempt to pursue further the relationship between infectious hepatitis and cirrhosis of the liver, the case records of all patients with cirrhosis admitted to the In-patient Services of the University of Minnesota Hospitals in the past 10 years were analyzed with special regard to previous episodes of jaundice. In the period 1935-1944, 100 patients were admitted to this Hospital with a diagnosis of cirrhosis of the liver. Thirty of these cases were proved by liver biopsy or at autopsy. Fifty-two of the remainder were clear-cut cases of cirrhosis clinically and on the basis of laboratory studies. The remaining 18 patients were somewhat doubtful cases of cirrhosis for the following reasons: (1) In 5 cases obstructive biliary cirrhosis on the basis of a "silent" calculous obstruction was not definitely ruled out; (2) In 5 cases, laboratory tests were not absolutely typical; (3) In 3 cases the blood serological tests for syphilis were positive giving rise to the possibility of luetic liver damage; and (4) In 5 cases the diagnosis of cirrhosis was in doubt because of miscellaneous reasons. It was the impression of the author that at least 10 of these cases did in fact represent cases of cirrhosis.

The control series consisted of 100 cases of miscellaneous disorders excluding liver disease of all types. This group corresponded to the cirrhosis group as far as sex distribution, age (in the same decade of life), and year of last admission to the hospital were concerned.

The criteria for the diagnosis of cirrhosis of the liver have already been discussed briefly. In 30 cases the diagnosis was established at autopsy or by liver biopsy. In 52 of the remainder a characteristic clinical picture combined with laboratory data indicative of damage to the hepatic parenchyma made the diagnosis quite certain Numerous tests of liver function, some of them no longer used, have been in use in the University Hospitals in this 10-year period. It is beyond the scope of this paper to discuss the validity of the various tests. Suffice it to say that since 1940, at least, the bromsulphalein retention test and the Takata-Ara or, more recently, the cephalin-cholesterol test have been carried out in almost all of the cases of cirrhosis. In all of the cases where these tests were carried out, one or both showed an

abnormal result. As stated previously 18 of the cases were in some doubt as to the diagnosis of cirrhosis for various reasons.

The establishing of a previous episode of jaundice as definitely representing a case of infectious hepatitis was in many cases difficult. It was felt that if an attack of jaundice occurring several years before the patient's presenting illness simultaneously involved other members of the patient's family or other persons in the neighborhood, it almost certainly represented infectious hepatitis.

In addition when a previous attack of jaundice had the following characteristics, the history was considered to be highly suggestive of infectious hepatitis: (1) Jaundice preceded or accompanied by anorexia, nausea, and usually vomiting; (2) Lack of pain or at most a vague right upper quadrant or epigastric distress; (3) Fever of varying degree, usually low grade; and (4) Spontaneous clearing. Further, if an episode of jaundice occurred in the patient's youth, i.e., before the age of 20, it was considered to be suggestive of infectious hepatitis even if no further details were given.

The criteria for alcoholism are admittedly inexact. Very few case records mentioned specific amounts of alcohol ingested; therefore, statements to the effect that a patient was a severe or moderately severe alcoholic were taken at their face value. Possibly a few cases of alcoholism were missed, but it is our experience that a history of alcoholism, if present, can usually be obtained from relatives or friends if not from the patient.

Of the 100 cases of cirrhosis, 67 (67%) occurred in men and 33 (33%) in women. Twenty-three of the men and 2 of the women, a total of 25 (25%), were classified as severe alcoholics.

Of the 100 cases 33 (33%) had been jaundiced at some time previously (see Table 3). Of these 17 (17% of the total) had histories strongly suggesting an episode of infectious hepatitis in the past. Two of these patients were also severe alcoholics. Three patients in addition

Table 3

Antecedent Jaundice in Cirrhosis of the Liver

A. Of 100 cases of cirrhosis of liver:
   1. 33 (33%) had history of previous jaundice.
      (a) 17 (17%) had had clear-cut infectious hepatitis.
   2. 36 (36%) had definitely had no jaundice in the past.
   3. 31 (31%) jaundice not mentioned in history.

B. Of 100 cases of miscellaneous disorders:
   1. 7 (7%) had a history of previous jaundice.
      (a) 3 (3%) had had possible attacks of infectious hepatitis.
   2. 43 (43%) had definitely had no jaundice in the past.
   3. 50 (50%) jaundice not mentioned in history.

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may have had infectious hepatitis in the past. One of these had had jaundice 30 years previously with no further details given. In this case the diagnosis of cirrhosis was not definite, the main problem being an anemia which did not respond to any form of therapy and the patient was considered to represent a case of latent cirrhosis. The second was a 3 year old male who had been jaundiced from age 6 weeks to 5 months, then symptom-free to the age of $2\frac{1}{2}$ years when he developed typical symptoms of cirrhosis. Biopsy showed a typical cirrhosis. The third case had had a 10 day bout of jaundice 10 years previously coincident with the use of iodine therapy for hyperthyroidism. There remain 13 patients who had had a previous jaundice which probably was not infectious hepatitis. Seven of these, including three alcoholics, had had intermittent jaundice for 1 to 9 years previous

to hospital admission, most probably accounted for by the onset of cirrhosis at that time. Three others were patients with ulcerative colitis which most probably accounted for the development of cirrhosis. Of the 3 other cases with a previous jaundice, one was a question of hemolytic anemia, one had had gall stones, and in the 3rd primary carcinoma of the liver with scarring of the remainder of the liver was found at autopsy.

Thirty-six (36%) of the whole group had definitely had no jaundice previous to the onset of the presenting complaint. Ten of these were severe alcoholics. In the remaining 31 cases (31%) the records failed to indicate whether jaundice had or had not been present at any time in the past. Nine of these patients were severe alcoholics.

In the control series of 100 patients with miscellaneous disorders, 7 (7%) had had jaundice at some time previous to hospital admission, 43 (43%) had definitely had no jaundice at any time, while the records of the remaining 50 (50%) failed to indicate whether jaundice had or had not ever been present. Of the 7 cases who had had jaundice previously, 3 (3% of the total) had histories suggesting episodes of infectious hepatitis.

It was felt that for statistical analysis, the cases in which previous jaundice was not mentioned should be eliminated from both series. Accordingly, it will be noted that 33 (48%) of 69 cases in the cirrhosis group, and 7 (14%) of 50 cases in the control group had had jaundice previously. The probability that such a difference would arise through chance alone is less than one in 10,000. In terms of histories of probable hepatitis the figures are: 17 (23%) of 69 cases in the cirrhosis group compared with 3 (6%) of the control series of 50 cases. The statistical probability is similarly less than 1 in 10,000 that chance alone accounts for the difference.

Of 75 cases where there was no history of alcoholism, 27 (36%) had had jaundice previous to the onset of the presenting complaint. Fifteen (20%) had histories strongly suggesting hepatitis previously, while an additional 3 (4%) had had a possible hepatitis in the past.

Of the 30 autopsy - or biopsy - proved cases of cirrhosis (Table 4), 14 (46%) had been jaundiced previously and 7 (23%) of these had histories highly suggestive of infectious hepatitis. Seven (23%) definitely had had no jaundice in the past, while no definite statement was made in the records of the remaining 9 (31%). The correspondence between these figures and those for the group as a whole, it will be seen, is quite close, especially when the comparatively small size of the former group is considered.

Eighteen cases were mentioned previously in which, for various reasons, the diagnosis of cirrhosis of the liver was in some doubt. Two of these were

Table 4

Antecedent Jaundice in Cirrhosis of the Liver

Of 30 autopsy or biopsy proved cases of cirrhosis:

14 (47%) had a history of previous jaundice
7 (23%) had had clear-cut infectious hepatitis.
7 (23%) had definitely had no jaundice.
9 (30%) jaundice not mentioned in history.

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patients in whom a previous episode of hepatitis seemed likely. Of the 82 patients, then, in whom the diagnosis of cirrhosis was beyond reasonable doubt, 15, or 18%, had a history of probable hepatitis in the past. When the doubtful cases are excluded, the percentage of cases with a history of probable hepatitis is seen to be slightly higher than in the entire group.

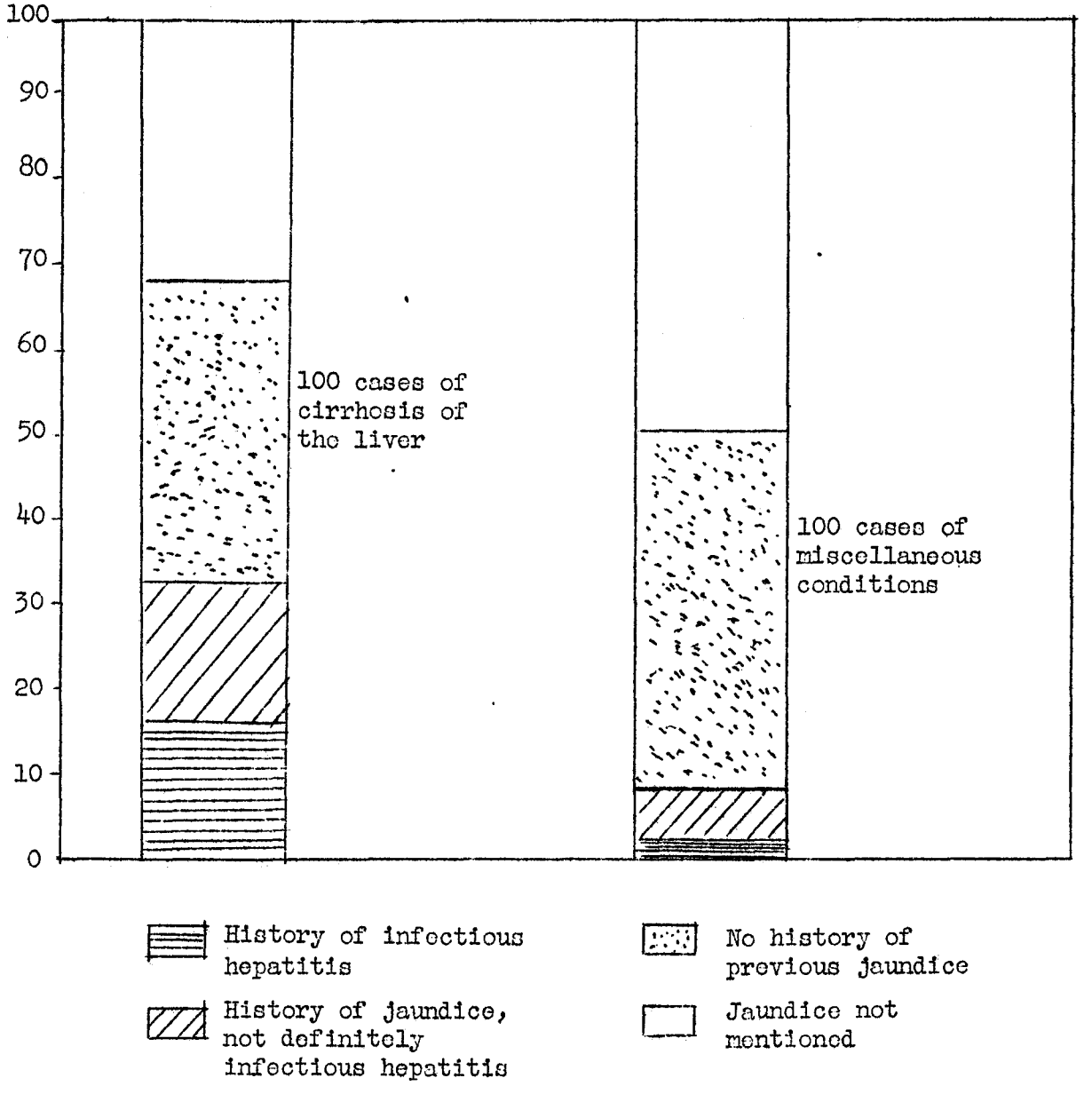
The data presented are briefly summed up in Chart 1. It is felt that these data show conclusively that a history of previous jaundice is present in a significantly greater proportion of cases of cirrhosis than in a similar

group of patients without liver disease. Likewise, a history of infectious hepatitis is more frequent among cirrhotics than non-cirrhotics, lending support to the concept that certain cases of infectious hepatitis run a chronic and/or recurrent course ultimately leading to the clinical and pathological picture of cirrhosis of the liver.

It must be emphasized that there are probably at least two mechanisms by which a so-called hypertrophic cirrhosis may gradually become atrophic: (1) The large fatty cirrhosis which loses fat and gains scar tissue, with concomitant shrinking; (2) The large relatively non-fatty cholangiolitic cirrhosis in which, initially, there are periportal lymphocytic foci, bile thrombi, bile

Chart 1

Antecedent Jaundice in Cirrhosis of the Liver



duct proliferation, hyperplasia of reticular cells, and beginning fibrosis; later extensive fibrosis with resultant hardening and shrinking. Lichtman[2] records an excellent example of the latter type. Fatty cirrhosis is regarded as probably not related to hepatitis, but rather to chronic dietary deficiency often on the basis of alcoholism; the non-fatty, cholangiolitic cirrhosis is believed, at least in many instances, to be the sequel to infectious hepatitis. It is regarded as very doubtful that the end stages of the two diseases can always be distinguished with certainty on anatomic or histologic grounds. This is intended to imply, simply, that what may first present an "hypertrophic" biliary, or Hanot type of cirrhosis, may eventuate in an ordinary portal or atrophic cirrhosis. It is believed that the distinction of fatty or dietary cirrhosis from the non-fatty or cholangiolitic type may well have therapeutic implications at least in the earlier stages since there is every reason to believe that cholin-cystin or methionine would be more effective in the former than in the latter type. In the foregoing we have emphasized the question of relationship between hepatitis and "biliary" cirrhosis because our own material lends support to such a concept. Cases 1, 2, and 3 have been selected as especially illustrative. In case 2 the manner of onset of the disease was indistinguishable from that of ordinary sporadic or epidemic hepatitis, although a history of definite contact was not established. The improvement during the first hospital admission, with subsequent relapse, when correlated with the progression from hepatitis without cirrhosis to hepatitis with cirrhosis, form a rather convincing picture of the development of cirrhosis in a case of prolonged hepatitis. We believe that case 3 likewise exemplifies this transition. Whether the initial hepatitis in either instance was identical with epidemic hepatitis is not known. The fully developed clinical picture in both of these cases was characterized by pruritis, regurgitation jaundice without ascites, and enlarged liver.

Summary

The problem of the relation of prolonged or cholangiolitic hepatitis to the development of cirrhosis is considered; examples representing transition from hepatitis to cirrhosis are discussed and the term cholangiolitic cirrhosis is suggested as being more appropriate and distinctive than "hypertrophic biliary cirrhosis". The prominence of regurgitation jaundice without ascites, but with pruritus, hypercholesterolemia and hyperphosphatasemia, in this group of cases, is emphasized. The end stages of the cholangiolitic cirrhosis following prolonged hepatitis may be indistinguishable, anatomically, from ordinary atrophic or portal cirrhosis. The cholangiolitic type of hypertrophic cirrhosis is believed, however, to be distinct from the "hypertrophic" fatty cirrhosis which represents an intermediate stage between the fatty liver and the atrophic cirrhosis of chronic alcoholics or other conditions in which dietary deficiency is probably the most important etiologic factor.

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III. GOSSIP

At the North Central Medical Conference held in Hotel St. Paul, Nov. 11, 1945, representatives from Iowa, the Dakotas, Nebraska, Montana, Wisconsin, and Minnesota met for the fourth consecutive year to discuss problems facing medicine in this area. Victor Johnson, M.D., Secretary, Council on Medical Education and Hospitals of the American Medical Association and John C. Parsons, M.D., Des Moines, Iowa, Secretary, Iowa State Medical Society told of plans for the returning medical officers. Dr. Johnson remained over to pay his first visit to the medical school of the University of Minnesota and to meet the administrative committee on Nov. 12. Apparently we at Minnesota see eye to eye with the American Medical Association on the needs of the returning medical officers. The majority seeking further training had their training interrupted by the war and now wish to complete it; a small minority are physicians with established practices who are returning for short brush-up courses before going back to their regular location. One midwestern university offering a so-called refresher course is reported to have had only 4 registrations. Refresher course programs often flit from subject to subject without any intent to develop any one theme, apparently because general practitioners move from one subject to another in the care of their patients. At best this is not an effective means of developing medical knowledge. Dr. Parsons told of efforts by his office to locate practitioners; in our state R. R. Rosell, Executive Secretary of the Minnesota State Medical Association, 493 Lowry Medical Arts Building, St. Paul 2, Minn. has also established a similar service. Official announcement has been received of the move to call to service all interns, assistant residents, and residents, in all the hospitals in this country. The trek will start April 1, 1946 for senior residents and will be completed by July 1, 1946 for all interns and junior residents. Their places will be filled by returning veterans and those not eligible to serve in a military capacity. This will free a large number of places for training. The length of military service for those entering at this time has not been acnounced.....In a panel discussion on rural health Mr. J. S. Jones, St. Paul, Minnesota National Committee on Rural Medical Service, American Farm Bureau Federation, L. W. Larson, M.D., Bismarck, North Dakota, Committee on Rural Medical Service American Medical Association; W. A. O'Brien, M.D., St. Paul, Minnesota, Director of Postgraduate Medical Education, University of Minnesota, appeared. Mr. Jones stated the case of the farmer most effectively. Farmers want better medical and hospital service and public health. They belong to Blue Cross and are back of the movement to build rural hospitals. They want more public health nursing and they want pre-payment plans for medical service as soon as they can be worked out. They are against the federal program to provide such service. They remember too well the inconvenience of the ration boards, and wonder what kind of tickets the government would issue to get medical service. Dr. Larson stated the case for well-organized medical and hospital service in larger places. He felt the difficulties in obtaining good medical service in the smaller places was caused by lack of opportunity to do good work. Yours truly told the story of proposed hospital development in this state. Medical Profession is in a good position to guide this program and prevent small communities from building unsuitable hospitals. Hospital and medical service are so intimately linked that future development in one field directly affects the other. Private hospitals must assume their obligations as teaching institutions.....Following a general discussion of these themes, Joseph S. Lawrence, M.D., Washington, D. C., Director, Washington Office Council on medical service and Public Relations of the American Medical Association reported on his activities. This is the national office which watches impending legislation and supplies information to interested law makers. Dr. Lawrence, who has been successful in this field elsewhere, urged physicians to let their representatives in Congress know how they felt about things as many senators and congressmen devote the major portion of their time to domestic issues. Do not complain if your voice is not heard in medical affairs which affect national interest but get in touch with Joseph F. Lawrence,

M.D., instead....Recent developments in the veterans administration are of great interest to us. The government has just announced its policy of locating new construction at medical centers where schools are located. Major General Paul R. Hawley is apparently going through with the proposal to include graduate training of medical officers serving in the veteran's administration hospitals with the above development....Mr. Jay C. Ketchum, Executive Vice President and Director, Michigan Medical Service and A. W. Adson, M.D., Rochester, Minn., Council on Medical Service and Public Relations, American Medical Association, discussed pre-paid Medical Service - A National Program.....The Michigan State Medical Association's prepayment service for surgical and obstetric conditions is a success. In the first two years, the average family uses the plan excessively for babies, mama's varicose veins, father's hernia, and the children's tonsils. Apparent success of the plan is the guarantee for payment for services rather than for total health protection, but as actuarial experience accumulates other conditions may be added. Many states have similar programs. The plan in Minnesota will soon be announced. Dr. Adson made a plea for unification of these projects into a national program. The conference is the North Central's answer to the question, "Why doesn't somebody do something?"....One of our most successful courses was held at the Center for Continuation Study. The pediatricians, in their first graduate course, scored a hit. Irvine McQuarrie and his group, with Dr. Haddow M. Keith of the Mayo Foundation made an outstanding contribution to the subject of convulsive disorders. Drs. Lippmann, Hanson, Bryngelson, and Hathaway contributed to the session on correlation of psychology and psychiatry in childhood. Milton J. E. Senn and Alan Challman gave two of the finest addresses on child psychiatry that we have heard. The round tables on psychosomatic pediatrics and the supervision of the development of the child in the first two years by Senn,Jensen, Kramer, Parkin, and Aldrich, and Roberts, was outstanding. Helen B. Taussig of Johns Hopkins brought us the story of the congenital heart, and Hugh McCulloch of Washington University, the story of infectious heart disease in childhood. These are rapidly developing fields and our clinic is right in step with the others. The discussions of Harold O. Petersen, Paul F. Dwan, M. J. Shapiro, O. H. Wangensteen, B. J. Clawson, W. W. Spink, John M. Adams, E. S. Platou, E. T. Bell, and Irvine McQuarrie rounded out a perfect two day presentation of these heart subjects. One of the most interesting reports was by Dr. Taussig on the surgical treatment of the Tetralogy of Fallot in which a branch from the aorta is anastomosed to the pulmonary artery to permit more blood to be aerated in the lungs....Next specialty course at the Center for Continuation Study will be December 3-7, in Anesthesiology. Lectures, demonstrations, and discussions, will be for physicians who practice anesthesiology, either part or full time; also for surgeons and internists. The faculty will be Joe W. Baird, Frank Cole, Duluth; Stuart C. Cullen, Iowa City; A. William Friend; Ralph T. Knight; T. Harry Seldon, Rochester; Ralph M. Tovell, West Hartford; Rolland J. Whitacre, East Cleveland; and others. Anesthesia as a specialty is well-developed in Iowa and Indiana. Minnesota lags except in the Twin Cities and Rochester. Frank Cole has just made the break in the state by going to St. Mary's Hospital in Duluth. Graduate students are urged to attend these sessions. Medical officers on duty and on terminal leave may attend without payment of the tuition or registration fee. Sessions start each day at 9 and 2. We are indeed fortunate to secure the teaching services of Drs. Cullen, Seldon, Tovell, and Whitacre. No other courses are planned until the first of the year, when the quarterly courses in basic medicine and basic sciences will start. Duckett T. Jones of Boston will be one of the first guest teachers.....