Acute Transient Hyperlipemia Due to Hepatopancreatic Damage in Chronic Alcoholics (Zieve's Syndrome)*

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IN 1958 Zieve [1] described a syndrome consisting of transient hyperlipemia, jaundice and hemolytic anemia, associated with alcoholic fatty liver and cirrhosis. Clinically, these patients were characterized by general malaise with occasional nausea and vomiting, anorexia, low grade fever and pain in the upper part of the abdomen which was almost always present, varying in intensity, changing in location, and described as cramps or dull pressure. The laboratory findings showed moderate anemia, elevated serum cholesterol levels up to a 1,000 mg. per cent and, in 50 per cent of the patients, cloudy or milky serum indicative of hyperlipemia which was, however, not measured by laboratory tests. Biopsy specimens of the liver showed varying degrees of cirrhosis and fatty infiltration, with only minimal or mild changes in 50 per cent of the specimens. The stools were, in all patients, negative for blood by the guaiac test. Examination of the bone marrow showed marked erythroid hyperplasia with over 50 per cent of normoblasts in six patients, and, in one, large foam cells. In seven patients osmotic fragility test results were abnormal but no erythrocyte survival studies were performed. The reticulocytes were increased in all patients. The serum amylase was measured in six patients and was found to be within normal limits. There was rapid improvement of the patients with symptomatic treatment only, and return of the laboratory findings to normal values after about four to six weeks. The patients were all chronic alcoholics and some had had several previous admissions for alcoholism, but without the symptoms described. Zieve considered that the hyperlipemia and jaundice were secondary to fatty liver and cirrhosis, whereas the hemolytic anemia could have been caused by an abnormal lipid in serum, probably a lysolecithin.

This syndrome does not seem to be rare. In our hospital, six cases were found during a period of two years, all similar to those described by Zieve.

CASE REPORTS

CASE 1. R. J., a thirty-seven year old Negro man, had had the usual childhood diseases. He was in good health until 1944, when he was treated symptomatically for a goiter, and the next year a thyroidectomy was performed. There was a history of chronic alcoholism since 1940. He had been admitted to local hospitals several times for chronic alcoholism. During his admissions in 1957 and 1958 he had complained of pain in the upper part of the abdomen. Infection of the urinary tract was suspected but work-up failed to reveal any renal pathologic disorder. In October 1958 he again experienced pain in the upper part of the abdomen, moving from the left to the upper right quadrant and sometimes radiating to his back. The pain was dull, changing in intensity, independent of food intake and sometimes accompanied by nausea and vomiting. The stools were regular and of normal color. He noticed, however, that his urine became dark but he had no itching of the skin. During the last three months prior to admission he lost about 20 pounds of weight because of poor appetite. He stopped drinking in October 1958 because of pain in the upper part of the abdomen but there was no improvement in his general condition. He was admitted to this hospital on January 19, 1959, primarily because of continued abdominal pain. He had not received any medication for the preceding three months.

The physical findings on admission were essentially within normal limits except for slight yellowish discoloration of the scleras and tenderness in the right and upper left quadrant. The liver was not enlarged. There was no lymphadenopathy. A scar due to a

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TABLE I

ELECTROPHORETIC PATTERN OF SERUM PROTEINS IN CASES I, III, V AND VI

Case No.	Date	Total Proteins (gm. %)	Albumin (%)	Globulin (%)			
				$Alpha_1$	$Alpha_2$	Beta	Gamma
Normal	*	6.4–7.8	53–59	4.3–5.5	8.3–10.7	10.8–13.4	14.8–20.2
I	1/22/59	6.4	43	6	6	15	30
III	3/28/60	7.8	42	6	8	21	23
V	2/23/61	8.2	59	3	10	13	15
VI	2/23/61	8.2	55	3	11	13	17

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TABLE II

FRACTIONAL SERUM LIPIDS IN SIX CASES

Case No.	Date	Neutral Fat (mg. %)	Total Lipid Fatty Acids (mg. %)	Total Phospho-lipids (mg. %)	Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Cholesterol Esters (mg. %)	Cholesterol Esters (%)
Normal	*	0–150	200–450	150–250	150–260	40–70	105–195	70–75
I	2/ 3/59	20	860	615	1,110	525	585	53
	3/18/59	134	460	265	291	91	200	68
II	2/ 2/60	3,220	4,200	1,130	775	512	265	34
III	3/18/60	4,450	4,950	425	636	350	286	45
	4/12/60	243	615	316	308	93	215	70
IV	5/11/60	864	1,031	368	229	71	158	69
V	2/ 1/61	10	923	1,400	648	590	58	9
VI	2/23/61	1,303	1,708	308	400	129	271	68

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partial thyroidectomy was noted; the remaining thyroid gland was not enlarged. The laboratory findings on admission were characteristic of Zieve's syndrome: hemoglobin 10.0 gm. per cent, hematocrit 33 per cent, serum total bilirubin 2.4 mg. per cent, alkaline phosphatase 5.9 units, cephalin flocculation test 1 plus in twenty-four and 2 plus in forty-eight hours, serum amylase 5 units (normal: 1 to 12 units). The serum was milky and the serum total cholesterol was 720 mg. per cent. For other laboratory findings see Tables I and II.

For the first two weeks, we considered as diagnostic possibilities decompensated liver cirrhosis with jaundice, viral hepatitis, common duct obstruction, hemolytic anemia or hypersplenism or chronic bleeding (esophageal varices, hemorrhagic gastritis or peptic ulcer) and acute pancreatitis combined with hyperlipemia and liver cirrhosis. However, results of the gastrointestinal and gallbladder series were reported as negative; also, the serum amylase, repeated twice, was within normal limits making the diagnosis of acute pancreatitis less probable. Bone marrow examination showed slight erythroid hyperplasia, but no evidence of megaloblasts. There were numerous large histiocytes containing many vacuoles filled with a substance which was probably not a neutral fat (negative with Sudan IV stain) and not a carbohydrate (negative with periodic acid-Schiff stain). With the polaroid microscope, the substance was found to be non-refractile, ruling out cholesterol. In view of the elevated level of serum phospholipids, it was considered that the substance might be a phospholipid. In addition to the histiocytes, there was a definite increase in the number of eosinophils, all mature.

A red cell survival test with Cr^{51}, carried out four weeks after admission, showed a survival time of twenty-two days (normal: twenty-eight to thirty-five days), indicating hemolysis. A study of the serum lipids revealed the total cholesterol increased to 1,110 mg. per cent and the phospholipids to 615 mg. per cent. The total lipid fatty acids were also elevated to

860 mg. per cent and the neutral fats were very low, only 20 mg. per cent (see Table II). Repeated determination of the serum lipids six weeks later showed essentially normal values. Because of a history of thyroidectomy in 1945, a protein-bound iodine test was performed but it was inconclusive. The red cell uptake of I^{131}-labeled L-triiodothyronin was 15.1 per cent (normal 9 to 17 per cent). An electrocardiogram, a Master two-step exercise test, and a ballistocardiogram were found to be within normal limits.

The patient's condition remained essentially unchanged for the first six weeks after admission. Then the hemoglobin and hematocrit started to rise slowly and the serum bilirubin returned to normal values; three months elapsed before the patient recovered completely, and all laboratory tests returned to within nomal limits. The hematocrit rose to 44 per cent and the serum total cholesterol fell to 190 mg. per cent on a regular diet. The patient did not receive any medication for his anemia (e.g., iron or vitamin B_{12} preparations). He was given a low fat diet at first, later a regular diet. The patient remained asymptomatic for more than a year, the time he has been followed in our clinic.

CASE II. F. J., a fifty year old Negro man, had had the usual childhood diseases. He was in good health until 1953 when he was treated for a duodenal ulcer. He was admitted to this hospital in 1956, when a gastrointestinal series showed the presence of a duodenal ulcer, with moderate hypermotility of the small intestines. He was also treated for recurrent pancreatitis because of repeated episodes of pain in the upper part of the abdomen. A gallbladder series at that time showed a functioning gallbladder and no calculi. The patient was asymptomatic from 1956 until November 1959, when he again started to have episodes of crampy epigastric pain which were independent of food intake, not well localized, and unaccompanied by nausea or vomiting. There was also general weakness, easy fatigue and lack of appetite, with loss of 25 pounds in weight during the preceding three months. The stools were normal in number, color and appearance. The patient had been drinking about a half pint of whiskey apparently only on weekends, until November 1959, when he stopped drinking because of epigastric pain. He had not been drinking since but, despite this, there had been no improvement in his condition. He had to stop working and, in March 1960, was admitted to this hospital.

The physical findings on admission were essentially within normal limits, except for slight yellowish discoloration of the scleras. The liver was not enlarged. There was no lymphadenopathy. The laboratory findings on admission were suggestive of Zieve's syndrome: severe anemia, with hemoglobin 7.0 gm. per cent and hematocrit 25 per cent, serum total bilirubin 2.0 mg. per cent, alkaline phosphatase 16 units, and cephalin flocculation test 0/0 in twenty-four and forty-eight hours. The serum was very milky and the serum total cholesterol was 832 mg. per cent. The serum amylase was 2 units (normal: 1 to 12 units). For other laboratory findings see Tables I and II.

As in the previous case, the patient was treated symptomatically with antacids and anticholinergics in addition to a bland diet. His condition remained unchanged for about five to six weeks, when he started slowly to improve. The hemoglobin rose to 12 gm. per cent and the hematocrit to 38 per cent, the serum total bilirubin fell to 0.6 mg. per cent. He did not receive any blood transfusions, iron or vitamin B_{12} preparations. His appetite improved and the pain in the upper part of the abdomen decreased considerably. The serum, which showed all the lipid fractions to be greatly increased on admission (see Table II) cleared almost completely in about ten days, but the serum cholesterol did not return to normal for about five weeks. A red cell survival test with Cr^{51} carried out about two weeks after admission showed the survival time to be 19.3 days (normal: twenty-eight to thirty-five days), indicating hemolysis. The hematocrit rose rapidly in the nineteen days during the test, from 26.8 per cent on February 10, when the test was started, to 39.5 per cent on February 29. A biopsy specimen of the bone marrow showed only moderate erythroid hyperplasia. No giant histiocytes with lipid-filled vacuoles were found, probably because the bone marrow was examined when the serum lipids had declined.

The patient was followed up as an outpatient and remained asymptomatic for more than six months, except for occasional epigastric discomfort and mild pain in both legs, which subsided after several months without treatment.

CASE III. A. A., a forty-one year old white man, had had the usual childhood diseases. There were numerous previous admissions to this hospital for acute and chronic alcoholism, liver cirrhosis, gastritis, duodenal ulcer and anxiety reaction. For the past three years he had consumed about 2 quarts of wine daily, with a few glasses of beer occasionally, but no whiskey. About six months prior to admission the patient noticed that his abdomen was slowly becoming larger. At the same time he started to have episodes of pain in the upper part of the abdomen not accompanied by nausea or vomiting, lasting ten to fifteen minutes and recurring from several times a day to only once in two to three days. The pain was crampy or dull, changing in location but always in the upper part of the abdomen, and independent of food intake. His appetite became poor. He ate very little but continued to drink his usual amounts of wine. Because of tiredness and general weakness, he had to stop working and, when his abdomen further increased in size, he decided to request admission to this hospital.

On admission there was marked distention of the abdomen with free fluid in the abdominal cavity and an enlarged liver, with yellowish discoloration of the scleras and of the skin. No lymphadenopathy was noted. The laboratory findings were suggestive of Zieve's syndrome, although no anemia was present. The hematocrit was 40 per cent and the hemoglobin was 15.3 gm. per cent, but a red cell survival test with Cr^{51} showed a survival time of only 21.3 days (normal: twenty-eight to thirty-five days), indicating definite hemolysis. The serum was very milky. The serum total cholesterol was 804 mg. per cent, serum total bilirubin 4.6 mg. per cent, alkaline phosphatase 5.3 units, cephalin flocculation test 2 plus/4 plus in twenty-four and forty-eight hours. The serum amylase was normal. For the remaining laboratory findings see Tables I and II.

The patient was given a high protein, high carbohydrate, low fat diet, in addition to large doses of vitamin B complex. Diuretics were given but with only very moderate response until the mercurials were combined with hydrochlorothiazide and methyl prednisolone. The jaundice cleared completely after about four weeks and the bromsulfalein retention declined from 44 per cent on admission to 8 per cent. The serum which on admission contained greatly increased neutral fats and total lipid fatty acids (see Table II) cleared completely after four weeks, when a repeat serum lipid determination showed almost normal values. Bone marrow examination was within normal limits but showed one large histiocyte with vacuoles containing lipid, indicating a subsiding hyperlipemia. The laboratory findings remained within normal limits in the next two months and the patient was discharged home asymptomatic.

CASE IV. F. J., a forty-three year old white man, was admitted to the hospital because of pain in both lower extremities. He had had the usual childhood diseases, and an appendectomy in 1938. There was a history of chronic alcoholism (three to four cans of beer daily with excessive drinking during weekends). About four months before admission the patient started to have pain in both legs which became so severe that he had to be admitted to a hospital, where a bilateral sympathectomy was performed. The pain, however, reappeared after several weeks and the patient then requested admission to this hospital. He apparently had had no pain in the upper part of the abdomen or other gastrointestinal complaints for several months.

The physical findings were essentially within normal limits but the laboratory findings were suggestive of Zieve's syndrome. The serum neutral fats and total fatty acids were about twice the upper limits of normal (see Table II), and the serum total bilirubin was 1.8 mg. per cent. The serum amylase was 2 units (normal 2 to 12 units). The serum total cholesterol was within the limits of normal. The hemoglobin and hematocrit were, as in the previous case, normal. The patient left the hospital against advice and no follow-up studies could be obtained. However, the hyperlipemia on admission, which was probably of the acute and transient type as it decreased rapidly during the six days of the patient's hospitalization, and the slightly elevated serum total bilirubin suggested the diagnosis of Zieve's syndrome (stage of recovery or abortive form) as one of the possibilities.

CASE V. J. E., a thirty-three year old Negro man, had had the usual childhood diseases. He was in good health until 1948 when he experienced "stomach trouble" from which he recovered completely after being treated in a hospital for seventeen days. The patient was then in perfect health until about six weeks before admission when he started to complain of general weakness, anorexia with weight loss (about 20 pounds in six weeks), nausea and vomiting, and occasional crampy pain in the upper part of the abdomen. For the preceding week he noticed that his stools had become light colored, the urine appeared dark, and he had generalized itching. There was no history of bloody or tarry stools. In 1947 he had syphilis, treated with penicillin. For the preceding two years he had been drinking daily, about a half pint of whiskey and several beers.

The physical findings on admission were essentially within normal limits except for enlargement of the liver (about three fingers below the costal margin) and yellowish discoloration of the scleras. A chest roentgenogram was within normal limits and an electrocardiogram was normal. The laboratory findings on admission were hemoglobin 8.8 gm. per cent, hematocrit 28 per cent, serum total bilirubin 13.2 mg. per cent, alkaline phosphatase 33.5 units, cephalin flocculation test 0/1 plus in twenty-four and forty-eight hours, serum total cholesterol 684 mg. per cent. For other laboratory findings see Tables I and II.

The hospital course was similar to the previous cases. The patient's condition started to improve after a week of symptomatic treatment. After six days his serum total bilirubin decreased from 13.2 to 3.6 mg. per cent, the serum total cholesterol from 684 to 380 mg. per cent, and the alkaline phosphatase from 33.5 to 17.5 units. The hemoglobin and hematocrit, however, remained unchanged and the reticulocytes continued to be increased for several weeks, an indication that the hemolysis had not improved. The lipid studies showed a considerable increase of the phospholipids to 1,400 mg. per cent and a moderate increase of the total lipid fatty acids to 923 mg. per cent. The neutral fats were very low (less than 10 mg. per cent), which would explain why the serum was not cloudy or milky. Bone marrow examination showed, as in previous cases, only erythroid hyperplasia with normal progression of maturation. A red cell survival time with Cr^{51} showed a T/2 of twenty-

three days (normal twenty-eight to thirty-five days), indicating the presence of hemolysis.

The patient's condition improved slowly and after about six weeks his serum bilirubin, alkaline phosphatase and cholesterol returned to normal, the hemoglobin rose to 12.8 gm. per cent and the hematocrit to 40 per cent, with normal numbers of reticulocytes. The patient remained asymptomatic for the next several weeks and was discharged.

CASE VI. T. T., a thirty-nine year old Negro man, had had the usual childhood diseases. He was in good health until 1954 when he was treated in a hospital for hypertension for four weeks. When discharged he was not advised to take any medication or to return for a check-up. He was again well until November 1959, when he was admitted to a Veterans Hospital for treatment of liver cirrhosis and alcoholic neuropathy. He apparently recovered completely after four months of treatment and was asymptomatic until December 8, 1960 when he was admitted to our hospital in a state of intoxication and complaining of epigastric pain with nausea and vomiting. The patient had been drinking for the past five years, about a half pint of whiskey daily with additional beer or wine. He stopped drinking completely about two months before, after the onset of epigastric pain, but this did not give him any relief. He was treated for two months in the outpatient clinic for alcoholic gastritis with diet, antacids and vitamins, but there was no improvement in his epigastric pain. His appetite became poor and he lost about 20 pounds of weight in two months. The pain was dull, changing in intensity and location, independent of food intake, and never subsiding completely. He also complained of cramps in both lower extremities, especially at night when lying in bed, but he was able to walk without difficulty.

On February 16, 1961, the serum was found to be milky, indicating the presence of hyperlipemia, and the serum total cholesterol was elevated to 424 mg. per cent. The laboratory findings, the characteristic epigastric pain and the history of alcoholism suggested the diagnosis of Zieve's syndrome and the patient was admitted to the hospital for observation. The physical findings on admission were essentially within normal limits except for slight tenderness in the region of the gallbladder. The laboratory findings on admission showed slightly elevated serum total bilirubin (1.8 mg. per cent), cephalin flocculation test 2 plus/3 plus (twenty-four and forty-eight hours), thymol turbidity 21 units, serum amylase 5 units (normal: 2 to 12 units) and the serum lipids markedly elevated. (See Tables I and II.) The hemogram was normal on admission and no manifest anemia was present. Bone marrow examination showed hyperplasia, with predominance of erythroid elements, and normal progression of maturation, compatible with hemolytic anemia. However, a red cell survival time with Cr^{51} showed a T/2 of 29.6 days (normal: twenty-eight to thirty-five days), indicating that no hemolysis was present. This patient, the only one in our series, had an elevated fasting blood sugar (260 mg. per cent) on admission, with 4 plus of sugar and acetone in urine. There was no previous history of diabetes and eight months before admission, during a routine examination, the result of his urine analysis was negative for sugar and acetone.

The serum cleared completely after about ten days and the serum total cholesterol returned to normal levels after about four weeks. The abdominal pain subsided completely after several weeks and the patient has remained asymptomatic since. His mild diabetes was well under control with the administration of 0.5 gm. of tolbutamide daily. Later the administration of tolbutamide was discontinued, and fractional urines for glucose and acetone remained negative for the next five days and two fasting blood sugars were within normal limits. On the fifth day a glucose tolerance test was performed and it showed normal values (fasting blood sugar 111 mg. per cent; after administration of 100 gm. of glucose: first hour, 188 mg. per cent; second hour, 125 mg. per cent; third hour, 86 mg. per cent. The urine was 1 plus positive for sugar only after the first hour.) The result of the urine analysis remained negative for sugar and acetone and the fasting blood sugar was normal two weeks after the tolbutamide was discontinued. Evidently the diabetes was mild and transient, like his transient hyperlipemia. The patient remained asymptomatic for the next several weeks and was discharged.

COMMENTS

Hyperlipemia is the most prominent manifestation of Zieve's syndrome and is always present. The lipid levels remain high enough to cause a cloudy or milky serum [*2*] only for a very short time, usually from one to several days. Once the serum has cleared hyperlipemia may be overlooked unless one is alerted by finding elevated serum cholesterol levels with relatively low serum bilirubin values. This would tend to rule out hypercholesterolemia secondary to obstructive jaundice in which the bilirubin levels are usually higher. Determination of the serum lipids will confirm the diagnosis.

In only ten of the twenty patients described by Zieve was manifest hyperlipemia with cloudy or milky serum present. In six of the remaining ten patients without manifest hyperlipemia, the serum cholesterol was elevated (400 to 720 mg. per cent), and of these six patients only three had a slightly elevated serum total bilirubin (1.4 to 2.3 mg. per cent). In the remaining patients the hypercholesterolemia and high serum bilirubin levels could have been due

to obstructive jaundice. It seems that the serum neutral fats and fatty acids do not return to normal at the same time as the cholesterol. Therefore it is possible to find the serum cholesterol elevated for a short time after the serum has cleared. It is also possible to find a cloudy serum with normal cholesterol.

In the ten cases presented by Zieve which showed manifest hyperlipemia (cloudy or milky serum), no detailed lipid studies were obtained and only serum cholesterol values were recorded. In our own cases the values for neutral fats, total lipid fatty acids, total phospholipids and cholesterol are presented in Table II. In Cases II and III there was an increase in neutral fats and total lipid fatty acids to almost tenfold normal values. The serum total cholesterols were increased to 775 and 636 per cent, respectively, the phospholipids to 1,130 and 425 mg. per cent. In Case IV, the neutral fats and total fatty acids were only moderately increased (864 and 1,031 mg. per cent, respectively), the serum cholesterol was within normal limits, the phospholipids only slightly elevated (368 mg. per cent). Case V was quite similar to Case I, with low values for neutral fats and about the same values for total lipid fatty acids. However, the serum cholesterol in Case V was twice as high as in Case I and the phospholipids in Case I twice as high as in Case V.

Hemolytic anemia is another manifestation of Zieve's syndrome, almost always present. In some cases the hemoglobin and hematocrit values are normal because the hemopoietic activity of the bone marrow is greater than the loss of red cells due to hemolysis (compensated hemolytic anemia). However, the presence of hemolysis can easily be demonstrated by red cell survival test. The red cell fragility is frequently normal in these cases. The finding of hemolysis is important as patients with a history of chronic alcoholism, with or without liver cirrhosis, frequently have anemias due to chronic blood loss from hemorrhagic gastritis, peptic ulcer, esophageal varices or due to hypersplenism.

The hemolytic anemia was explained by Zieve [*1*] as due to an abnormal lipid, probably lysolecithin. This lysolecithin can be produced from lecithin (normally present in serum) through the action of a pancreatic lipase, lecithinolipase. It is not known whether lecithinolipase is present normally in serum [*2*]. However, under certain conditions (in cases of hyperlecithinemia) lysolecithin could appear in the serum as a byproduct of lecithin metabolism. It is possible that in patients with hyperlecithinemia and damage to the liver or pancreas (release of lecithinolipase) larger amounts of lysolecithin would appear in blood and cause hemolysis. This could be possibly an explanation for the fact that of our six patients with Zieve's syndrome, two (Cases II and V) who had the most pronounced anemia, had the highest phospholipids, which consist of 80 to 90 per cent lecithin.

However, hemolytic anemia is a frequent finding in many diseases of the liver (such as cirrhosis, hepatitis and malignancy) [*3*]. Studies of red cell survival time with Cr^{51} in patients with liver disease reveal that 87 per cent of the patients have survival half-times of less than twenty-five days (lowest limit of normal). It has been suggested that the anemia may be due to suppression of bone marrow activity [*3*]. Similar results were reported in another survey [*4*] of nineteen patients (fifteen with cirrhosis, three hepatitis and one chronic biliary obstruction). In both these groups of patients, 50 per cent had mild leukopenia, thrombocytopenia and reticulocytosis which suggested the possibility of hypersplenism. There have also been reported instances of hemolytic anemia in patients with acute viral hepatitis [*5*] but again without satisfactory explanation of the etiology of hemolysis. In the patients described by Zieve, and in our own patients, the white blood cell counts were rather elevated and the spleen in the majority of patients was not enlarged, therefore hypersplenism as a cause of the anemia is not likely. The explanation given by Zieve (an abnormal phospholipid of the lysolecithin type) is more acceptable inasmuch as improvement of the anemia in these patients closely followed the decrease in serum lipids and took place rather rapidly (nineteen days in our Case III). In some cases of Zieve's syndrome hemolysis may be due to a combination of hypersplenism (which existed long before the patient had an acute hyperlipemia) and the presence of lysolecithins.

Jaundice, the last of the triad in Zieve's syndrome, is almost always present and is attributable chiefly to intrahepatic cholestasis with varying degrees of hepatocellular damage. This is suggested by the laboratory findings showing elevated serum bilirubin and alkaline phosphatase levels with negative reactions to cephalin flocculation tests. In the ten patients of Zieve

TABLE III

LIVER BIOPSY FINDINGS IN SIXTEEN CASES REPORTED BY ZIEVE*

No. of Cases	Negative	Minimal	Mild	Moderate	Severe	Very Severe	Non-diagnostic
Total of twenty cases (16 biopsies):							
Cirrhosis	0	6	3	5	1	0	1
Fatty liver	1	5	4	2	2	1	1
Ten cases, with manifest hyperlipemia (7 biopsies):							
Cirrhosis	0	3	2	1	0	0	1
Fatty liver	1	1	2	2	0	0	1

* ZIEVE, L. [1].

with manifest hyperlipemia, the serum bilirubin ranged from 1.5 to 20 mg. per cent, and the alkaline phosphatase from 9 to 68 units. The reaction to a cephalin flocculation test was negative after forty-eight hours in all patients except one, in whom it was 2 plus, and this was the patient with the highest serum bilirubin, 20 mg. per cent. There are also cases in which jaundice is absent completely, although some laboratory findings indicate that liver damage is present. These cases can be compared with the anicteric form of infectious hepatitis which has some similarities in regard to symptoms (such as fatigue, anorexia and pain of the upper right part of the abdomen) and duration of disease (four to six months).

Zieve considers that liver cirrhosis and fatty liver play an important role in his syndrome. However, the sixteen biopsy specimens of the liver performed in his patients fail to support this view, since (see Table III) one was non-diagnostic and nine (60 per cent) showed only minimal or mild cirrhosis. Fatty liver was found to be absent, minimal or mild in ten (66 per cent) of these biopsy specimens. The percentage of minimal or mild cirrhosis and fatty liver is even higher (over 80 per cent) in the seven biopsies obtained from the ten patients with manifest hyperlipemia. The changes found in these biopsies are what one would expect in patients with a long history of alcoholism. It is, however, significant that not one of the seven biopsy specimens from the patients with manifest hyperlipemia showed severe cirrhosis or fatty liver. Apparently, severe damage of the liver parenchyma prevents the appearance of hyperlipemia and hypercholesterolemia whereas cholestasis without hepatocellular damage, under certain conditions, promotes their appearance. Biopsy specimens of the liver seem to be of little help in the diagnosis of Zieve's syndrome as the changes found in them are common in chronic alcoholics.

It would seem that the pancreas plays an important role in the pathogenesis of Zieve's syndrome although the serum amylase levels in most of the cases were found to be within normal limits. This is not surprising, as the serum amylase is usually elevated only for a very short period (twenty-four to seventy-two hours) in cases of acute pancreatitis and may remain normal in chronic pancreatitis. The clinical symptoms in some cases of pancreatic cellular damage may be similar to those in obstructive type of pancreatitis in which obstruction of the pancreatic duct by calculi, edema of the mucosa or spasm of the sphincter causes increased intraductal pressure with destruction of alveolar cells and passage of enzymes into the blood stream. Both of these forms of pancreatitis (pancreatocellular and obstructive type) are frequently combined with liver disease and it is often difficult to decide whether the symptoms are due to liver damage or to pancreatic disease, or to a combination of both [6]. Some authors [7] consider that in viral and toxic hepatitis, alcoholism and malnutrition, both organs are simultaneously injured and that the clinical picture depends on the degree of damage in each of the organs. Cole and Howe [8] described a pancreaticohepatic syndrome with severe malnutrition and hepatic lesions preceding the lesions in the pancreas. In the cases of Zieve, the serum amylase was estimated in only six patients and was normal. In our six patients the test was performed twice in the first

three, once in two (Cases IV and V), and three times in the last patient (Case VI), and the results were also within normal limits. The serum amylase was also not elevated in five well documented cases of acute transient hyperlipemia associated with pancreatitis described by Albrink and Klatskin [*9*]. Dragstedt et al. [*10*] showed in depancreatized dogs that the pancreas has a definite influence on the lipid metabolism and, in some instances, damage to the pancreas may cause a rise in serum lipids with changes in the liver. It is reasonable to assume that in cases of Zieve's syndrome, despite some negative laboratory findings, the pancreas is damaged and that the transient hyperlipemia may be due to insufficiency of some endocrine pancreatic function.

The abdominal crises, manifested by recurrent episodes of pain in the upper part of the abdomen, are one of the most characteristic symptoms of Zieve's syndrome. The pain is crampy or dull, changing in localization but always in the upper part of the abdomen, independent of meals, lasts for minutes or hours, and is not controlled by conservative treatment. Depending on localization, the pain may be suggestive of peptic ulcer, pancreatitis, gallbladder disease, kidney stones, common duct obstruction or even high retrocecal appendicitis. Because of the alarming symptoms and severity of pain, some of those patients underwent emergency surgery with essentially normal findings except for some indurated areas in the pancreas in patients in whom the surgeons suspected pancreatitis. The cause of those abdominal crises is unknown. Klatskin and Gordon [*11*] suggested that fat embolization could cause recurrent abdominal pain in patients with hyperlipemia. This however, was not, substantiated. Other authors [*12,13*] consider the pain to be due to sudden engorgement of the liver and spleen following deposition of large amounts of fat, as was observed in patients with essential hyperlipemia when the serum level of lipids reached 8,000 mg. per cent. Both these theories are not satisfactory as they do not explain why the pain is present even when the lipids return to normal levels, and persists for long periods afterwards. It is possible that these episodes of recurrent pain, which never subside completely, are due to disturbances of lipid metabolism in the nerves or nerve cells similar to those found in diabetic neuropathies or in tabetic gastric crises. This would explain why the pain changes in localization, its recurrence, its persistence for long periods, its resistance to treatment and its independence of the actual lipid levels in serum. It would be quite difficult to prove that the neuropathy is not of toxic origin, due to chronic alcoholism, as all patients with Zieve's syndrome are alcohol addicts. One of our six patients (Case II) has complained of continuous pain, radiating from both hips down to the calves, for six to eight months. Strangely enough, the pain subsided at about the same time as his epigastric discomfort. This might suggest that both these neuralgias were of the same etiology. The pain in his legs started during his stay in the hospital, and about two months after he stopped drinking completely. This would be against the toxic (alcoholic) origin of his neuropathy.

One patient (Case IV) had such severe pain in both legs that a bilateral sympathectomy was performed with only temporary relief. The pain reappeared after several weeks and the patient requested admission to our hospital. As there were no signs of vascular insufficiency and reappearance of the pain coincided with an elevation of the serum lipids, one would be tempted to relate the pain to the hyperlipemia. This patient did not experience, at any time, pain in the upper part of the abdomen so characteristic of Zieve's syndrome.

Alcoholism is a constant feature of Zieve's syndrome. All the patients presented by Zieve, and those of the present report, were chronic alcoholics for many years and many of them were treated before in hospitals for the post-alcoholic state, gastrointestinal disturbances secondary to alcoholism and pancreatitis. Reviewing the hospital records of these patients, there is no previous history of hyperlipemia in the laboratory findings or treatment for a disease which clinically would resemble Zieve's syndrome. However, thousands of alcoholics, with or without liver cirrhosis, are treated in hospitals and despite this, there are few reports of patients with hyperlipemia or with the clinical picture of Zieve's syndrome. One may draw the conclusion that alcoholism or liver cirrhosis alone cannot be the cause of Zieve's syndrome. It may be the predisposing factor which makes some of these patients susceptible to toxic or possibly infectious agents responsible for specific changes in the liver and in the pancreas. These changes have to affect cells, both in the liver and in the pancreas, which are important for

lipid metabolism and which usually are not damaged in patients with simple pancreatitis or hepatitis. This would explain why Zieve's syndrome is relatively rare despite the great number of alcoholic and cirrhotic patients treated in hospitals.

The clinical picture of this new syndrome is quite characteristic. The onset of the disease is rather insidious; the patient complains of loss of appetite, progressive general weakness and fatigability. Episodes of pain in the upper part of the abdomen follow and are one of the most significant symptoms in this syndrome. The pain is independent of meals, is crampy or like dull pressure, not well localized, more often on the right side than on the left, accompanied by nausea and occasionally by vomiting. The acute pain lasts usually from a few minutes to several hours and never subsides completely. The patients then usually reduce their alcohol intake to a minimum, but this does not bring relief. They lose weight, sometimes 10 to 15 pounds or more in several weeks. It is generally after a month or two when they realized that their condition was worse or when they noticed that they were jaundiced that they requested admission to a hospital. The patients with pain in the upper part of the abdomen are usually treated for gastritis, peptic ulcer or pancreatitis and, if jaundice is present, for incomplete common duct obstruction, hepatitis or liver cirrhosis. The prognosis is good in most of the cases and the patients' condition improves with symptomatic treatment and diet. In some instances, however, the symptoms are so alarming (such as epigastric pain, nausea and vomiting) that frequently an exploratory laparotomy is performed, with findings usually within normal limits. In most patients recovery is complete after four to six months, although recurrent dull epigastric pain may persist for many months.

The diagnosis of Zieve's syndrome would be easy on admission if the triad of hyperlipemia, anemia and jaundice were present. Frequently, however, the patient is admitted when the hyperlipemia has partially subsided and the serum is no longer cloudy. Hemolytic anemia may be absent if bone marrow activity compensates for the loss of red cells by hemolysis and sometimes the bilirubin may be only slightly elevated, without apparent jaundice. However, even in the absence of manifest hyperlipemia, anemia and jaundice, the diagnosis can be established by studies of fractional serum lipids, by the red cell survival time and liver function tests. Bone marrow examination also can be of help in making the diagnosis. The finding of large phagocytic histiocytes, loaded with lipid granules, would indicate that hyperlipemia is, or was present, as some of these cells remain in the bone marrow for several weeks after the serum has cleared completely. Also, erythroid hyperplasia of the bone marrow, in the presence of a normal hemogram, may be indicative of chronic blood loss or hemolysis and, if the former can be ruled out by usual tests, the latter can be proved by the red cell survival time test.

Some instances of transient hyperlipemia, pancreatitis and episodes of abdominal pain described in the literature during the past twenty-five years may have been cases of Zieve's syndrome. Thannhauser [*2*] in the chapter "Hyperlipemia in Chronic Pancreatitis and Eruptive Xanthoma" mentions Friedreich who, as early as 1876, suggested that there must be a connection between pancreatic cirrhosis and fatty liver in patients with chronic alcoholism. Others mentioned by Thannhauser are Marcus (four cases of pancreatitis, transitory hyperlipemia and abdominal pain), Joel (two cases of pancreatitis with hyperlipemia without diabetes), Brunner (one case of pancreatitis with hyperlipemia proved by exploratory laparotomy) and several others. Gross [*6*], from the Mayo Clinic, presented a review of the literature on the association of pancreatitis with hyperlipemia. He stated that in the course of a century only forty cases were reported of coexistence of pancreatitis and hyperlipemia and from these in only seventeen cases was the diagnosis of pancreatitis confirmed by surgical exploration or autopsy, whereas the hyperlipemia was proved by laboratory tests. He also presented his own two cases which were very characteristic, as in both cases the patients had undergone a laparotomy twice because of severe pain in the upper part of the abdomen and in each instance the pancreas was found to be hard and indurated. In these two patients the serum amylase and lipase were within normal limits and during surgery no other pathologic disorder was found in the abdomen. The episodes of epigastric pain continued after surgery despite conservative treatment. The serum lipids were only slightly elevated in the first patient (total fatty acids = 648 mg. per cent; total lipids = 882 mg. per cent) and the serum cholesterol was normal (234 mg. per

cent). In the second patient, the serum lipids were quite elevated (total fatty acids = 1,860 mg. per cent and total lipids = 2,096 mg. per cent) and the serum cholesterol also was normal (236 mg. per cent). No hemograms were available and it is therefore not known whether these patients had a hemolytic anemia. Serum bilirubin values were not determined because of the turbidity of the plasma. The clinical picture, however, and the course of the disease were similar to those described by Zieve.

Five cases of acute transient hyperlipemia in patients with chronic alcoholism and pancreatitis were described in 1957 by Albrink and Klatskin [*9*]. All these patients had recurrent episodes of epigastric pain, transient hyperlipemia and three of them were jaundiced. In these patients there was an increase in serum neutral fats to levels between 37 and 104 mEq. per L. (i.e., 1,348 and 3,068 mg. per cent) and in serum total fatty acids to levels between 64 and 172 mEq. per L. (i.e., 1,772 and 4,764 mg. per cent). The serum cholesterols were elevated (304 to 1,105 mg. per cent) and the lipid phosphorus was up to between 18 and 54 mg. per cent, corresponding to 450 and 1,350 mg. per cent of phospholipids. Normal serum amylase values were obtained. Hemograms or red cell survival studies were not recorded, so it is not clear whether a hemolytic anemia was present. The hyperlipemia cleared in all these patients in a few days, as in Zieve's syndrome, and the patients recovered on symptomatic treatment in about two to three weeks. The authors were inclined to accept the possibility that the hyperlipemia was due to embolization of liquefied fat arising at the site of necrosis in the pancreas.

Gross [*6*] also mentions fat embolization as one of the possible causes of transient hyperlipemia but he considers it more probable that the hyperlipemia is due to damage of the alpha cells, with insufficiency in production of a hormone that regulates the lipid levels in blood, but different from glucagon which is believed to be produced by these same alpha cells. Gross refers to the experiments of Caren and Carbo [*14*], who regularly observed hypercholesterolemia in rabbits after administration of cobaltous chloride, which selectively destroys the alpha cells of the islets of Langerhans, leaving the beta cells intact. These authors reported that there was evidence of alpha cell damage one hour after administration of cobalt and, after four hours, almost no alpha cells could be found. The beta cells remained intact and no other tissue (pancreas or liver) showed any signs of injury. Regeneration of alpha cells occurred in about five to six days and was complete after about ten days. The rise and decline of serum cholesterol levels coincided well in time with the destruction and regeneration of the alpha cells. There was a marked rise in serum cholesterol levels after twenty-four hours, with a peak between the second and third day and a slow fall to normal values about the seventh day. These experiments would suggest that the alpha cells "exercise endocrine control over blood cholesterol concentration and therefore must secrete a hormone that regulates lipid metabolism [*14*]." In these experiments, no studies of other lipids (such as neutral fats and fatty acids) were made and the question as to whether the levels of other lipids are also elevated after administration of cobalt remains unanswered. It would, however, appear reasonable to assume that, even if the other serum lipids were increased, a normally functioning liver would be able to clear the resulting hyperlipemia, as with hyperlipemia of postprandial origin. Only if the liver were damaged, and unable to metabolize larger amounts of lipids, would one expect the serum lipid levels to remain elevated. This would explain why in the thousands of cases of pancreatitis or liver damage (hepatitis, liver cirrhosis or fatty liver), that we rarely find a transient hyperlipemia such as occurs in Zieve's syndrome. To cause hyperlipemia, both these organs have to be damaged at the same time and, in addition, the damage has to be specific: in the pancreas involving the islets of Langerhans, possibly the alpha cells, and in the liver causing intrahepatic cholestasis with retention of some factors which normally inhibit lipid metabolism. All these assumptions admittedly are hypothetic since, up to the present, the alpha cell factor has not been isolated and relatively few studies have been made in this direction.

SUMMARY

Zieve recently described a syndrome consisting of transient hyperlipemia, jaundice and hemolytic anemia associated with alcoholic fatty liver and cirrhosis. Five cases of this syndrome are described herein and the relevant literature is reviewed. In almost all the patients there was pain in the upper part of the abdomen

sometimes so severe that exploratory laparotomy was performed.

It is suggested that this syndrome is due to specific damage to the pancreas (alpha cells of the islets of Langerhans ?) and to the liver (intrahepatic cholestasis with or without hepatocellular damage ?).

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