JAUNDICE, HYPERLIPEMIA AND HEMOLYTIC ANEMIA: A HERETOFORE UNRECOGNIZED SYNDROME ASSOCIATED WITH ALCOHOLIC FATTY LIVER AND CIRRHOSIS*

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THE data to be presented were derived from 20 patients seen at the Minneapolis Veterans Hospital over the last eight years. The symptom complex, findings and predictable course were so strikingly similar one could not escape the conclusion that they comprised a definite syndrome. However, the data were assembled largely retrospectively from records made by physicians unaware of the correlated changes taking place, so they are of necessity incomplete and spotty in individual cases. Nevertheless, in the aggregate the characteristics of the syndrome seem fairly clear.

SEQUENCE OF CHANGES IN INDIVIDUAL PATIENTS

The sequence of changes in individual patients best illustrates the characteristic features of the illness following hospitalization. The following five patients are representative of the group, having been selected for completeness of the data. To economize on space and yet allow for comprehensiveness of presentation, the abbreviations and units of various measurements referred to subsequently have been assembled for ready reference in table 1.

CASE REPORTS

Case 1. A 35 year old man who drank beer excessively noticed anorexia, diarrhea, cough, fever, chilliness and right upper abdominal pain seven weeks before admission. The pain lasted approximately two weeks; the other symptoms, however, persisted. He became very weak, and lost 30 pounds in weight. Four weeks after onset of symptoms a physician noted he was intensely jaundiced and gave him "pills" for his fever. However, by the time of admission to this hospital, his jaundice had receded markedly and he felt better. He had had no vomiting, melena, edema or abdominal swelling. In the past he had six or more similar episodes, beginning 11 years previously.

He was slightly icteric on admission and slightly febrile, registering a temperature of 100° F. His blood pressure was 145/85 mm. Hg. His liver descended 5 cm. below the right costal margin on deep inspiration. The tip of the spleen was barely

* Presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 12, 1957.

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TABLE 1

Abbreviations and Units of Various Measurements

A/G	—serum alb./glob., gm. %	MCV	—mean corp. vol., cu μ.
AP	—alkaline p'tase, KA units	Nu RBC	—nucleated red cells
BM	—bone marrow	OsFr	—osmotic fragility
BSP	—bromsulfalein, %	PC	—prothrombin conc., %
BSPc	—corrected BSP, %	Plt	—platelets, thousands/cu. mm.
BT	—bleeding time, min.	RTC	—reticulocytes, %
BUN	—blood urea nitrogen, mg. %	SAm	—serum amylase, u. %
Cbs	—Coombs' test	Sph	—spherocytic red cells
CF	—ceph. flocc., 48 hr.	SR	—sedimentation rate, mm./hr.
CT	—clotting time, min.	StG	—stool guaiac
FBS	—fasting blood sugar, mg. %	TB	—tot. ser. bilirubin, mg. %
FE	—fecal Ehrlich, u./100 gm.	TC	—tot. ser. cholesterol, mg. %
FU*	—fecal urobilinogen, mg./d.	Trsfn	—transfusion
Hb	—hemoglobin, gm. %	TT	—thymol turbidity, units
Ht	—hematocrit, %	UCP	—urine coproporphyrin, μg./d.
Im WBC	—immature wbc	UA	—urine amylase, u./hr.
LB	—liver biopsy	UE	—urine Ehrlich, u./2 hrs.
LE	—"LE" clot test	UU	—urine urobilinogen, mg./d.
Lip	—Lipemia	WBC	—white bl. ct., c./cu. mm./10^3
MCC	—mean corp. hb. conc., %	ZT	—zinc sulfate turb., units

* All values reported in this paper have been corrected for anemia and body weight, taking 15 gm. per 100 ml. as the reference Hb value, and 160 lbs., the approximate average of a large group of normal men, as the reference weight. The calculation was: 15/observed Hb × 160/usual or ideal weight × observed FU = FU corrected for anemia and weight, or indirectly and approximately, for total circulating Hb. FE values were not corrected for anemia.

palpable. Urinalysis was normal except for the presence of bilirubin; VDRL was negative; chest x-ray was normal. Sequential changes in the pertinent laboratory studies are given in table 2. The patient's hemoglobin rose from 9.5 to 15 gm./100 ml. over six weeks, and his reticulocytes reached a peak of 7.9%. The serum cholesterol dropped in six weeks from 656 to 182 mg./100 ml. His jaundice, regurgitation in type, had largely receded by the day of admission, and the serum bilirubin was normal by the third week. The hepatic tests were essentially normal except for slight alterations in the serum proteins and the protein-dependent tests. Liver biopsies obtained during the second and seventh weeks both showed minimal portal cirrhosis (figures 1 A and B).

TABLE 2

Sequential Changes in Various Hematologic and Functional Measurements of Case 1*

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	9.5	2.0	—	2.2	WBC 8.0. SR 85. Ht 37.5. MCV 96. MCC 26.
1	9.8	7.9	656	—	Plt 187. OsFr +. FU 252. 2 StG —. Cbs —. BM: 58% Normoblasts. Foam cells. BSPc 5. CF 1+. TT 8. ZT 8. UU 0.4. A/G 3.7/3.8. PC 70. SAm 112. FBS 75.
2	11.8	7.6	435	1.2	OsFr +. Liver biopsy.
3	14.2	1.9	260	0.7	WBC 14.5 and 6.7. SR 61. Plt 176. FU 98. AP 7. A/G 5.0/2.1. PC 94.
4	13.5	2.9	290	—	WBC 10.0. SR 45. Ht 44. MCV 105. MCC 31.
6	15.2	1.7	182	—	WBC 9.1. SR 5.
7	14.7	1.7	182	—	WBC 10.5. SR 6. BT 4.5, CT 15. BM: 28% Normoblasts. LB.

* Abbreviations and units of measurement in this and the following tables are explained in table 1.

The patient's anemia was macrocytic in type. Two stool guaiac examinations were negative. His fecal urobilinogen excretion was 252 mg. per day despite his having received medicine (probably antibiotics) three weeks previously for his febrile illness. This value falls just at our limit of normal which, for the healthy male of average weight and hemoglobin concentration, is approximately 250 mg. per day. He served as his own control, however, since in the third week his fecal urobilinogen excretion was 98 mg. per day. The osmotic fragility was slightly increased. A screening test was positive during the first week, and the following percentages of hemolysis were observed during the second week:

% NaCl:	.60	.57	.54	.51	.48	.45	.42
Patient, %:	0	3	3	11	24	63	75
Control, %:	0	0	0	1	13	51	64

His Coombs' test was negative.

A bone marrow examination during the first week showed marked erythroid hyperplasia, with 58% of the marrow cells normoblasts. Large phagocytic foam cells (figure 1 C) were relatively abundant. A repeat examination during the seventh week showed only 28% normoblasts and rare foam cells.

X-ray studies of the stomach and gall-bladder were normal. A bone survey, including the skull, pelvis and legs, was negative.

The patient's subjective improvement was rapid, and his enlarged liver receded commensurately. A low grade fever persisted for four weeks. Until the second liver biopsy was obtained he was a perplexing problem to the resident and consulting physicians. The various tentative diagnoses recorded in the chart were: liver disease, type undetermined; hemolytic anemia, cause unknown; and idiopathic hypercholesterolemia. Common duct stone and pancreatitis were considered seriously for a short time after admission, but eliminated because of the rapid, spontaneous improvement and a normal serum amylase. The patient was discharged after 42 days of hospitalization.

Comment: The patient was a puzzling problem of jaundice, anemia and hypercholesterolemia. The first biopsy was considered to be nondiagnostic until it was reviewed with an azocarmine stain at the time of the second biopsy. Hemolysis was suspected but discounted because the alterations were minimal rather than striking. The discovery of foam cells in the bone marrow was a surprising and unexplained finding. The condition improved as the other abnormalities improved. The foam cells probably reflect the previous existence of lipemia. The existence of lipemia was not documented; however, it was not looked for, and the patient had been improving for three weeks before admission. The fact that his first cholesterol was still as high as 656 mg. per 100 ml. after such an interval, in which his jaundice had largely receded, makes one suspect a striking initial hyperlipemia.

Case 2. A 39 year old alcoholic had had anorexia, fever, chilliness and pain in the eyes for 10 days. He had had occasional upper abdominal "gas pains," nausea and vomiting. Four days before admission he noticed jaundice, dark urine and light stools. Two days later all symptoms became worse following excessive brandy drinking; however, he worked until admission.

He was slightly febrile and moderately jaundiced on admission. His liver was palpable 5 cm. below the right costal margin and was tender. His spleen was not

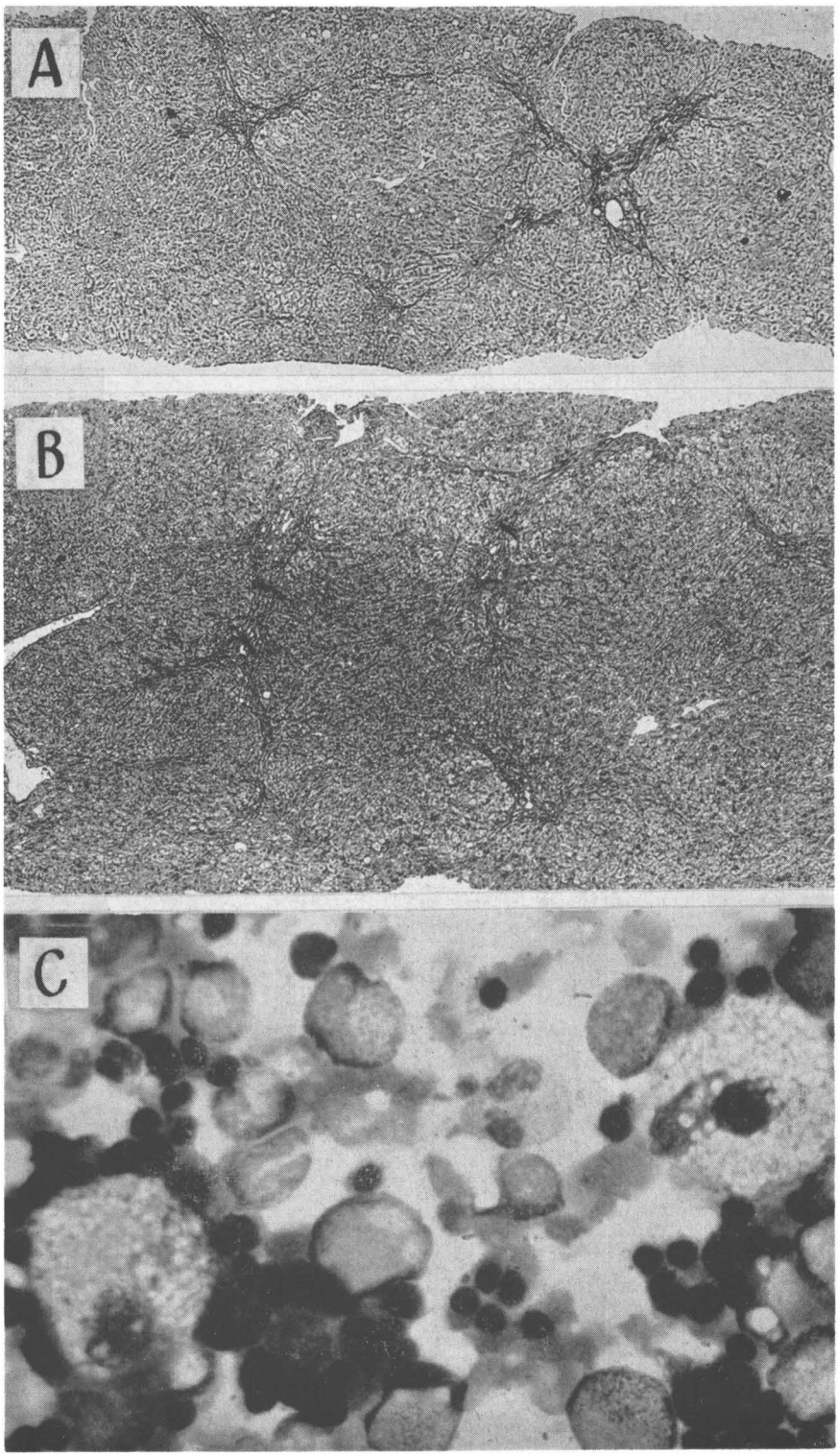

FIG. 1. Liver biopsies, A and B (× 50), and bone marrow aspiration, C (× 400), of case 1.

palpable. His liver receded rapidly, being no longer palpable after one week. His low grade fever, however, persisted for six weeks.

Except for the presence of bilirubin, the patient's urinalysis was negative, as were his VDRL slide test and chest x-ray. The sequential changes in his most pertinent laboratory studies are given in table 3. His hemoglobin remained about 9.5 gm. per 100 ml. until transfusions were given in the fifth week. His maximal reticulocyte response was 7.4%, occurring in the third week. His serum was milky on admission, as noted by the laboratory technician when asked to perform a turbidity test. It cleared rapidly. The serum cholesterol dropped from 536 to 294 mg. per 100 ml. in four weeks. His jaundice was regurgitation in type and improved rapidly, the serum bilirubin decreasing from 9.6 to 1.0 mg. per 100 ml. in four weeks. Hepatic function was mildly disturbed and improved rapidly. His alkaline phosphatase was 68 King-Armstrong units, dropping to 27 by the second week and to 10 by the fourth week.

TABLE 3

Sequential Changes in Various Hematologic and Functional Measurements of Case 2

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	9.6	—	536	9.6	Serum milky. Plt decr. WBC 5.9. SR 29.
1	9.5	5.3	538	5.0	WBC 7.8. SR 75. FE 145. 3 StG —. BSPc 15. CF 0. TT 12. AP 68. UU 2.8. A/G 2.8/3.1. PC 100.
2	9.2	5.9	403	2.2	WBC 7.8. SR 70. Ht 31. MCV 103. MCC 30. Sph. LE —. 3 StG —. A/G 3.9/2.7. AP 27. CF 0. TT 6.
3	8.9	7.4	—	1.6	Sph 1%. Plt 662. Ht 34. FE 121–180. OsFr ±. BM: 64% Normoblasts. UU 0.5. ZT 9.
4	9.5	6.3	294	1.0	FU 276. WBC 14.3. Ht 35. BT 2, CT 10. Trsfn 500 ml. AP 10. TT 4. ZT 11. UU 0.6.
5	16.5	1.6	—	—	Trsfn 1150 ml. Exploration. LB.
7	15.2	0.6	—	0.4	WBC 8.7. SR 6. BSP 3. CF 0. TT 2.

The patient's anemia was macrocytic-normochromic in type. Six stool guaiac examinations were negative. Several random fecal Ehrlich examinations were normal; however, a four-day fecal urobilinogen study during the fourth week was slightly abnormal (276 mg. per day). Spherocytes were seen in the peripheral blood, but an osmotic fragility test was only minimally abnormal. His platelets, which were observed to be decreased in the initial blood smear, rose to 662,000 per cubic millimeter by the third week. An L.E. clot test was negative. A bone marrow examination during the third week showed erythroid hyperplasia with 64% normoblasts.

General improvement was rapid after admission. A gastrointestinal series and cholecystogram were normal. The patient's hematologic findings as well as the initially high cholesterol and alkaline phosphatase values were perplexing to those observing his illness, and diagnoses of hemolytic anemia and common duct obstruction or viral hepatitis were entertained. Following transfusions he was explored surgically during the fifth week, at which time his biliary system was normal, and a liver biopsy was obtained. The biopsy was considered nondiagnostic at the time, so the patient was discharged after 63 days with a diagnosis of hepatitis. However, careful review of the biopsy reveals minimal cirrhosis (figure 2 A).

Comment: The patient presented with hyperlipemia which was unrecognized at the time by all but the laboratory technician. It lasted but a few days. The hypercholesterolemia and jaundice receded over four weeks. During this time the evidences for hemolysis became more marked. The

prominent alkaline phosphatase, together with the hypercholesterolemia in a jaundiced patient, with slight alterations in hepatic function, led to the suspicion of common duct stone and to the surgical exploration in the fifth week.

Case 3. A 46 year old truck driver had been drinking beer excessively for many years. Four years previously he had been explored surgically for abdominal pain and found to have acute pancreatitis. Three weeks prior to this admission he noticed marked tremulousness, weight loss and weakness. Two weeks later he had watery

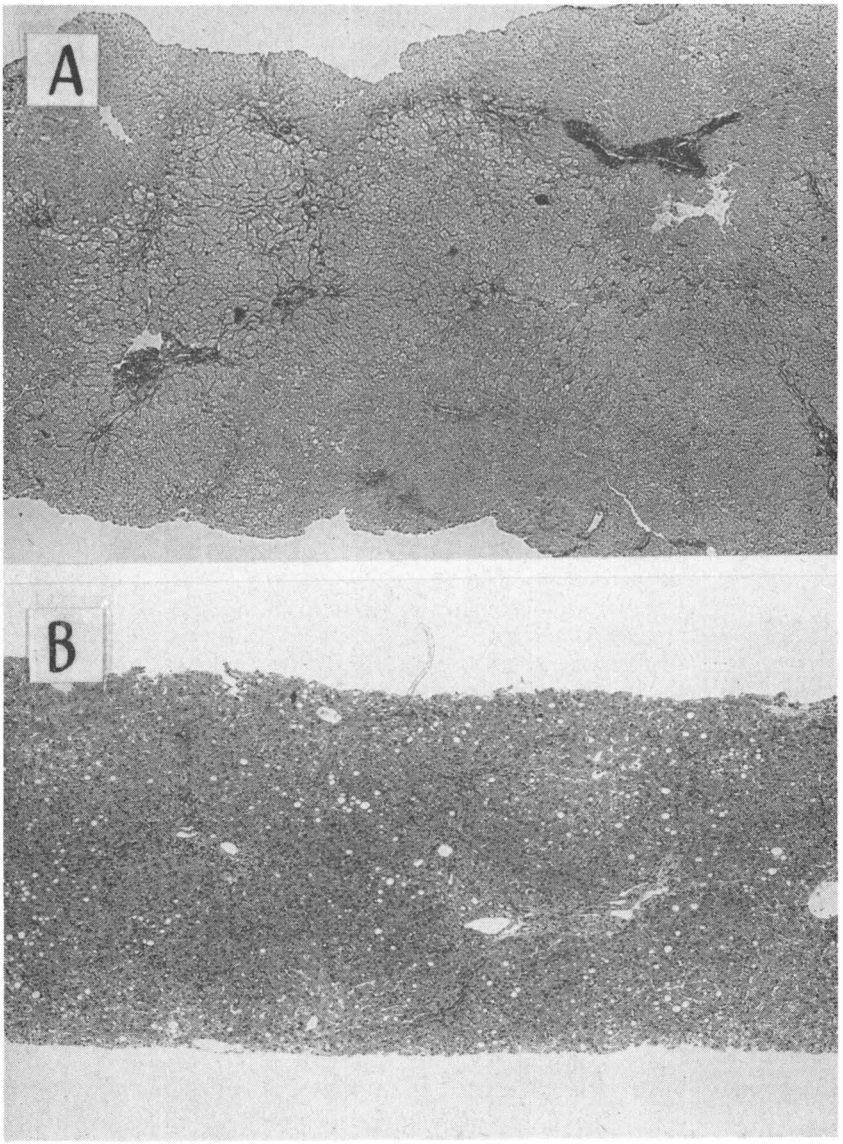

FIG. 2. A. Liver biopsy of case 2 (× 50). B. Liver biopsy of case 3 (× 50).

TABLE 4

Sequential Changes in Various Hematologic and Functional Measurements of Case 3

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	12.5	1.0	—	5.9	Serum v. milky. WBC 8.4. SR 65. Ht 40.
1	11.6	5.3	—	3.6	Nu RBC. Im WBC. FE 159. WBC 10.6. SR 91. A/G 3.3/2.9. SAm 84. FBS 137.
2	11.8	7.6	394	2.5	Nu RBC. Sph. OsFr +. FU 514. Cbs —. BM: 53% Normoblasts. 2 StG —. Plt 303. Ht 37. MCV 104. MCC 32. WBC 10.4. SR 83. BT 2, CT 14. BSP 11. AP 17. CF 0. TT 6. A/G 4.6/2.8. PC 100. BUN 9. SAm 78.
3	11.0	8.8	—	1.6	OsFr +. FE 199. 3 StG —. FBS 107.
4	11.5	6.5	—	1.0	FE 119.
5	12.5	3.8	—	0.7	WBC 12.9. SR 92. FE 213. BT 2, CT 13.
6	13.1	2.6	247	0.5	OsFr +. Plt 324. FU 67. LE —. LB. BSP 11. CF 0. TT 3. A/G 4.4/2.6.
8	12.9	2.0	—	—	———
12	13.6	2.9	—	—	OsFr —.

diarrhea lasting several days, and passed several stools containing dark red blood. One week before admission he became jaundiced and noticed epigastric burning and vomiting. On one occasion he vomited a small amount of blood while experiencing a retrosternal burning sensation.

On initial examination he was slightly febrile, markedly tremulous, obese and jaundiced. He had diffuse telangiectasia and erythema of his face and neck, and coughed frequently. His liver was markedly enlarged (16 cm. below the costal margin) and tender. His spleen was not palpable, and was normal in size on x-ray examination. Thrombosed hemorrhoids were apparent on rectal examination, and bloody stool was noted on the examiner's finger. Later, five stool guaiac examinations during the second and third weeks were negative. Except for the presence of bilirubin, his urinalysis was normal. His VDRL slide test and chest x-ray were negative. Sequential changes in his pertinent laboratory findings are given in table 4.

The patient's blood hemoglobin at its lowest was 11 gm. per 100 ml. and improved slowly over many weeks. The maximal reticulocyte response was 10.9%, occurring during the third week, in which the median value recorded was 8.8%. The serum was very lipemic on the day of admission, but cleared over a period of three weeks. This went unnoticed by all but the laboratory technicians. The first cholesterol determination was not obtained until the fourteenth day, at which time it was 394 mg. per 100 ml. By the sixth week it had dropped to 247 mg. per 100 ml. His serum bilirubin decreased from 5.9 (one minute, 3.8) to 0.5 mg. per 100 ml. in six weeks. The hepatic tests were very mildly abnormal or normal. A liver biopsy was not obtained until the thirty-fifth day, at that time showing mild fatty cirrhosis (figure 2 B).

The anemia was macrocytic-normochromic in type. Nucleated red cells, spherocytes and immature white cells were noted in repeated blood smears. Osmotic fragility tests (including one qualitative screening test) on the thirteenth, twenty-first and forty-third days were abnormal (table 5). By the twelfth week the screening test was negative. A Coombs' test was negative, as was an L.E. clot test. His fecal urobilinogen was 514 mg. per day during the second week. In the sixth week this had dropped to 67 mg. per day. A bone marrow examination in the second week showed increased cellularity, with 53% of the cells normoblasts.

X-ray studies of the esophagus, stomach, colon and gall-bladder were normal. The patient's initial fasting blood sugar was abnormal, later decreasing as he improved. He had no family history of diabetes, and a flat plate of the abdomen showed

no calcification in the pancreas. Pancreatitis was strongly suspected initially, but discarded as a diagnosis when serum amylases were normal.

The patient improved symptomatically very rapidly. His liver receded within two months. A low grade fever persisted for six weeks. The hemolytic process was the primary problem that concerned and puzzled his physicians. The mild cirrhosis established by liver biopsy during the sixth week was not considered sufficient to account for the hemolysis, particularly in the absence of splenomegaly. His improvement was progressive, and he was discharged after 55 days of hospitalization with the hemolytic anemia unexplained.

Comment: Though this patient presented with hyperlipemia and jaundice as well as anemia, attention was focused primarily upon the latter. The alterations in his red cells were more pronounced and prolonged than in the preceding two patients, and the evidences of hemolysis more striking. Fa-

TABLE 5

Osmotic Fragility Studies in Case 3
(Percentage Hemolysis)

% NaCl	13th day C*	13th day P*	43rd day P*	43rd day C*
.66	0	5	0	0
.60	0	14	2	0
.54	4	54	9	0
.51	9	71	29	6
.48	30	83	74	37
.45	49	91	89	67
.42	74	92	91	90
.36	94	93	94	94

* C, control; P, patient.

milial hemolytic anemia was suspected, and various hematologic studies, including osmotic fragility determinations, were made in a brother and in his two children. These were normal.

Case 4. A 59 year old bartender complained of jaundice, malaise, weakness and fatigue of three weeks' duration. He had noted an intermittent gnawing pain and eructations for two months. The pain was often relieved by food. On admission he was very tremulous and markedly jaundiced, and appeared to have lost much weight. He had a "black" eye. His liver was diffusely enlarged, extending below the level of the umbilicus. The spleen was barely palpable. A few spider nevi were noted. His blood pressure was 154/98 mm. Hg. His initial urinalysis was normal except for the presence of bilirubin. The serologic test for syphilis and chest x-ray were negative.

The sequential changes in the pertinent laboratory findings are recorded in table 6. The patient's hemoglobin at its lowest was 10 gm. per 100 ml., rising slowly. A reticulocyte count of 16.9% was recorded during the second week. His serum was very cloudy on admission, at which time his serum cholesterol was 501 mg. per 100 ml. Five weeks later it had fallen to 208 mg. per 100 ml. During the same interval his serum bilirubin decreased from 20 (one minute of 10) to 1.3 (one minute of 0.7) mg. per 100 ml. His hepatic function was only mildly disturbed. A liver biopsy was not obtained.

The anemia was macrocytic and normochromic. Five stool guaiac examinations were negative. Fecal urobilinogen excretion during the first week was 440 mg. per

TABLE 6

Sequential Changes in Various Hematologic and Functional Measurements of Case 4

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	11.4	—	501	20.0	Serum v. cloudy. WBC 15.1. SR 68. UE 15.
1	10.0	10.0	—	—	Ht 32. MCV 119. MCC 31. BT 15+, CT 9. Plt 198. FU 440. StG —. A/G 3.6/2.6. BSPc 2. CF 2+. TT 9. ZT 11. UU 7.8. PC 47.
2	10.0	16.9	—	—	Sph. WBC 9.3. SR 113. StG —. AP 25. CF 2+. TT 8. PC 48. UE 1. BUN 6.
3	10.9	—	—	4.1	OsFr +. Cbs —. AP 19. A/G 4.2/3.3.
4	12.0	—	—	1.9	3 StG —. BSP 6. AP 13. TT 5. ZT 13.
5	12.1	2.4	208	1.3	OsFr +. Ht 38.5. MCV 100. MCC 32. BSP 10. TT 4. A/G 4.5/2.1.
6	12.4	—	—	—	———
31	14.2	3.1	—	—	———

day. An initial two-hour urine Ehrlich determination showed 15 units, while a repeat study in the second week yielded a value of 1 unit. Spherocytes were observed in the blood smear, and osmotic fragility tests on the fifteenth and thirty-first days were abnormal (table 7), though showing improvement during the interval between tests. The Coombs' test was negative. The bleeding time and clot retraction were abnormal initially; however, no followup studies were recorded.

The patient improved very rapidly after admission. Within two weeks he had a voracious appetite, and his liver had receded greatly. A mild fever persisted for five weeks. X-ray studies of his entire gastrointestinal tract, including the gall-bladder, were normal. The various diagnoses entertained were: infectious hepatitis, portal cirrhosis, obstructive jaundice of intra- or extrahepatic origin, and hemolytic anemia of unknown cause. The latter was the most perplexing aspect of his illness. He was discharged after 45 days of hospitalization.

Comment: The jaundice and the alterations in this patient's red cells were the focus of the evaluating physician's attention. The lipemia would have gone unrecognized except for the comments of the laboratory technician. The bleeding time was prolonged at the time that the platelet count was 198,000 per cubic millimeter. Repeat studies were not made, so we are unable to say how rapidly this abnormality might have cleared up. It was used, however, as a contraindication to liver biopsy.

TABLE 7

Osmotic Fragility Studies in Case 4
(Percentage Hemolysis)

% NaCl	15th day C*	15th day P*	31st day P*	31st day C*
.66	0	1	0	0
.60	0	8	2	0
.54	0	41	7	0
.51	0	46	22	0
.48	9	90	74	8
.45	73	94	94	62
.42	93	97	97	84
.36	95	97	99	96

* C, control; P, patient.

TABLE 8

Liver Function Test Results Observed in Case 5 at Each Admission

Date		1'B	TB	TC	AP	BSP	CF	TT	UU	Other Tests[10,11]
1-7-49	I	0.1	0.3	193	—	22	0	3	2.7	ZT 8. GT 116. HA 0.79. UCP 432.
4-1-49	I	0.2	0.9	—	—	7	0	—	0.2	SAm 138. LB on 4-7-49.
	F	0.1	0.2	165	—	9	0	4	0.6	ZT 8. GT 27. HA 0.63. UCP 364.
7-18-49	I	0.2	1.0	—	9	6	0	5	—	SAm 48. A/G 5.6/2.3.
11-25-49	I	3.5	5.5	335	—	19c	3+	11	136	ZT 7. GT 42. HA 0.53. UCP 814. SAm 68. FU 249.
	F	0.1	0.5	155	11	—	1+	4	2	A/G 4.7/1.8.
6-21-50	I	10.2	16.2	160	31	32c	3+	10	42	GT 34. HA 0.59. UCP 1091. A/G 3.2/4.5. FU 59.
	F	1.3	2.5	239	14	—	0	5	0.6	ZT 14. A/G 4.0/3.7. LB on 7-1-50.
8-7-51	I	5.7	10.4	332	29	45c	—	25	169	ZT 17.
	F	1.5	3.3	242	20	18c	—	—	—	——
8-26-53	I	10.5	14.5	685	20	13c	0	4	—	ZT 7. FU 320.
	F	0.2	0.5	270	13	15	0	3	—	ZT 7.
6-27-54	I	10.0	17.5	464	39	—	0	14	—	ZT 11. A/G 4.5/2.9.
3-20-55	I	4.6	8.3	548	32	19c	0	4	17	SAm 56. A/G 4.4/3.1.
	F	0.5	1.0	200	10	11	0	5	—	LB on 4-2-55.
6-7-56	I	6.2	9.7	494	44	35c	0	2	2.2	A/G 3.3/2.6.
	F	0.9	1.9	215	24	—	—	—	—	FU 88.

Tests not previously defined: 1'B, One-minute Bilirubin, mg./100 ml. GT, I-V Galactose Tolerance, mg./100 ml. in 60'. HA, I-V Hippuric Acid Excretion, gm./hr. BSPc, bromsulfalein values corrected for presence of jaundice.

I, Initial Studies. F, Final Studies.

Case 5. A 36 year old man was originally called into the hospital on January 7, 1949, during a follow-up study of veterans who had had viral hepatitis during World War II. He had been listed erroneously as having had hepatitis; his service episode was verified by Army hospital records as one of urethritis. He drank excessively and was tremulous at this examination. He was obese, weighing 188 pounds and standing 66 inches. His liver was enlarged. His spleen had been removed 13 years previously for an unexplained rupture. He was not jaundiced, and showed the functional alterations listed in the first line of table 8.

The patient was asked to return for liver biopsy, but did not do so until April 1, 1949, when he became ill following excessive drinking, noting nervousness, chest pain, nausea, vomiting, and tingling and numbness of his hands. His essential physical findings were marked tremulousness and telangiectasia. The liver was not palpable, and he was not jaundiced. He improved very rapidly, and showed the test results recorded in lines two and three of table 8. A liver biopsy obtained on April 7, 1949, showed severe fatty infiltration and possibly minimal portal cirrhosis (figure 3 A).

TABLE 9

Sequential Changes in Various Hematologic and Functional Measurements of Case 5 (Admission of 11-25-49)

Week	Hb	RTC	TC	TB	Other Laboratory Data
1	10.1	13.7	335	5.5	WBC 11.4. SR 37. Ht 36. MCV 102. MCC 31. Nu RBC. Im WBC. FE 308. UU 136. UCP 814. BSPc 19. CF 3+. TT 11. ZT 7. SAm 68.
2	11.7	11.4	—	2.1	Sph. Nu RBC. Im WBC. FU 249. 2 StG —. BM: 50+ % Normoblasts. PC 50. CF 0. TT 5. ZT 8. A/G 4.7/1.8.
3	13.2	5.0	155	1.6	OsFr +. WBC 10.2. SR 17. 2 StG —. UU 10. CF 1+. TT 4. AP 11. PC 72.
4	13.9	0.8	—	0.5	WBC 8.4. SR 17. StG —.
5	14.3	—	—	0.3	UU 2.

On July 18, 1949, the patient was re-admitted with delirium tremens, and the test results listed opposite this date in table 8 were observed.

He continued his excessive drinking, which led to a re-admission on November 25, 1949. At this time he was tremulous, jaundiced and febrile. He had had a cough, chest pain, nausea, vomiting, diarrhea and right upper abdominal pain intermittently for one month. His urine had become dark, and his fingers and toes tingled and were numb. His liver was tender, and was palpable 13 cm. below the right costal margin. Except for the presence of bilirubin his urinalysis was normal. The Kahn test and chest x-ray were negative.

Sequential changes in the pertinent laboratory studies are given in table 9. The patient's hemoglobin rose from 10.1 to 14.3 gm. per 100 ml. in five weeks, and his maximal reticulocyte response was 13.7%. The serum cholesterol was found to be elevated for the first time, and dropped from 335 to 155 mg. per 100 ml. in two weeks. His serum bilirubin similarly decreased rapidly. The hepatic tests were moderately disturbed but improved very rapidly. His urine urobilinogen was disproportionately elevated, probably a reflection of its excessive formation in the presence of a damaged liver, but decreased rapidly.

The patient's anemia was macrocytic-normochromic. Spherocytes, nucleated red cells and immature white cells were seen in the peripheral smear. Five per cent basophils were noted during the second week. An osmotic fragility test obtained during the third week was slightly abnormal, showing the following percentages of hemolysis:

% NaCl:	.57	.54	.51	.48	.45	.42	.36
Patient, %:	0	1	9	18	41	78	96
Control, %:	0	0	0	0	19	45	95

A random fecal Ehrlich determination was 308 units during the first week, and a fecal urobilinogen during the second week was 249 mg. per day. Five stool guaiac examinations were negative. A bone marrow examination during the second week showed erythroid hyperplasia, with over 50% of the cells normoblasts. X-ray studies of his esophagus, stomach and colon were normal. General improvement was very rapid, though a low grade fever persisted for two weeks. All studies improved commensurately, and the patient was discharged after 34 days.

Six months later (June 21, 1950) the patient was re-admitted with delirium tremens and jaundice after continuing his excessive drinking. His liver was enlarged to the iliac crest, and his function was poor, as seen in line seven of table 8. His cholesterol was 160 mg. per 100 ml. initially, and rose to 239 mg. per 100 ml. as he improved, in contrast to his preceding admission. A liver biopsy obtained on July 1, 1950, showed very severe fatty infiltration and moderate cirrhosis (figure 3 B). His fecal urobilinogen during the second week of this admission was only 59 mg. per day. He improved slowly over a period of 37 days and was discharged not yet achieving stabilization.

The patient was next seen one year later (August 7, 1951) with jaundice, epigastric pain, cough, anorexia, nausea and vomiting. He claimed to have abstained from drinking for six months, only to have relapsed following this. However, he had worked only 10 days out of the whole year. He was tremulous, and had a low grade fever, a very large liver and a few spider nevi. His initial and final hepatic studies are given in lines nine and 10 of table 8. Improvement was slow, and he was discharged after a month of hospitalization.

Two years passed before the patient was next hospitalized (August 26, 1953). During this interval he had worked steadily and had abstained from drinking until four months preceding admission, when he again reverted to his previous habits. He developed chest pain, cough, purpura of arms and legs, and jaundice. The liver was very large (palpable 9 cm. below the costal margin).

Sequential changes in the patient's most pertinent laboratory studies are given in table 10. His hemoglobin rose from 10.8 to 14.1 gm. per 100 ml. in seven weeks. Only one reticulocyte count was obtained, the value being 4% in the third week. His cholesterol dropped from 685 to 270 mg. per 100 ml. in four weeks. During the same interval the serum bilirubin decreased from 14.5 to 1.1 mg. per 100 ml. Hepatic function was only mildly disturbed. Unfortunately, a liver biopsy was not obtained at this time.

The patient's anemia was macrocytic and normochromic. He had had no blood loss by history, and one stool guaiac test was negative. Nucleated red cells and immature white cells were seen in the blood smear. The fecal urobilinogen excretion during the third week was 320 mg. per day. A bone marrow examination during the second week showed very marked erythrocytic hyperplasia, with 61% normoblasts and abundant megakaryocytes. Improvement was rapid and progressive, and the patient was discharged after 41 days of continuous hospitalization.

Eight months later (June 27, 1954) he was admitted again with delirium tremens. His drinking habits had changed in that he now drank sporadically and intensely rather than continuously. He was severely jaundiced and had marked hepatomegaly. His function test results are shown in line 13 of table 8. Subjective improvement was rapid, and he was discharged in two weeks when his jaundice was no longer apparent clinically.

Though the patient denied drinking as heavily as previously, he was re-admitted again with mild delirium tremens approximately nine months later (March 20, 1955).

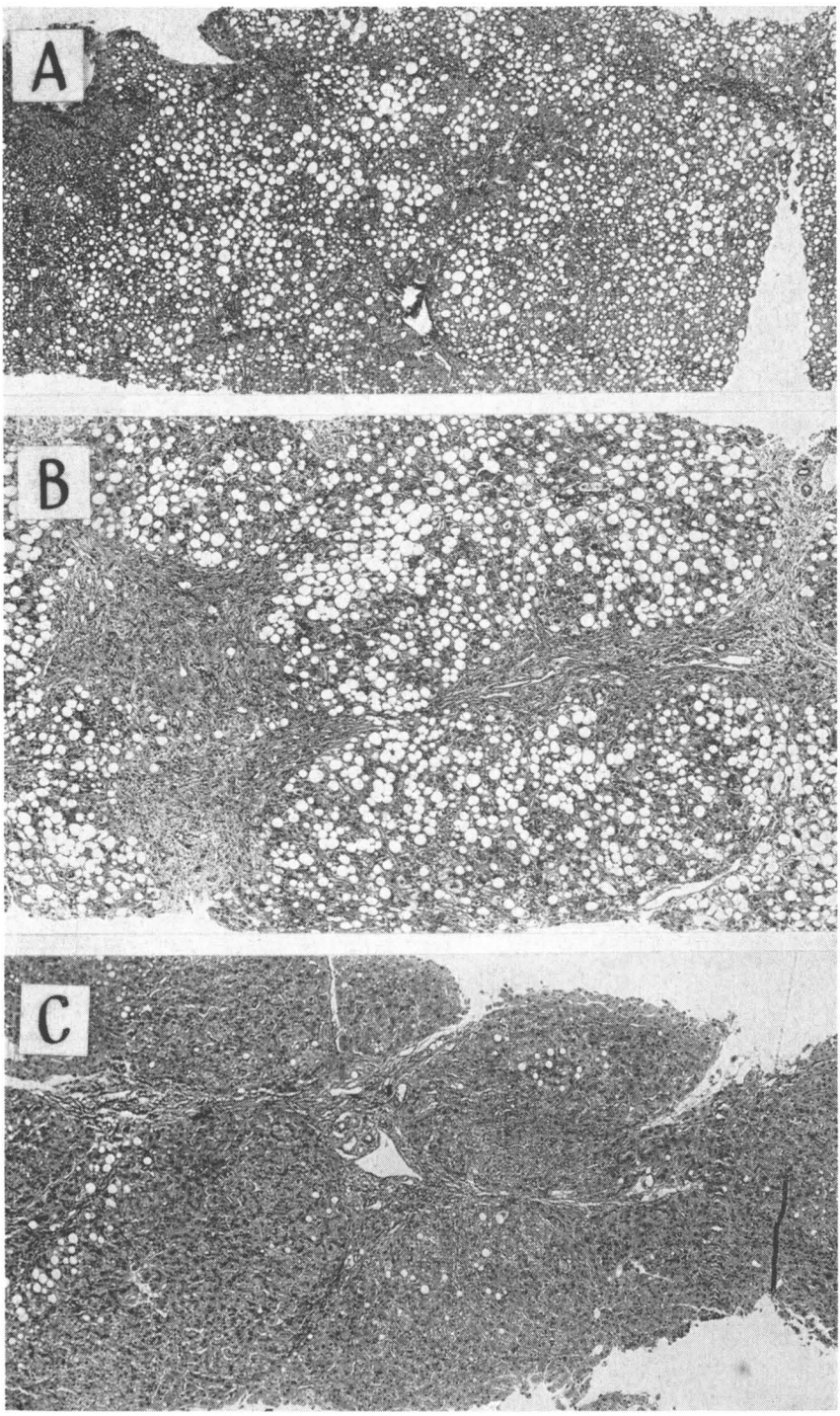

FIG. 3. Liver biopsies in case 5 (× 50). A, 1949. B, 1950. C, 1955.

He was again jaundiced and anemic, and showed rapid, spontaneous improvement in both respects. His initial and final function studies are given in lines 14 and 15 of table 8. A liver biopsy obtained on April 2, 1955, showed mild fatty cirrhosis (figure 3 C). This was greatly improved over the biopsy obtained almost five years previously. Presumably the two-year period of abstinence (1951 to 1953) was beneficial, and his improvement persisted to some extent despite his later relapses.

The last admission (June 7, 1956) was for hematemesis and melena. He had continued to drink, becoming markedly tremulous and finally jaundiced. His function studies are shown in the last two lines of table 8. He required replacement with 4,500 ml. of blood. Fecal urobilinogen excretion two weeks after admission, and after the transfusions, was 88 mg. per day. Esophagoscopy revealed no varices. A gastrointestinal series revealed a questionable lesser curvature ulcer, which was no longer visible on repeat examination one week later. Alcoholic gastritis was strongly suspected but not proved. His response to an ulcer regimen and general hospital care was dramatic, and he was discharged after 34 days.

TABLE 10

Sequential Changes in Various Hematologic and Functional Measurements of Case 5 (Admission of 8-26-53)

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	11.4	—	—	—	Nu RBC. Im WBC. Plt 186. WBC 9.6. SR 82.
1	10.8	—	685	14.5	Ht 39. MCV 118. MCC 28. CF 0. TT 4. ZT 7. PC 68.
2	—	—	—	6.5	BM: 61% Normoblasts.
3	—	4.0	292	—	FU 320. AP 20.
4	—	—	—	2.8	BSPc 13.
5	12.8	—	270	1.1	SR 22. AP 13.
7	14.1	—	—	1.1	SR 12. BSP 17. CF 0. TT 4. ZT 8.
10	14.6	—	—	0.5	SR 5. BSP 15. TT 3. ZT 7. PC 63.

Comments: This patient was seen 10 times over a seven-year period, during which his drinking habits changed successively from severe continuous imbibing to complete abstinence to severe intermittent alcoholism. Three reasonably well-timed liver biopsies taken over this period showed, in sequence, severe fatty liver, probably with minimal cirrhosis; very severe fatty infiltration with moderate portal cirrhosis, and mild fatty cirrhosis. At the time of the first biopsy he was not jaundiced and his serum cholesterol was normal. Seven months later he had his first episode of jaundice, hypercholesterolemia, and probable hemolytic anemia. Seven months after this episode the second biopsy showed severe damage. This time his cholesterol was normal at the height of his jaundice and rose slightly as he improved. Three years later, following a two-year interval of complete abstinence and then relapse, he had another fairly well studied episode of jaundice, hypercholesterolemia and mild hemolytic anemia. Then after an interval of two years he was seen in a similar, incompletely studied episode, at which time the third liver biopsy showed mild cirrhosis. All told, he was seen in six episodes in which jaundice and hypercholesterolemia occurred together and improved rapidly in parallel fashion, and once in association with severe liver abnormality when jaundice was not associated with hypercholesterolemia.

Lipemia was never recorded, but it was never looked for. Only twice was hemolysis thought of and looked for, and in both instances it was dismissed (prematurely, perhaps) as an explanation for the anemia.

Characteristics of the Group

General Clinical Characteristics: The 20 patients were all men aged 26 to 65 years; their average age was 39 years. Alcoholism was uniformly present, though often minimized by the patients. Anorexia, nausea or vomiting, diarrhea and weight loss were common. Malaise, weakness, cough and chilliness were also frequent. Upper abdominal pain was almost always present but varied in severity, at times being very severe. The pain was diffuse or localized to the right upper quadrant or epigastrium. Pancreatitis was frequently suspected initially but not supported by the serum amylase, and so was discounted.

Low grade fever lasting several weeks after admission was the rule. Tremulousness was common, and frank delirium tremens occurred occasionally. Signs suggestive of vitamin B complex deficiency, tongue changes or peripheral neuritis, were sometimes described. Jaundice was uniformly present, though it had often improved greatly by the time of admission. The liver was enlarged, usually markedly, and generally receded rapidly. The spleen was either not palpable or barely palpable; it was never prominent. Edema and ascites were not frequent and, when present, were associated with low serum proteins. Rapid return of serum proteins to normal and loss of retained fluid were typical. An unexplained pleural effusion was observed twice; it was not related to the presence of ascites. Telangiectasia was common, and spider nevi were described occasionally, probably, however, occurring much more frequently than was recorded.

A good appetite was present on admission or became evident within a few days. The patients were often ravenous. Symptomatic and objective improvement was almost invariably rapid, generally surprisingly so.

Liver Function Abnormalities: The maximal abnormalities observed in each patient with various hepatic tests are given in the central portion of table 11, which also lists similar abnormalities in the available hematologic measurements. Though the values recorded in table 11 are the most abnormal ones recorded in the charts of the patients, it must be recognized that they may underestimate the true abnormality that might have been recorded had the test been performed at the optimal time in the course of the patient's illness.

The average maximal abnormality observed with each hepatic test is summarized in table 12, which also lists the week in which the abnormal value occurred. Hepatic function was in general mildly disturbed, though occasionally bromsulfalein retention was marked initially. The more marked functional abnormalities were in general associated with the more severe anatomic alterations on liver biopsy, which are indicated in the next-to-the-

TABLE 11

Maximal Abnormality Observed with Each Measurement in Each Patient

Case	Hb	RTC	TC	TB	Lip	AP	BSP	CF	TT	ZT	A/G	PC	UU	WBC	SR	MCV	MCC	StG	LB*	Miscellaneous
1	9.5	7.9	656	2.2	−	7	5c	1+	8	8	3.7/3.8	70	0.4	14.5	85	105	31	2−	F1+C1+	Sph. OsFr+. FU 252.
2	8.3	7.8	538	9.6	+	68	15c	0	12	11	2.8/3.1	100	2.8	14.3	75	103	30	6−	C1+	Sph. FU 276.
3	11.1	10.9	394	5.9	+	17	11	0	6	u	3.3/2.9	100	u	12.9	92	104	32	5−	F2+C2+	Sph. OsFr+. FU 514.
4	10.0	16.9	501	20.0	+	25	10	2+	11	11	3.6/2.6	47	7.8	15.1	113	119	31	5−	—	Sph. OsFr+. FU 440. UE 15.
5	9.4	13.7	335	5.5	−	11	18c	3+	11	7	4.7/1.8	50	136	11.4	37	102	31	5−	F4+C1+	Sph. OsFr+. FU 249.
6	9.8	11.7	600	14.5	+	31	23c	0	3	u	3.0/2.5	100	u	15.4	102	100	33	10−	—	OsFr±. Clotting defect.
7	10.4	7.2	720	2.3	−	6	7	0	10	11	3.3/2.8	90	u	9.5	86	90	30	3−	F1+C1+	———
8	9.8	9.0	520	14.4	+	20	u	0	6	u	3.8/3.3	76	u	15.1	90	101	32	u	—	FE 452. UE 39.
9	11.4	4.8	500	16.8	−	24	40c	2+	14	21	5.4/2.2	100	80	19.1	95	114	31	6−	F4+C3+	FE 300.
10	11.1	8.4	984	1.5	+	34	30c	0	10	8	2.1/1.9	90	u	15.8	106	96	32	1−	F3+C1+	———
11	10.1	13.2	250	2.6	−	29	15	1+	4	14	4.6/3.1	94	u	5.1	77	119	32	6−	F1+C2+	Sph. OsFr+. FU 207.
12	11.2	7.8	343	21.0	−	19	17c	0	6	u	4.2/2.7	37	u	13.6	87	u	u	2−	F5+C3+	Nu RBC.
13	11.9	7.0	440	1.4	−	20	7	3+	8	17	4.2/3.9	95	40	14.5	110	u	u	4−	F1+C3+	FE 380.
14	11.7	5.2	354	14.3	−	25	31c	2+	8	u	4.2/2.7	75	1.1	5.0	58	100	31	2−	—	FE 205.
15	12.2	u	584	2.2	+	19	27	0	6	7	4.9/2.2	95	24	11.5	80	91	34	3−	F2+C2+	FU 137.
16	10.8	u	530	43.0	−	25	21c	1+	8	u	3.2/2.6	64	u	6.7	116	u	u	u	F2+C3+	Nu RBC.
17	14.8	u	560	2.2	+	9	26	0	6	16	u	60	u	7.8	20	u	u	u	ND	———
18	10.4	4.9	1117	u	+	11	13	0	5	u	u	100	u	7.1	30	u	u	2−	F3+C1+	OsFr+.
19	11.2	8.9	406	8.0	−	26	36c	3+	6	9	2.2/3.5	58	125	11.5	68	117	31	3−	F2+C4+	Sph. OsFr−. FU 204. UA 752.
20	11.0	7.3	361	4.6	+	23	27c	0	5	u	3.2/4.2	100	70	13.6	u	112	34	u	F1+C3+	Sph. OsFr+. FE 449. UA 303.

* F, fatty infiltration. C, cirrhosis. 1+, minimal. 2+, mild. 3+, moderate. 4+, severe. 5+, very severe. ND, nondiagnostic. u, unknown.

last column of table 11. The hepatic tests were as a rule most abnormal during the first or second week following admission, and improved rapidly thereafter.

In addition to the hepatic tests, data on the blood urea nitrogen, serum amylase and fasting blood sugar were available in some patients. The average blood urea nitrogen in 14 patients was 7 mg. per 100 ml., with a range of 3 to 12 mg. per 100 ml. The average serum amylase among six patients was 98 units per 100 ml., with a range of 68 to 144 units per 100 ml. In the last two patients, studied only recently, several urinary amylase studies [7] (normal limit, 300 units per hour) were obtained. In each, abnormal values were observed (752 units per hour in case 19 and 305 units per hour in case 20). Fasting blood sugars were obtained on 11 patients. The values ranged from 65 to 137 mg. per 100 ml., with an average of 92 mg. per 100 ml.

TABLE 12

Maximal Abnormality of Hepatic Tests

Measure	N	Values Observed		Week of Abnormality	
		Average	Range	Average	Range
AP	20	23	7–68	2	1–5
BSP	19	20	5–40	1	1–5
CF	20	1+	0–3+	1	1–4
TT	20	8	3–14	2	1–3
ZT	12	12	7–21	2	1–5
$\frac{A}{G}$	18	$\frac{3.7}{2.9}$	$\frac{2.1–5.4}{1.8–4.2}$	1	1–3
PC	20	80	37–100	1	1–2

Pathology: Liver biopsies were obtained in 16 of the 20 patients. The results are listed for each patient in table 11. Fatty infiltration was evident in 14, the involvement covering all degrees of severity. Portal cirrhosis was present in 15, being minimal in six, mild in three, moderate in five and severe in one. The one patient with severe cirrhosis had a repeat biopsy within four weeks which showed striking improvement and could no longer be classified as severe. One biopsy was abnormal but nondiagnostic. It was obtained late in a very mildly ill patient.

In addition to those already presented, the following six biopsies (figure 4) illustrate the pathologic changes observed. All of these biopsies were obtained during the second week after hospitalization, though in two instances this was long after improvement had begun.

The first biopsy (figure 4 A) from case 11 shows early portal cirrhosis with minimal residual of fatty infiltration in an azocarmine-stained section. The patient had already improved significantly by admission. He was only slightly jaundiced, and his bromsulfalein retention was 15%.

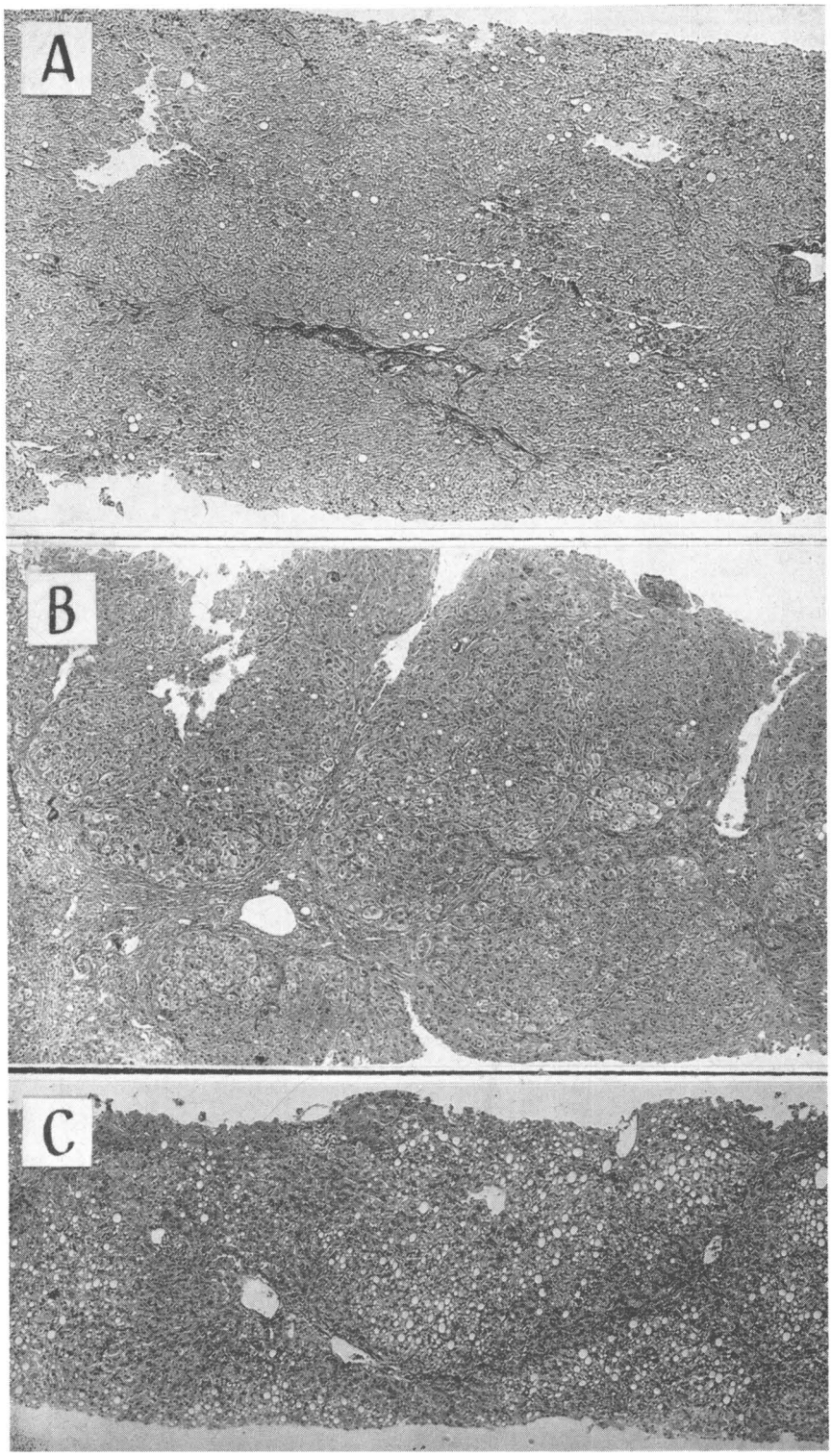

FIG. 4. Illustrative liver biopsies (× 50) obtained from cases 11 (A), 13 (B), and 18 (C).

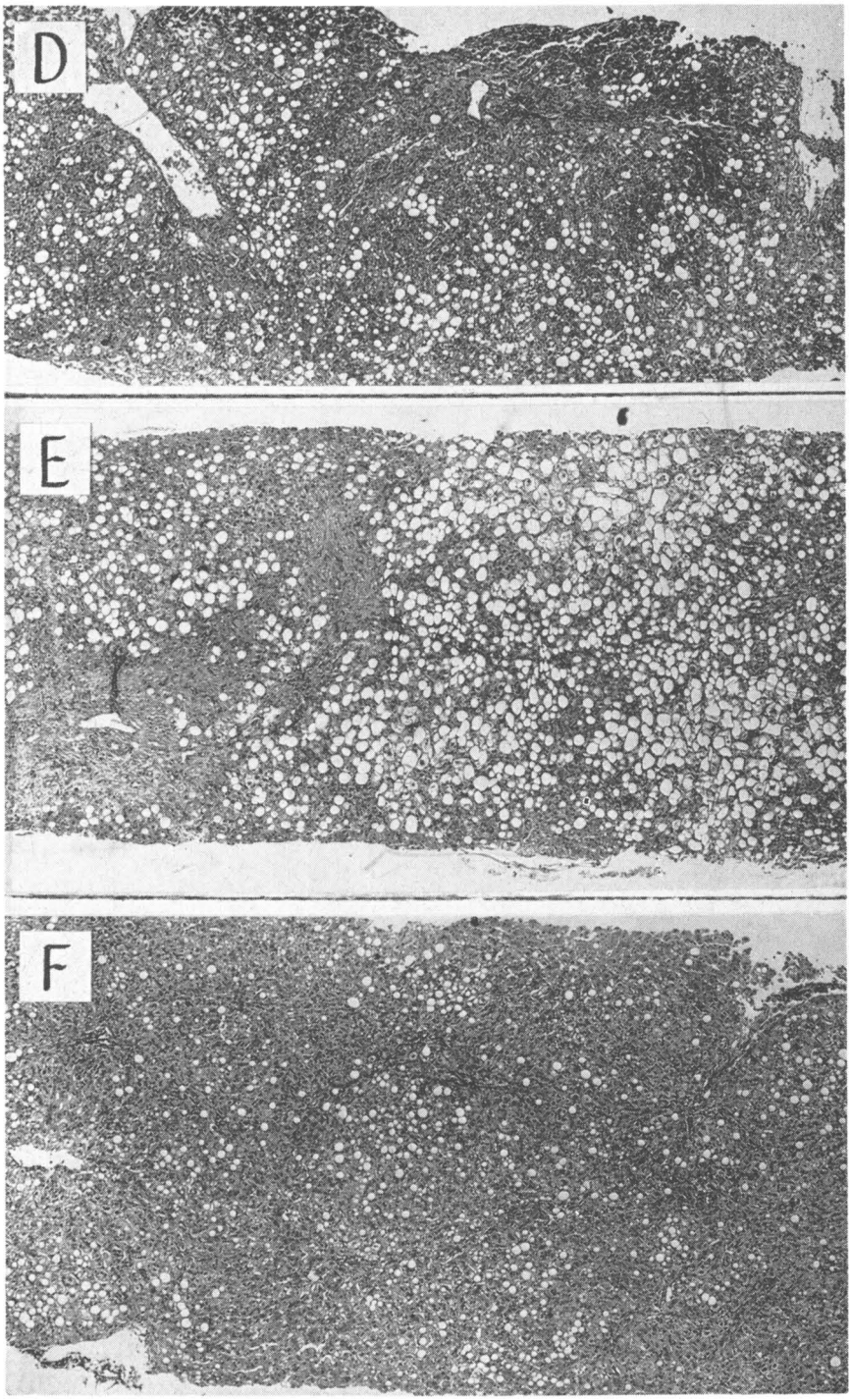

FIG. 4 (continued). Illustrative liver biopsies (× 50) obtained from cases 9 (D), 12 (E), and 10 (F).

The second biopsy (figure 4 B) from case 13 shows moderate portal cirrhosis with minimal residuals of fatty infiltration. This patient's jaundice had receded entirely by the time of admission, and his bromsulfalein retention was 7%. His cholesterol decreased from 440 to 229 mg. per 100 ml. in six weeks, while his bilirubin went from 1.4 to 0.6 mg. per 100 ml. and his cephalin flocculation from 3 plus to zero.

The third biopsy (figure 4 C) from case 18 shows moderate fatty infiltration with the earliest evidences of cirrhosis. The patient's dysfunction was mild; however, his lipemia was intense, the total lipid being 12,106 mg. per 100 ml. In one week it was down to 1,148 mg. per 100 ml.

The fourth biopsy (figure 4 D) from case 9 shows moderate fatty cirrhosis. The hepatic tests of this patient were moderately abnormal, and the recession of his jaundice and dysfunction was a little slower than usual.

TABLE 13

Maximal Abnormality of Hematologic Measurements

Measure	N	Values Observed		Week of Abnormality	
		Average	Range	Average	Range
WBC	20	11.9	5.0–15.4	3	1–5
SR	20	80	20–116	2	1–5
MCV	15	105	90–119	2	1–4
MCC	15	32	30–34	2	1–4

StG − in all patients tested.
OsFr + in 7 of 9 patients.
Plt rise striking in 5 of 6 patients.
FU or FE abnormal or borderline in 9 of 13 patients.
UU or UE disproportionately elevated in 8 of 11 patients.
BM: Over 50% normoblasts in 6 of 8 patients.

His serum bilirubin dropped from 16.8 to 1.4 mg. per 100 ml. in five weeks, while his cholesterol went from 500 to 269 mg. per 100 ml. His hemoglobin dropped after admission from 15.7 to 12.1 gm. per 100 ml. before the biopsy.

The fifth biopsy (figure 4 E) from case 12 shows moderate cirrhosis with very severe fatty changes. The patient's dysfunction was also moderate. His bilirubin on admission was 21 mg. per 100 ml., dropping to 1.3 mg. per 100 ml. in seven weeks.

The last biopsy (figure 4 F) from case 10 shows moderate fatty infiltration with possibly minimal cirrhosis. The patient was only slightly jaundiced and swollen with fluid. His serum was very milky, and proteins were low. His bromsulfalein retention dropped from 30% to 5% in three weeks, during which time his cholesterol went from 984 to 306 mg. per 100 ml., and albumin from 2.1 to 3.7 gm. per 100 ml. His appetite was voracious.

Hematologic Abnormalities: The maximal abnormalities observed with various hematologic measurements are listed for each individual in

table 11 and summarized for the entire group in table 13. The average maximal white count was 11.9 thousand per cubic millimeter; sedimentation rate, 80 mm. per hour; MCV, 105 cubic microns; MCC, 32%. These abnormalities occurred in the second or third week as a rule. Stool guaiac examinations were negative in all patients tested. An average of four stools was examined per patient because of the uniform concern among the ward physicians that the anemia might be due to gastrointestinal bleeding. Osmotic fragility studies were performed in nine patients, in seven of whom the test was abnormal. Platelets were observed to rise strikingly following an initial depression in five of six patients in whom serial values were obtained. Fecal urobilinogen or fecal Ehrlich values were borderline or abnormal in nine of 13 patients in whom valid determinations were made. In only one of the patients were the stool collections made at an optimal time in relation to the course of the illness and the anemia. The values obtained must therefore be taken as minimal estimates of the abnormality actually existing. Urine urobilinogen or urine Ehrlich values were disproportionately elevated initially in eight of 11 patients in whom such determinations were obtained. The values decreased precipitously as the illness improved. The disproportionate abnormality is most likely a reflection of the coexistence of liver dysfunction and increased red cell destruction, since patients with much more liver disease and dysfunction than was shown by these patients do not excrete urobilinogen in such large quantities. Bone marrow studies were obtained in eight patients, six of whom had marked erythroid hyperplasia with over 50% normoblasts.

Abnormalities of Defining Measurements: These are the blood hemoglobin, reticulocyte count, serum cholesterol and serum bilirubin, the four measurements which reflect the essential features of the syndrome. The value of each measure for each individual is given in the first four columns of table 11. The maximal abnormality observed with each of these measures is summarized for the group in table 14. The average maximal hemoglobin abnormality was 10.3 gm. per 100 ml. The lowest hemoglobin was 8.3 gm. per 100 ml. In 11 of 20 patients the hemoglobin decreased after admission by at least 1 gm. per 100 ml. The average decrease was 2.9 gm. per 100 ml. The average maximal reticulocyte count was 9.0%. The average maximal total serum cholesterol was 535 mg. per 100 ml. The highest value observed was 1,117 mg. per 100 ml. The average maximal total serum bilirubin concentration was 10.1 mg. per 100 ml. The highest single value was 43.0 mg. per 100 ml. The jaundice was a regurgitation-type jaundice, the average bilirubin ratio being 57%.

These maximal abnormalities occurred in the first or second week as a rule. Improvement in the jaundice was very rapid, near-normal values being recorded on the average by the third week. Correspondingly, near-normal values for the serum cholesterol and reticulocyte counts were recorded on the average by the sixth week. The response of the anemia was

TABLE 14
Maximal Abnormality of Defining Measurements

Measure	N	Values Observed		Week of Abnormality		Week Values Nearly Normal	
		Average	Range	Average	Range	Average	Range
Hb	20	10.3	8.3–14.8	2	1–4	>5	1–>12
RTC	17	9.0	4.8–16.9	2	1–4	6	4–9
TC	20	535	250–1117	1	1–2	6	2–20
TB	19	10.1	1.4–43.0	1	1–2	3	0–7

Initial serum lipemic in 50%.

variable, the average interval to near-normal hemoglobin values being over five weeks.

The initial serum was lipemic in 50% of the cases. The true incidence of frank lipemia is undoubtedly underestimated, since patients were often not seen at the peak of their illness, and abnormalities of serum lipids were not suspected and so were recognized only inadvertently.

Diagnoses Entertained: The various diagnoses recorded in the charts, either tentatively or finally, are listed in table 15. The diagnosis of portal cirrhosis was generally arrived at following a liver biopsy, being suspected only one-half as often at the initial examination. The variety of diseases included among the tentative diagnoses indicates the confusing aspects of the illness. The elevated cholesterol values in association with some elevation of alkaline phosphatase, slight or absent abnormality of the cephalin flocculation, and the presence of right upper quadrant or epigastric pain and tenderness led to the diagnosis of obstructive jaundice seven times. In one instance a surgical exploration was undertaken despite rapid subsidence of the illness. In the other cases the very rapid evolution and subsidence of the illness precluded surgical intervention and led to a change in diagnosis.

Viral hepatitis was recorded as a diagnosis seven times. In those instances where this was the final diagnosis, it was arrived at by exclusion

TABLE 15
Tentative or Final Diagnoses Recorded

Diagnosis	Times Recorded
Portal cirrhosis	13
Cholangiolitic cirrhosis	2
C.D. obstruction	7
Viral hepatitis	7
Fatty liver	1
Liver disease, c.u.*	4
Acute pancreatitis	4
Anemia, c.u.	4
Hemolytic anemia, c.u.	6
Hyperlipemia or hypercholesterolemia, c.u.	7
Delirium tremens	4
Nephritis	1

* c.u., cause unknown.

rather than on the strength of positive findings. Acute pancreatitis was suspected six times, though recorded prominently as an initial diagnosis only four times. In each instance the diagnosis was discarded because the serum amylase was normal. In the last two patients studied recently, pancreatitis was not suspected clinically, though mild epigastric pain was present. However, urinary amylases were ordered because of a suspicion that these patients in general might have subclinical or atypical pancreatitis with release of enzymes. In both instances the urinary amylase was slightly abnormal.

The anemia was recognized in every patient but one whose hemoglobin was practically normal; however, it was given sufficient consideration to be recorded as one of the diagnoses in only 10 patients. In six of these hemolysis was strongly suspected, though its etiology was invariably perplexing. Hyperlipemia or hypercholesterolemia was recognized as a prominent part of the patient's illness in seven instances; however, its existence was likewise invariably perplexing. Fatty liver, which is probably of preeminent importance in the syndrome, was recorded as a clinical diagnosis only once.

Comment

A rise in serum lipids, including cholesterol, phospholipids and neutral fat, has been recognized in alcoholic fatty liver, though it has usually been considered a slight or at most a moderate abnormality.[8] Documentation of such changes in the published literature has been sparse, and it is not generally appreciated how striking the rise in cholesterol may be, or how frequently frank lipemia will be found if looked for early enough in the course of the illness. In 1918 Feigl [2] made a careful study of the problem, observing some very marked increases in all fractions of the blood lipids in severe acute alcoholism. He noted visible lipemia in one fifth and a rise in blood lipid concentration in two thirds of 30 chronic alcoholics. Lipemia was present in at least one half of my patients, and cholesterol elevation above 500 mg. per 100 ml. was observed in three fifths. These are probably minimal figures, since the observations were usually not made at an optimal time in the course of the patient's illness. Once the patient stops drinking, improvement begins, and proceeds apace. One cannot avoid the delay, usually one to four weeks, due to the patient's failure to seek prompt medical attention. However, one can secure blood for lipid analysis promptly after the initial examination of the patient, and thereby improve on the observations of this report. It is evident from the sequential data of cases 1, 2, 3, 4 and 5 that a delay of only one or two weeks alters the blood findings significantly.

The rise in serum cholesterol, and presumably the other serum lipids, appears to be less extensive the more chronic and the more marked the cirrhotic changes on liver biopsy, and the more severe the dysfunction. Conversely, the more acute the episode and the less evident the cirrhotic changes,

the more intense the lipemia and the more rapid the improvement after hospitalization. This phenomenon is particularly well illustrated by case 5, in whom an episode of jaundice associated with extensive functional as well as anatomic abnormalities (admission of June 21, 1950) was not accompanied by hypercholesterolemia and was slow to improve, whereas one prior and four subsequent episodes associated with milder functional and anatomic alterations were characterized by hypercholesterolemia and rapid improvement.

At present I can only speculate as to the mechanisms involved in the syndrome described herein. The hyperlipemia seems clearly related to an episode of fatty infiltration of the liver. However, one cannot say with assurance whether the lipemia first occurs before or after the beginning of the healing process. Increased mobilization of lipid, whether on the way to or from the liver, is probably the primary etiologic factor. From a consideration of the sequence of serum lipid changes in relation to the clinical histories and physical findings of the patients presented, it seems most likely that the lipemia follows the release of lipid from the fatty liver during the early phase of the healing process.

Another possible etiologic factor is decreased clearing of serum lipids. Two substances of known importance in the clearing action are heparin or a heparin-like compound, and serum albumin. Both could be deficient in these circumstances, and in fact serum albumin was markedly diminished in cases 10 and 19 at the time of its measurement. However, one can hardly consider this a sufficient explanation for the lipemia, since cirrhotics with far more dysfunction and hypoalbuminemia than these patients demonstrated do not show elevated lipids.

Deficiency of nutritional factors very likely contributed to the anemia observed in these patients. However, it seems to me that deficiency alone cannot account for the findings. Hemolytic anemia has been known for a long time [4, 9] to occur in chronic well developed cirrhosis with splenomegaly, though until the recent studies of cell survival [1, 5, 6] it had been considered uncommon. We still do not know its exact incidence, though it is much more frequent than was formerly believed. The hemolytic anemia in these cirrhotics has generally been relatively persistent and associated with prolonged moderate or severe hepatic dysfunction or decompensation. It has not been associated with hyperlipemia or hypercholesterolemia.

The hemolytic anemia in the syndrome of this report is of brief duration, not associated with prominent or persistent hepatic dysfunction, not associated with a prominent spleen, but associated with transient hyperlipemia or hypercholesterolemia. The red blood cells are perhaps altered by an abnormal lipid, becoming fragile. The logical lipid to suspect is lysolecithin. This potent hemolytic agent differs from lecithin, the predominant phospholipid in serum, only in the replacement of one fatty acid by a hydroxyl group. The conversion can be accomplished by pancreatic lipase, which also, in-

cidentally, has a clearing action.[3] Since minute amounts of lysolecithin will affect red cells significantly, one should need only a trace of circulating lipase in the presence of elevated lipids to produce significant hemolysis. Though obvious pancreatitis with amylasemia was not established in these patients, and lipase measurements have not been made under these circumstances, it is tempting to suggest this mechanism in the alcoholic who comes in with fatty liver, hyperlipemia and upper abdominal pain.

Summary

Twenty patients have been observed who exhibited an interesting group of manifestations heretofore not recognized as a distinct syndrome with a predictable course. The essential clinical features are jaundice, hyperlipemia or hypercholesterolemia, and hemolytic anemia. The illness follows excessive drinking, and improves rapidly once the drinking stops, the hyperbilirubinemia and hypercholesterolemia receding over a few weeks. Hemolysis is generally slight and of short duration. The anemia is mild or moderate and does not persist. Hepatic function is usually mildly disturbed and improves rapidly. The anatomic abnormality on liver biopsy is fatty infiltration and minimal to moderate portal cirrhosis.

The patients were generally diagnostic problems until the syndrome was defined. Obstructive jaundice was often suspected initially, and one patient was explored surgically. The anemia was always recognized; however, hemolysis was usually not suspected. Repeated examinations of stools for occult blood were made, with negative findings. In one instance the hemolytic anemia was extensively studied without recognition of the related alterations in blood lipids or in hepatic function. The mechanism of the hemolytic anemia is unknown; however, I suspect that the hemolysis is related to the hyperlipemia, and that an abnormal lipid may be present.

Summario in Interlingua

Esseva observate 20 patientes exhibiente un gruppo interessante de manifestationes que ha non previemente essite recognoscite como un syndrome distincte a curso predicibile. Le aspectos clinic essential es jalnessa, hyperlipemia o hypercholesterolemia, e anemia hemolytic. Le morbo seque excessos alcoholic e se meliora rapidemente si tosto que le uso de alcohol es arrestate. Le hyperbilirubinemia e le hypercholesterolemia recede alora in le curso de alicun septimanas. Le hemolysis es generalmente leve e de breve duration. Le anemia es leve o moderate e non persistente. Le function hepatic es levemente disturbate in le majoritate del casos e se meliora rapidemente. Le anormalitate anatomic trovate in biopsias hepatic consiste de infiltration grasse con leve o moderate grados de cirrhosis portal.

Ante le definition del syndrome, le patientes esseva generalmente problemas diagnostic. Jalnessa obstructive esseva frequentemente suspicite al initio, e in un caso un exploration chirurgic esseva effectuate. Le anemia esseva recognoscite in omne casos, sed le hemolyse remaneva generalmente non suspicite. Repetite examines de feces pro le presentia de sanguine occulte esseva effectuate con constatationes negative. In un caso le anemia hemolytic esseva studiate extensemente sin recognition del re-

lationate alterationes del lipidos del sanguine o del function hepatic. Le mechanismo del anemia hemolytic es incognoscite. Le autor stipula le possibilitate que le hemolyse es relationate al hyperlipemia e que un lipido de natura anormal es presente.

BIBLIOGRAPHY

1. Chaplin, H., and Mollison, P. L.: Red cell life-span in nephritis and in hepatic cirrhosis, Clin. Sc. **12**: 351, 1953.
2. Feigl, J.: Neue Untersuchungen zur Chemie des Blutes bei akuter Alkoholintoxikation und bei chronischen Alkoholismus mit besonderer Berucksichtigung der Fette und Lipoide, Biochem. Ztschr. **92**: 282, 1918.
3. Hollett, C., and Meng, H. C.: Comparison of fat emulsion clearing activities of post-heparin plasma and pancreatic lipase, Am. J. Physiol. **184**: 428, 1956.
4. Hyman, G. H., and Southworth, H.: Hemolytic anemia associated with liver disease, Am. J. M. Sc. **221**: 448, 1951.
5. Jandl, J.: The anemia of liver disease: observations on its mechanism, J. Clin. Investigation **34**: 390, 1955.
6. Jones, P. N., Weinstein, I. M., Ettinger, R. H., and Capps, R. B.: Decreased red cell survival associated with liver disease. Use of radioactive sodium chromate in measurement of red cell survival, Arch. Int. Med. **95**: 93, 1955.
7. Saxon, E. I., Hinkley, W. C., Vogel, W. C., and Zieve, L.: Comparative value of serum and urinary amylase in the diagnosis of acute pancreatitis, Arch. Int. Med. **99**: 607, 1957.
8. Thannhauser, S. J.: Serum lipids and their value in diagnosis, New England J. Med. **237**: 515, 1947.
9. Watson, C. J.: Studies of urobilinogen. III. The per diem excretion of urobilinogen in common forms of jaundice and disease of the liver, Arch. Int. Med. **59**: 206, 1937.
10. Zieve, L., Hill, E., Nesbitt, S., and Zieve, B.: The incidence of residuals of viral hepatitis, Gastroenterology **25**: 495, 1953.
11. Zieve, L., Hanson, M., and Hill, E.: Studies of liver function tests. II. Derivation of a correction allowing use of the bromsulfalein test in jaundiced patients, J. Lab. and Clin. Med. **37**: 40, 1951.